THE JOURNAL OF Organic Chemistry®

Volume 26, Number 7

July 25, 1961

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER]

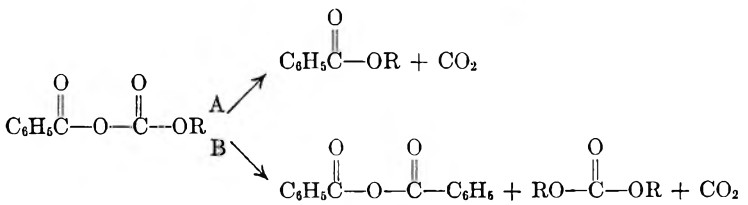
Aspects of the Mechanism of Decomposition of Mixed Carboxylic-Carbonic Anhydrides[1]

EDWARD J. LONGOSZ[2] AND D. STANLEY TARBELL

Received October 24, 1960

A kinetic study of the conversion of benzoic *n*-butylcarbonic anhydride to *n*-butyl benzoate (path A), and to benzoic anhydride and di-*n*-butyl carbonate (path B) has been made by measuring the rate of carbon dioxide evolution. The reaction, which shows erratic kinetics in the absence of added catalysts, is catalyzed by *N*-methylpiperidine, sodium methoxide, lithium fluoride, chloride and bromide, dry hydrogen chloride, dimethylaniline hydrochloride, and is not catalyzed by lithium perchlorate, benzoic acid, *n*-butyl benzoate, di-*n*-butyl carbonate, benzoyl peroxide, or tri-*n*-butylamine. The rate (in absence of added catalysts) is roughly the same in butylcarbitol, *n*-hexadecane and nitrobenzene, but is greatly accelerated in dimethylformamide. The proportions of products (paths A and B) are not altered by changes in solvent, temperature, or presence of catalysts. The results agree with the idea that the products are formed by a series of ionic chain reactions, which are initiated by the catalysts acting as nucleophiles. Optically active benzoic 2-octylcarbonic anhydride yields 2-octyl benzoate and dioctyl carbonate in refluxing pyridine with complete retention of configuration.

In an earlier paper,[3,4] it was shown that mixed carboxylic–carbonic anhydrides yield on heating two sets of products: the ester and carbon dioxide (path A), and the disproportionation products, the symmetrical anhydride, the dialkyl carbonate, and carbon dioxide (path B).



A study of the effect of changes in structure of R on the proportions of A and B showed that path A is favored when the point of attachment of R is a secondary carbon, or a primary carbon with heavy substitution on the β-carbon. Both paths A and B occurred about equally when the alkyl group was primary, as in ethyl or butyl. Tertiary amines were found to increase the rate of formation, but not to alter the proportions, of products. Rearrangement of the mixed anhydride from (−)-2-octanol by heating at 150° without solvent proceeded with complete retention of configuration.[5]

(1) A preliminary account of this work appeared in *Science*, **130**, 1425 (1959).

(2) National Science Foundation Predoctoral Fellow, 1958–1959.

(3) D. S. Tarbell and E. J. Longosz, *J. Org. Chem.*, **24**, 774 (1959 .

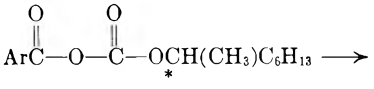
(4) (a) In a previous paper, dealing with the isolation of stable mixed anhydrides (D. S. Tarbell and N. A. Leister, *J. Org. Chem.*, **23**, 1149 (1958)) several references were missed, in addition to those cited, describing isolation of this type of structure: (b) E. Fischer and H. Strauss, *Ber.*, **47**, 317 (1914); (c) K. v. Auwers and E. Wolter, *Ber.*, **63**, 479 (1930); (d) J. E. Leffler, *J. Am. Chem. Soc.*, **72**, 67 (1950); (e) D. B. Denney, *J. Am. Chem. Soc.*, **78**, 590 (1956).

(5) The possibility that a mixed anhydride with an optically active alkyl group might yield ester with retention of configuration of the alkyl group was suggested by F. D. Greene, *J. Am. Chem. Soc.*, **77**, 4872 (1955), to explain some observations on formation of optically active alcohol from active methylphenylacetyl chloride and sodium peroxide. *Cf.* also P. D. Bartlett and F. D. Greene, *J. Am. Chem. Soc.*, **76**, 1091 (1954).

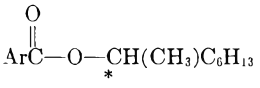
The present paper describes some further stereochemical observations, and reports a kinetic study of the rearrangement of benzoic *n*-butylcarbonic anhydride. From the effects of many agents as catalysts, or noncatalysts, a fairly definite picture of the reaction mechanism emerges.

STEREOCHEMICAL STUDIES

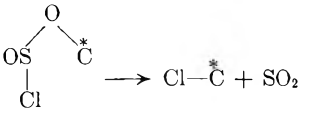
The decomposition of the mixed anhydride by path A, where R is optically active, can be written with a formal similarity to the S_Ni reaction involving the chlorosulfite:



I. Ar = C_6H_5
II. Ar = 2,4,6-$(CH_3)_3C_6H_2$



III. Ar = C_6H_5
IV. Ar = 2,4,6-$(CH_3)_3C_6H_2$



In some cases, thionyl chloride and an optically active alcohol in absence of pyridine lead to a chloride with retained configuration,[6] while a chloride of inverted configuration is formed in the presence of pyridine.[6] Later significant studies[7,8] have shown that the stereochemistry of the decomposition of chlorosulfites is dependent on the nature of the solvent; the whole range of results, from retention to inversion of configuration, can be obtained by varying the solvent.

We have therefore extended our previous observations,[3] and have found that, in refluxing pyridine, benzoic octylcarbonic anhydride (I) was rearranged to the ester (path A) and to dioctyl carbonate with complete retention of configuration, just as in the absence of pyridine. The corresponding mesitoic octylcarbonic anhydride (II) was also rearranged (without added solvent) to give octyl mesitoate (IV), with complete retention of configuration; the ester IV of the same rotation was prepared from optically active octyl alcohol and mesitoyl chloride. Thus, the stereochemistry of the reaction is unchanged by a change from no solvent to pyridine, and by an increase of hindrance around the carboxyl carbonyl group.

(6) Summaries from the earlier literature are given by W. A. Cowdrey, E. D. Hughes, C. K. Ingold, S. Masterman, and A. D. Scott, *J. Chem. Soc.*, 1266 (1937).

(7) E. S. Lewis and C. E. Boozer, *J. Am. Chem. Soc.*, **74**, 308 (1952); **75**, 3182 (1953).

(8) D. J. Cram, *J. Am. Chem. Soc.*, **75**, 332 (1953).

KINETIC STUDIES

The rate of rearrangement of benzoic *n*-butylcarbonic anhydride (V) was studied, following the reaction by measuring the rate of carbon dioxide evolution. Studies using dibutyl carbitol (dibutyl ether of diethylene glycol) as solvent at 155° showed that 70–75% of the theoretical amount of carbon dioxide was evolved, just as in the decomposition without solvent[3]; this corresponds to 40–50% of *n*-butyl benzoate (path A), with the remainder going to dibutyl carbonate and benzoic anhydride (path B).

The kinetic runs showed in some cases a first-order reaction, but the numerical values were not reproducible, varying from 2 to 13 $\times 10^{-4}$ sec.$^{-1}$, at 155.1°; most of the runs, however, did not yield linear first-order plots, but showed an increase in rate as the reaction proceeded, and also showed a lack of reproducibility from one run to another.

The possibility that these erratic results were due to systematic faults in equipment or technique was ruled out by measuring the rate of decomposition of benzyl chlorcarbonate in dibutyl carbitol at 155°:

$$C_6H_5CH_2OCOCl \longrightarrow C_6H_5CH_2Cl + CO_2$$

This reaction gave excellent first-order plots over the whole course of the reaction,[9] and its rate was unaffected by the presence of the reaction products.

The obvious explanation for the increase of rate during the reaction—that the products were catalyzing the reaction—was shown to be untenable, as far as the major products were concerned; addition of butyl benzoate, dibutyl carbonate, or benzoic anhydride to the mixed anhydride V in dibutyl carbitol did not affect the rate of decomposition of V. Nevertheless, there was no doubt about the autocatalytic effect of something present in the reaction mixture. This was demonstrated by using the reaction mixture from a completed kinetic run as the solvent for a second run; the rate for the second run was about ten times faster than the first run. Still a third experiment in the same reaction mixture gave a rate which was nearly twenty times the original rate. These observations were checked several times and although the amount of rate increase varied, an increase was always observed.

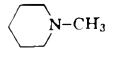
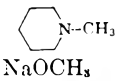
These observations suggested catalysis by trace impurities, which were produced in the reaction, and which might vary from one run to another in pure solvent, even though numerous procedures for washing the glass reaction flask and for washing the benzoic butylcarbonic anhydride were tried. There was no reaction between butyl carbonate and benzoic anhydride under the conditions of the kinetic runs.

(9) K. B. Wiberg and T. M. Shryne, *J. Am. Chem. Soc.*, **77**, 2774 (1955), reported good first order constants for this reaction in toluene and dioxane at 60–90°.

The effect of various possible catalysts on the rate of the reaction was investigated, with the results shown in Table I.

TABLE I

DECOMPOSITION OF BENZOIC-*n*-BUTYLCARBONIC ANHYDRIDE IN DIBUTYL CARBITOL; 155 ± 0.1°. EFFECT OF ADDITIVES ON RATE OF DECOMPOSITION

Additive	Solubility	Mole % of Additive	Relative Rate
None		—	1
$(n\text{-}C_4H_9)_3N$	+	8	1
$(n\text{-}C_4H_9)_3N$	+	90	1
	+	8	8
	+	19	12
$NaOCH_3$	−	5	15
$(C_6H_5—\overset{O}{\overset{\|}{C}}—O)_2$	+	3	1[a]
$n\text{-}C_4H_9—OH$	+	30	1[a]
$C_6H_5—COOH$	+	4 to 12	1[b]
$C_6H_5—COONa$	−	5	Too fast to measure
$C_6H_5—N(CH_3)_2$	+	90	1
$C_6H_5—N(CH_3)_2.HCl$	−	1.4	20
Dry HCl	+	?	Too fast to measure
LiCl	−	2	Too fast to measure

[a] Solvent was butyl benzoate. [b] Solvent was also butyl benzoate and nitrobenzene.

The very strong catalytic effect of agents like sodium methoxide, lithium chloride, sodium benzoate, and dimethylaniline hydrochloride, which are apparently insoluble in dibutyl carbitol, is notable. Equally notable is the lack of catalytic activity of tri-*n*-butylamine, whereas the less sterically hindered *N*-methylpiperidine shows strong catalytic effects.

The first-order rate plots for the experiments using *N*-methylpiperidine and sodium methoxide are illustrated in Fig. 1. In these cases, the rate of decomposition steadily increased until approximately 50% reaction, then leveled off to follow a first-order rate law. The rate in the second half of the decomposition was at least two to three times the fastest rate observed in pure dibutyl carbitol, so it must be due to the presence of the bases. Moreover, a curve of this particular shape was never observed in pure solvent. Despite the fact that sodium methoxide was insoluble in the reaction medium, its influence seems to be similar to that of *N*-methylpiperidine.

Evidently, the catalytic action of the bases was greater than that of the by-products that caused rate increases in the determinations using pure dibutyl carbitol. A small interference from this source, however, can be seen from the slight curvature toward the completion of the reaction in experiments B and C.

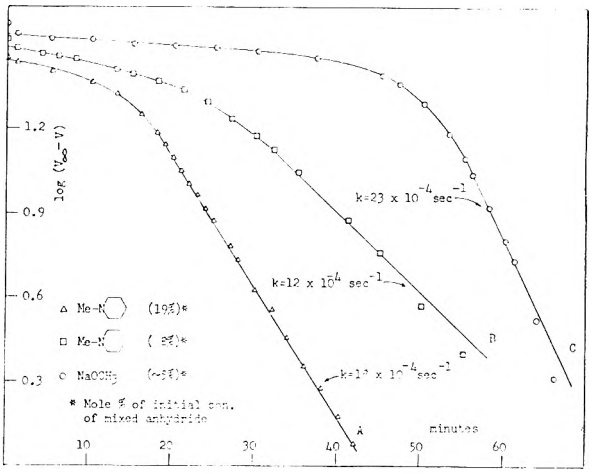


Fig. 1. Decomposition of benzoic-*n*-butylcarbonic anhydride in dibutyl carbitol; 155 ± 0.1°. Effect of bases. First-order rate plots

It was of interest to determine if the kinetic results of the very potent catalyst lithium chloride were similar to that of the basic substances. A measurable rate of decomposition of benzoic-*n*-butylcarbonic anhydride was observed at 115° in the presence of trace quantities of lithium chloride, and the first-order rate plots are illustrated in Figure II. In two experiments, the shape of the first-order plot was similar to that from the base catalyzed decompositions. With lithium chloride, however, the difference in rate between the initial and final stages of the decomposition was not as great. A run in the presence of lithium perchlorate was also made, but even though this salt was completely soluble in dibutyl carbitol, only a very small acceleration was observed.

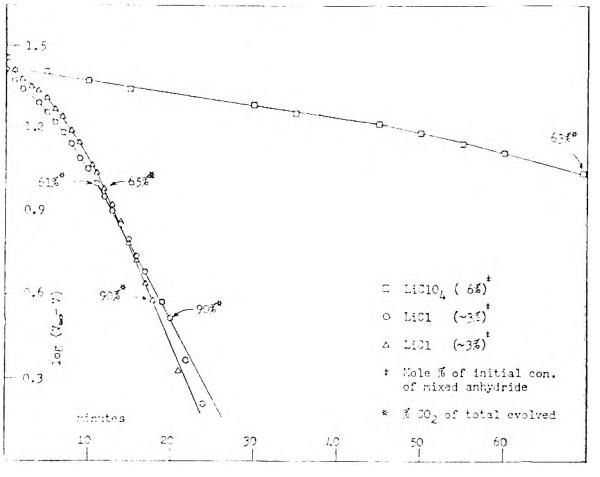


Fig. 2. Decomposition of benzoic-*n*-butylcarbonic anhydride in dibutyl carbitol; 115 ± 0.1°. Effect of lithium chloride. First-order rate plots

A series of rate measurements was also made in dibutyl carbitol containing a known quantity of hydrogen chloride. The shape of the first-order curves obtained from these decompositions at 115°

resembled the curves from the decomposition in pure solvent at 155°. A fairly linear portion was obtained from 10 to 50–70% carbon dioxide evolution, then the rate increased to approximately 100% its value in the linear portion. The rate of carbon dioxide evolution was roughly proportional to the hydrogen chloride concentration, although some erratic behavior was observed.

The effect of solvents of different polarity on the rate of a chemical process often establishes grounds for a possible reaction mechanism for that process. To this end, a measure of the rate of decomposition of benzoic-*n*-butylcarbonic anhydride at 155° was made in nitrobenzene, *n*-hexadecane, and *n*-butyl benzoate. In none of these solvents did the rate of decomposition depart greatly from the slowest rate measured in pure dibutyl carbitol. In fact, the rate of evolution of carbon dioxide from decomposition of the mixed anhydride in nitrobenzene and *n*-hexadecane was remarkably similar to that found in dibutyl carbitol. Although the evolution of carbon dioxide was faster when butyl benzoate was used as the solvent, the rate was still within the ranges found in dibutyl carbitol. The faster rate of decomposition in butyl benzoate may have been due to one of the factors causing the discrepancies in the measurements in pure dibutyl carbitol, or it may have been due to impurities indigenous to the solvent. A less thorough purification of the butyl benzoate was made compared to the other solvents used.

Although the dielectric constant of dimethylformamide (DMF) is similar to that of nitrobenzene, decomposition of benzoic-*n*-butylcarbonic anhydride in this solvent was accelerated to a great extent.[10] Whereas the rate of decomposition of the anhydride was too slow to be measurable in dibutyl carbitol at 97°, the decompositions in dimethylformamide at this temperature were complete in sixty to seventy minutes. The first-order plots of carbon dioxide evolution were not unlike the plots derived from reactions conducted in pure dibutyl carbitol at 155°.

The course of decomposition of the mixed anhydride in dimethylformamide was the same as the course of decomposition without solvent. The yield of carbon dioxide obtained was 75 ± 5%, indicating that approximately 50% of the anhydride decomposed to ester, and 50% to disproportionation products. This fact was verified by identity of the infrared absorption curve of the mixture freed of dimethylformamide with the mixture of products resulting from decomposition of the anhydride without solvent.

The greater solvating ability of dimethylformamide provided an opportunity to study the effect of ionic additives on the stability of the mixed anhydride. The salts listed in Table I, which were not soluble to any appreciable extent in dibutyl carbitol, were soluble in dimethylformamide, at least in the concentrations studied. The relative rates reported in Table II, using various soluble additives, afford a comparison of the times for 100% decomposition of benzoic-*n*-butylcarbonic anhydride. The rate accelerations observed were probably real, as measurement of the rate of decomposition in five separate experiments with no catalyst, showed fair agreement.

TABLE II

DECOMPOSITION OF BENZOIC-*n*-BUTYLCARBONIC ANHYDRIDE IN DIMETHYLFORMAMIDE; 97.5 ± 0.1°

Additive	Mole %	Relative Rate
None	—	1
LiCl	1.3	3
	2.7	3.5
	5.2	9
LiBr	3.9	3
LiF	3	2
$LiClO_4$	4.1	1
$(CH_3)_4NCl$	4.5	Too fast
$C_6H_5—\overset{\overset{O}{\|}}{C}—Cl$	3	1
$n\text{-}C_4H_9—O—\overset{\overset{O}{\|}}{C}—Cl$	3.7	1
$C_6H_5—\overset{\overset{O}{\|}}{C}—OH$	3	1
$C_6H_5—\overset{\overset{O}{\|}}{C}—ONa$	3	Too fast
	0.8	Too fast
	7.4	3

Lithium chloride, as well as lithium bromide, and, to a lesser degree, lithium fluoride acted as catalysts in the decomposition. As observed in the solvent dibutyl carbitol, lithium perchlorate again had no effect. Tetramethylammonium chloride was found to be a potent catalyst, but organic chlorine compounds such as benzoyl chloride and *n*-butyl chlorocarbonate were ineffective.

Whereas benzoic acid had no effect on the decomposition, its sodium salt was an extremely active catalyst. Even when less than 1 mole % of sodium benzoate was present, the evolution of carbon dioxide was too fast to measure; *N*-methylpiperidine had about the same effect as lithium chloride, but had to be present in five times the quantity of the latter to produce the same rate.

It is interesting to note that a first-order plot of carbon dioxide evolution in experiments where lithium chloride or *N*-methylpiperidine were used in dimethylformamide yielded curves similar to those obtained when these reagents were used in conjunction with dibutyl carbitol. The rate of

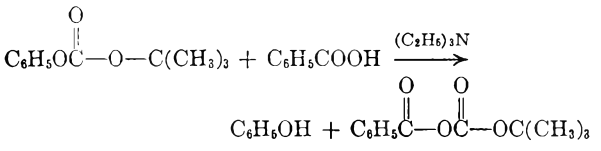
(10) The qualitative effect of dimethylformamide in accelerating displacement reactions at a saturated carbon is well known, and has been documented by quantitative measurements by H. E. Zaugg *et al.*, *J. Am. Chem. Soc.*, 82, 2895, 2903 (1960).

evolution of carbon dioxide increased until approximately 50% reaction, when it leveled off to follow a first-order rate law.

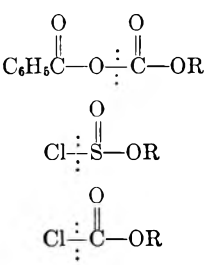
Several decompositions were made in dimethylformamide using sodium benzoate or sodium acetate in small amounts. Because of the speed of the reaction, these measurements were made at 75°. The initial induction period was suppressed in two cases, although it still appeared in a third.

Several other qualitative observations may be mentioned. Benzoic benzylcarbonic anhydride was prepared, but it decomposed even at room temperature in the absence of added catalysts; the products could not be separated by distillation, but it was apparent from the infrared spectrum that decomposition had followed both paths A and B.

Benzoic 2-octylcarbonic anhydride appeared to decompose more slowly at 155° than the *n*-butyl compound. Decomposition of a crystalline sample of *p*-nitrobenzoic ethylcarbonic anhydride[4a] in dibutyl carbitol at 155° gave a rate ten times faster than the fastest rate observed for benzoic butylcarbonic anhydride. Recrystallization of this sample of mixed anhydride twice more, however, reduced the rate to one tenth of the former value; the first-order plot was curved in this case also. Apparently the *p*-nitrobenzoic mixed anhydride should be purified with great care before conclusions are drawn from its behavior.[11] Mesitoic 2-octylcarbonic anhydride failed to decompose at 155° at a measurable rate; attempts were made to prepare benzoic *t*-butylcarbonic anhydride from phenyl *t*-butylcarbonate,[12] benzoic acid, and triethylamine, but none of the desired product was obtained. Apparently the benzoate ion is too weak a nucleophile to bring about the desired reaction.



Mechanism of mixed anhydride decomposition. The formal similarity, already mentioned, between the decomposition of the mixed anhydrides, the chlorosulfites and the chlorocarbonates is indicated below. Recent work[7-9] on the latter two types

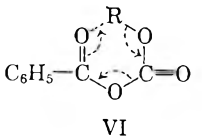


makes it clear that they split to ion pairs (Cl^-, ^+SOOR or Cl^-, ^+COOR) which then collapse with loss of sulfur dioxide or carbon dioxide, and the cleavage of the alkyl-oxygen bond. The stereochemical consequences when R is optically active depend on the nature of the solvent.

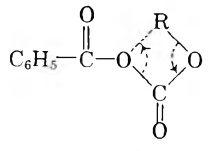
There is considerable evidence that this scheme does not obtain with the carboxylic carbonic anhydrides, except possibly in the case of the benzoic benzylcarbonic anhydride.[3,12a] The complete retention of configuration, even in the presence of pyridine, when R is optically active, the fact that the 2-octyl compound decomposes more slowly than the *n*-butyl compound, and that the neopentyl compound gives neopentyl benzoate without any evidence for skeletal rearrangement of the neopentyl group,[3] makes it unlikely that alkyl-oxygen cleavage does occur, with possible formation of a carbonium ion intermediate. The possibility of alkyl-oxygen cleavage is now being investigated by O^{18} studies.

The possibility that the decomposition of the mixed anhydrides is a free radical reaction is made unlikely by the fact that benzoyl peroxide does not act as a catalyst, and that the potent catalysts discovered in this study are all ionic compounds.

The mechanism for the decomposition of the mixed anhydride to ester, involving a cyclic transition state, cannot be ruled out on the basis of our stereochemical results, at least in the absence of pyridine. The two cyclic transition states VI and VII below, involve alkyl-oxygen cleavage and retention of configuration.



VI



VII

A transition state such as VI or VII does not explain the much greater tendency for the mixed anhydrides with heavy substitution on the β-carbon of the alkyl component to form ester. This result, however, can be justified on the basis that the heavy substitution inhibits the disproportionation reaction, thus allowing ester formation through VI or VII. The same may apply when the point of attachment is a secondary carbon atom.

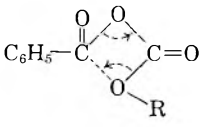
(11) *Cf.* T. B. Windholz, *J. Org. Chem.*, **23**, 2044 (1958).

(12) W. M. McLamore, S. Y. P'an, and A. Bavley, *J Org. Chem.*, **20**, 1379 (1955).

(12a) The very rapid rate of decomposition of the benzoic benzylcarbonic anhydride may be correlated with the observation that the mixed anhydrides, which may be intermediates in the ionic decomposition of phenylacetyl peroxides, cannot be isolated from bisphenylacetyl peroxide [P. D. Bartlett and J. E. Leffler, *J. Am. Chem. Soc.*, **72**, 3030 (1950)] or from bis-*o*-iodophenylacetyl peroxide [J. E. Leffler and A. F. Wilson, *J. Org. Chem.*, **25**, 424 (1960)]. Decomposition of 4-methoxy-3′,5′-dinitrobenzoyl peroxide apparently gives the mixed anhydride 3,5-$(O_2N)_2$-$C_6H_3COOCOOC_6H_4OCH_3$ (4) as an unstable intermediate, which forms the ester 3,5-$(O_2N)_2C_6H_3COOC_6H_4OCH_3$ (4) [J. E. Leffler and C. C. Petropoulos, *J. Am. Chem. Soc.*, **79**, 3068 (1957)].

By increasing the polarization of the carboxylic carbonyl group, the tendency for the rearrangement to occur by the cyclic mechanism of VI might be expected to be increased. Indeed, when the mixed anhydride was made from a stronger acid, such as *p*-nitrobenzoic[11,13] or trifluoroacetic,[14] the reaction was reported to proceed predominantly to ester. Conversely, when the polarization of the carbonyl group is decreased, as it should be in the mesitoic carbonic anhydride, there should be a reduction in the tendency for ester formation. This seems to be the case with mesitoic ethylcarbonic anhydride, which underwent almost exclusive disproportionation. On the other hand, mesitoic-2-octylcarbonic anhydride exhibited almost exclusive ester formation, but again, this may be due to the constitution of the alkyl group in the carbonate portion of the mixed anhydride.

Another possible cyclic transition state for ester formation from a carboxylic-carbonic anhydride is that represented by structure VIII. This formulation involves acyl-oxygen cleavage in the carbonate portion of the mixed anhydride. This



type of transition state has been proposed in a similarly constituted system.[14]

The cyclic transition states VI, VII, and VIII, possible for the decomposition of a carboxylic carbonic anhydride, cannot be excluded for the mesitoate system on the grounds that the carbonyl group is sterically unavailable for reaction; many examples exist in which similarly hindered carbonyl groups do not react intermolecularly, but do so intramolecularly, with formation of five or six membered rings.[15]

The postulation of a mechanism involving a cyclic transition state for the formation of ester from a carboxylic-carbonic anhydride (path A) necessarily implies a different mechanism for the disproportionation reaction (path B), the formation of symmetrical anhydride and carbonate. It was shown that the specific mixtures of products obtained in the decomposition of the mixed anhydride were not determined by an equilibration process, as interconversion of the products did not occur under the conditions of the experiments. If the two processes under consideration (ester formation, path A; disproportionation, path B) occur by different mechanisms the ratio of path A to path B would be determined by the relative speed of the two paths. Alteration in the speed of one path relative to the other should be reflected in a change in the product ratios.

Decomposition of the mixed anhydrides in the presence of less than 5 mole % of tertiary amine, or lithium chloride, however, yielded practically the same product ratios as were obtained in the absence of these substances, although the reaction as a whole was accelerated to a marked degree. The temperature at which complete decomposition was usually attained within a short time in the presence of *N*-methylpiperidine was as much as 80° lower. Also, the temperatures at which decompositions were made in the presence of the amines differed by about 50°. In no case, however, was the ratio of products significantly changed.[16]

It is very unlikely that a substance accelerating the rate of one chemical process would accelerate the rate of a competing process to precisely the same degree. Yet, it would be necessary to draw this conclusion on the basis of two distinct mechanisms for the decomposition of the mixed anhydride, one for path A, and another for path B. Furthermore, decomposition of the mixed anhydride at widely different temperatures should be equivalent to altering the relative rates of the two paths, as it is unlikely, although possible, that two unrelated chemical processes have identical temperature coefficient.

If path A occurs by a unimolecular process, in which one molecule is involved in the rate determining step and path B occurs by a bimolecular process, in which two molecules are involved in the rate determining step, decomposing the mixed anhydride in solution should reduce the rate of path B to a much greater degree than the rate of path A. Hence, a decided increase in the yield of ester (path A) should be observed. However, when the mixed anhydride was decomposed in a 5% solution, by weight, in benzene or toluene, no alteration in product ratio was observed. In addition, the many decompositions of benzoic-*n*-butylcarbonic anhydride made under a variety of conditions, with and without catalysts for the purpose of kinetic measurements, never yielded more than 75 ± 5% carbon dioxide on the basis of the initial quantity of mixed anhydride. This indicates that the product ratio is immune to changes in concentration of anhydride and environment.

Our results indicate, therefore, that decomposition according to both paths A and B proceeds by a single rate-determining step. The results are best explained by the idea that decomposition of the mixed anhydride proceeds through a set of ionic

(13) A. Einhorn, *Ber.*, **42**, 2772 (1909).

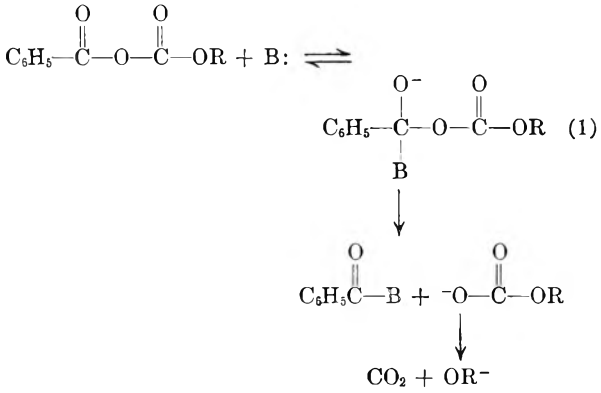
(14) R. Boschan, *J. Am. Chem. Soc.*, **81**, 3341 (1959).

(15) R. C. Fuson and Q. F. Soper, *J. Org. Chem.*, **9**, 193 (1944); R. C. Fuson, W. D. Emmons, and R. Tull, *J. Org. Chem.*, **16**, 648 (1951); R. C. Fuson and W. C. Hammann, *J. Am. Chem. Soc.*, **74**, 1626 (1952).

(16) In a paper which appeared after this paper was submitted, T. B. Windholz, [*J. Org. Chem.*, **25**, 1703 (1960)] reported that some mixed anhydrides form more ester at 200° than at 160°; high concentrations of boron trifluoride etherate favored ester formation. Windholz proposed a cyclic transition state analogous to VI for the ester formation.

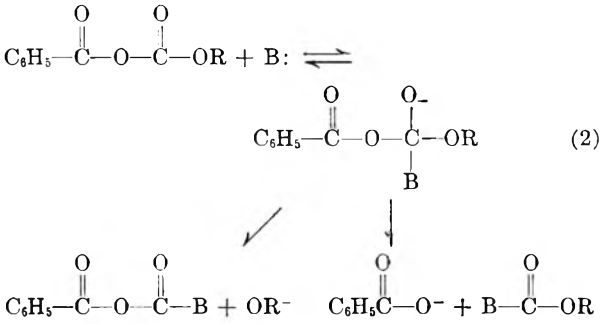
chain reactions, of which some of the possibilities are indicated below.[17]

Representing a nucleophile, as B: which may be uncharged (a tertiary amine) or charged (a halide ion, for example), attack on the mixed anhydride may take place at the carboxyl carbonyl or the carbonate carbonyl.[18] In the former case, we can have the following, the charge on the structure in (1) depending of course on the charged or uncharged



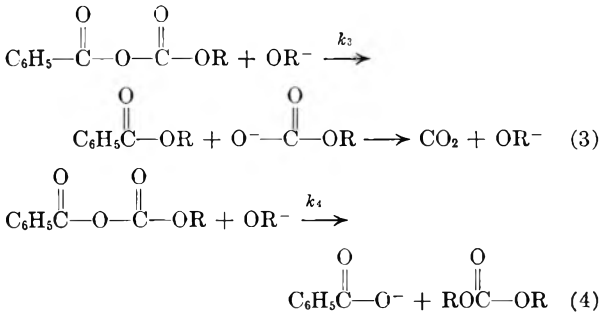
(1)

state of B:. Attack at the carbonate carbonyl can give:



(2)

The alkoxide ion OR^- generated according to (1) and (2) is the chain carrier, because it can attack at either carbonyl, as in (3) and (4), to generate products.



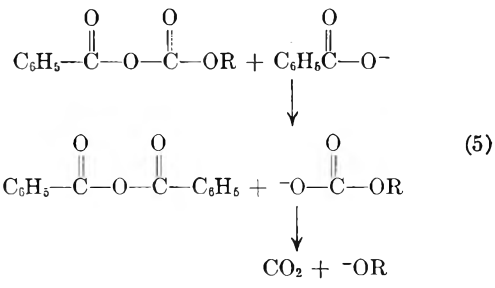
(3)

(4)

(17) Ionic chain reactions have been suggested in other cases by P. D. Bartlett and H. F. Herbrandson, *J. Am. Chem. Soc.*, **74**, 5971 (1952); *cf.* W. E. Bissinger, F. E. Kung, and C. W. Hamilton, *J. Am. Chem. Soc.*, **70**, 3940 (1948).

(18) Evidence supporting the existence of intermediates analogous to those below is given by V. Gold and E. G. Jefferson, *J. Chem. Soc.*, 1409, 1416 (1953), and by D. B. Denney and M. A. Greenbaum, *J. Am. Chem. Soc.*, **79**, 3701 (1957).

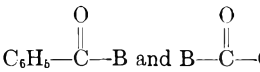
The $C_6H_5C(=O)-O^-$, generated in (2) or (4), can attack unchanged anhydride at the carboxyl carbonyl:



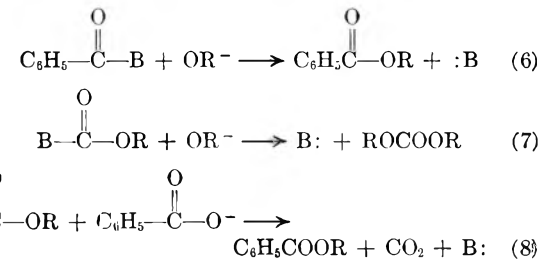
(5)

Attack of $C_6H_5C(=O)-O^-$ at the carbonate carbonyl gives no overall change. The formation of ester (path A) is due to reaction (3), and the disproportionation reaction (path B) is due to (4) followed by (5). Each benzoate ion produced in (4) can disappear only by (5), with the formation of an equal number of molecules of ROCOOR and $(C_6H_5CO)_2O$. The ratio of path A to path B products will be the ratio of the rates of attack of OR^- at the carboxyl carbonyl (reaction 3) to attack at the carbonate carbonyl (reaction 4) (*i.e.*, k_3/k_4). Since we observe experimentally that the A/B ratio is not affected by dilution, change in temperature or the nature of B:, it appears that the rate-determining stage of the decomposition is the attack of nucleophile B: according to (1) and (2). Presumably reactions (3) and (4) are very fast, and the temperature dependence of the ratio k_3/k_4 is close to unity.

The above discussion has neglected the reactions of products containing the catalyst B:, such as:



These may react with OR^- or $C_6H_5COO^-$ to regenerate B:, with the termination of a chain by using up the chain-carrying species.



(6)

(7)

(8)

In the supposedly uncatalyzed reaction, it is not certain whether there are traces of catalyst present, or whether there is a thermal cleavage of the anhydride to form ions which can initiate the chain reaction.

EXPERIMENTAL

Preparation of alkyl chlorocarbonates. All the chlorocarbonates used in this study were prepared by the action of phosgene on the respective alcohol. Details of the experimental procedure are described in a previous publication.[3]

Preparation of carboxylic-carbonic anhydrides. The carboxylic-carbonic anhydrides necessary in this study were synthesized from the respective carboxylic acid and alkyl chlorocarbonate. The method is described in detail in a previous publication.[3]

Rearrangement of optically active benzoic 2-octylcarbonic anhydride in pyridine. The mixed anhydride was generated in the usual way using 2-octyl chlorocarbonate generated from 2-octanol having b.p. 75° (4 mm.), n_D^{25} 1.4235, α_D^{25} + 6.19 ± 0.02° (neat, l = 1). The optically active benzoic 2-octylcarbonic anhydride (8.0 g., 0.029 mole) was placed in a 50-ml. round bottomed flask containing 20 ml. of pyridine, which had been purified by distillation from barium oxide. The mixture was heated at reflux (113°), during which time the color of the solution progressively changed from pink to red to brown. After 8 hr. of heating, the mixture was cooled, taken up in ether, and washed with water, dilute hydrochloric acid, saturated sodium bicarbonate solution, and water. After drying the ether solution over anhydrous sodium sulfate, the ether was removed at reduced pressure, leaving behind a dark brown oil. Distillation of this material yielded 1 g. of almost pure 2-octanol with α_D^{25} + 6.52 ± 0.01°, and 3.5 g. of a mixture of 2-octyl benzoate and di-2-octyl carbonate, b.p. 122–129° (1 mm.), n_D^{25} 1.4628–1.4753. The reported[19] b.p. for 2-octyl benzoate is 171° (20 mm.), n_D^{25} 1.4840. An authentic sample had b.p. 113–116° (0.5 mm.), n_D^{20} 1.4885. The reported[20] b.p. for di-2-octyl carbonate is 168° (13 mm.); an authentic sample had b.p. 118–123° (0.7–1 mm.), n_D^{25} 1.4280. The dark brown residue from the distillation yielded 1.5 g. of benzoic anhydride upon recrystallization.

Saponification of the mixture of 2-octyl benzoate and carbonate with alcoholic potassium hydroxide yielded 2-octanol with b.p. 72–73° (8 mm.) n_D^{25} 1.4232, α_D^{25} + 6.17 ± 0.01° (neat, l = 1).

Preparation of optically active 2-octyl mesitoate from mesitoyl chloride and (+)-2-octanol. Mesitoyl chloride (4.2 g., 0.023 mole) and 2-octanol (3.0 g., 0.023 mole) with α_D^{25} + 6.19 ± 0.02° (neat, l = 1) were placed in a 25 ml., round bottomed flask containing 15 ml. of dry pyridine. After heating the mixture on a steam-bath for 2 hr., it was cooled, taken up in ether and washed successively with water, dilute hydrochloric acid, dilute sodium hydroxide, and water. After drying the ether solution, the solvent was removed under reduced pressure and the nonvolatile oil purified by fractionation through a vacuum-jacketed Vigreux column (100 × 10 mm.). There was obtained 3.93 g. (62%) of 2-octyl mesitoate having b.p. 139–140° (0.5 mm.), $n_D^{24.5}$ 1.4869, α_D^{25} + 24.03 ± 0.02° (neat, l = 1). This corresponded with the properties previously reported[3] for an authentic sample of 2-octyl mesitoate.

Rearrangement of optically active mesitoic-2-octylcarbonic anhydride. The mixed anhydride was generated from mesitoic acid and the chlorocarbonate of 2-octanol; the 2-octanol had α_D^{25} + 6.19 ± 0.02° (neat, l = 1). The rearrangement was carried out in the usual way, and yielded mainly 2-octyl mesitoate. The last, and most pure fraction had b.p. 153–154° (1.5 mm.) $n_D^{24.5}$ 1.4869, α_D^{25} + 24.01 ± 0.02° (neat, l = 1).

Rearrangement of benzoic benzylcarbonic anhydride. When prepared in the usual manner, this anhydride decomposed with evolution of carbon dioxide at room temperature, and heating to 50° hastened this decomposition. Distillation of the rearrangement product yielded fractions boiling between 120–140° (0.2 mm.), n_D^{25} 1.5615 to 1.5641. The b.p. for benzyl benzoate[21] is 185° (15 mm.) n_D^{21} 1.5681; dibenzyl carbonate,[22] b.p. 203° (12 mm.); benzoic anhydride,[23] b.p. 360°, n_D^{15} 1.5767. The infrared absorption curve of the distillate showed the presence of all three products in all fractions, with benzyl benzoate concentrated in the lower boiling fractions, and dibenzyl carbonate and benzoic anhydride concentrated in the higher boiling fractions.

Preparation of phenyl-t-butyl carbonate. This mixed carbonate was prepared from *t*-butyl alcohol and phenyl chlorocarbonate following the method of McLamore.[12] It was not purified by distillation, as the infrared absorption spectrum of this carbonate had a strong peak at 5.69 μ, but no others in this region.

Attempted preparation of benzoic-t-butylcarbonic anhydride. Phenyl-*t*-butyl carbonate (3.55 g., 0.0183 mole), 15 ml. of ether, and 0.5 ml. of triethylamine were placed in a 50 ml. flask. Benzoic acid (2.23 g., 0.0183 mole) in 10 ml. of ether was slowly added to this mixture. After heating the solution at the boiling point of ether for 1 day, it was obvious from the infrared absorption curve of a sample of the mixture, that no chemical change had taken place. Stripping the mixture of ether and heating it to 75° in the presence of *N*-methylpiperidine likewise produced no change.

Purification of solvents used in kinetic measurements. A. *Dibutyl carbitol* was purchased from Carbide and Carbon Chemicals Co. It was vigorously shaken with water to extract alcoholic impurities, all of which were soluble in water. It was then dried over Drierite, and fractionally distilled from sodium under reduced pressure through a Vigreux column (15 × 1 in.). The main fraction boiled at 110–110.5° (5 mm.), n_D^{25} 1.4210. The reported[24] index of refraction is n_D^{20} 1.4241.

B. *n-Hexadecane* was Eastman Kodak practical grade. Approximately 500 g. of *n*-hexadecane with 80 ml. of concd. sulfuric acid was heated on a steam bath with vigorous stirring. When the sulfuric acid turned dark, it was replaced with fresh acid. This treatment was continued until the acid remained colorless, and required approximately eight changes. The hexadecane was washed thoroughly with water, a saturated solution of sodium bicarbonate and more water, then dried over sodium sulfate. Fractional distillation under reduced pressure through a Vigreux column (25 × 2 cm.) yielded constant boiling material with b.p. 114–115° (1.5 mm.), n_D^{26} 1.4320.

C. *Nitrobenzene* was Eastman Kodak white label grade. It was further purified by treatment with phosphorus pentoxide, then fractionally distilled under reduced pressure. The constant boiling material had b.p. 80° (7 mm.).

D. *n-Butyl benzoate* was Eastman Kodak white label grade. It was purified by drying over Drierite, then fractionally distilling under reduced pressure. This material had b.p. 113° (6 mm.).

E. *N,N-Dimethylformamide* was purified by the method of Thomas and Rochow,[25] which involved thorough drying over Drierite, vigorous shaking with barium oxide, and fractional distillation under reduced pressure. The material obtained by this treatment was neutral and had b.p. 64° (31 mm.).

Kinetic measurements of the decomposition of benzoic-carbonic anhydrides. The reaction vessel used for the kinetic measurements was a 50-ml. Erlenmeyer flask, fitted with a standard taper joint for attachment to an Allihn Condenser (12 × 1 in.) and a stopcock (4 mm. bore) for gaining entry to

(19) A. J. H. Houssa and H. Phillips, *J. Chem. Soc.*, 2510 (1929).

(20) H. Hunter, *J. Chem. Soc.*, 1389 (1924).

(21) C. A. Kohn and W. Trantom, *J. Chem. Soc.*, 75, 1155 (1899).

(22) C. A. Bischoff, *Ber.*, 36, 159 (1903).

(23) A. Kaufmann and A. Luterbacher, *Ber.*, 42, 3483 (1909).

(24) J. Kooi, *Rec. Trav. Chim.*, 74, 137 (1955).

(25) A. B. Thomas and E. G. Rochow, *J. Am. Chem. Soc.*, 79, 1843 (1957).

the flask. The top of the condenser was attached to a gas buret through a three-way stopcock by means of flexible rubber tubing. All stopcocks and joints were lubricated with Dow-Corning silicone grease. The system was often checked for leaks by pressuring it with carbon dioxide, but always found to be satisfactory.

The reaction vessel was constantly agitated during the course of a kinetic experiment by a shaking device attached to the reaction flask.

The constant temperature bath consisted of a stainless steel beaker (9 × 6.5 in.), filled with Fisher bath wax, and inserted into a metal can (12 × 9 in.), with the space between the vessels packed with insulating material. The wax was heated to within 10–20° of the desired temperature by means of a 750 watt immersion heater. Final temperature control was maintained by means of a vapor pressure type thermostat, attached to a 125-watt knife blade heater through a relay. The shaking motion of the reaction flask in the wax bath was sufficient to provide adequate circulation, since temperature control to within 0.2° could generally be maintained during an experiment.

A kinetic measurement was preceded by cleaning of the reaction flask. At the beginning stages of the work, sulfuric acid–dichromate was used, but it was found that hot caustic was equivalent to the acid wash as far as the effect on the rates was concerned. In either case, the flask was repeatedly rinsed with distilled water and acetone, and dried overnight at 120°. Glass wool was placed in the reaction flask and the latter inserted into the constant temperature bath and attached to the condenser. The entire apparatus was flushed with carbon dioxide, which was dried by passing it through Drierite. The solvent to be used in the experiment was thoroughly saturated with carbon dioxide at room temperature, then injected into the reaction flask by means of a syringe. The shaker was started, and the system equilibrated for approximately 1 hr. In order to start a kinetic measurement, a weighed sample of the carboxylic-carbonic anhydride was injected into the solvent in the reaction flask through the stopcock, the opening of which was protected from the atmosphere by a rubber diaphragm. After the addition of sample, which generally took less than 30 sec., the shaker was started, and readings of carbon dioxide evolution were taken at appropriate time intervals, depending on the speed of the particular decomposition. A shield surrounding the gas buret was effective in keeping its temperature fairly constant. The decomposition was allowed to continue until a constant volume of gas was evolved, and this was taken as V_∞. Each volume was corrected to volume at STP and a plot of log $(V_\infty - V)$ versus time was made.

In the catalyzed decompositions, the catalyst was added to the solvent before the latter was saturated with carbon dioxide, or if insoluble, it was placed in the reaction flask.

When hydrogen chloride was used as catalyst, a small quantity was bubbled into dibutyl carbitol, and its concentration determined by titration with standard sodium hydroxide, using 95% ethanol as solvent. The end-point was determined with a *p*H meter. Solutions with a desired concentration of hydrogen chloride were made up by dilution of this stock solution with pure dibutyl carbitol, and the concentrations were always checked by titration.

ROCHESTER, N. Y.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, RENSSELAER POLYTECHNIC INSTITUTE]

Trifluoroacetonitrile Addition Reactions. I. Ethylene

G. J. JANZ AND J. J. STRATTA

Received February 24, 1960

It is shown that trifluoroacetonitrile reacts readily with ethylene in the homogeneous gas phase at moderately high temperatures (300°–500°) with the formation of 4,4,4-trifluorobutyronitrile when the reactants are mixed in equimolar ratio at atmospheric pressure. Some evidence for the formation of another product, most likely 4,4,4-trifluorocapronitrile in smaller amounts is reported. Equilibrium yields of 4,4,4-trifluorobutyronitrile as predicted from thermodynamics are apparently readily attained at 400°, *i.e.* thermodynamic control can be achieved.

In the preceding communications in this series the reactions of simple dienes with trifluoroacetonitrile have been described. The nitrile group exhibited dienophilic properties with the facile formation of 2-trifluomethyl-substituted pyridines at atmospheric pressure and moderately high temperatures (350°–520°). The present paper is the first in a series describing the results of similar studies of the reactions of simple olefins and acetylenes with trifluoroacetonitrile in this laboratory. The thermal addition of trifluoroacetonitrile to ethylene, and the thermodynamics of the process are reported.

EXPERIMENTAL

Chemicals. The trifluoroacetonitrile (b.p. −68°) was a commercial sample (Columbia Organic Chemicals) of minimum 95% purity. The ethylene (b.p. −104°) was a commercial C.P. grade sample (Matheson Co.). Portions of both chemicals were repeatedly redistilled by vacuum transfer techniques to remove dissolved air and other noncondensable gases before use in the experiments.

Apparatus and procedure. A static system was used, since an interest was to explore the thermal stabilities of the reactants, and the possibility of thermodynamic control for the addition reaction. Vacuum transfer techniques were used in an all glass system as illustrated in Fig. 1. Predetermined amounts of the reactants (sufficient to give a pressure of about 1 atm. initially at the reaction temperature) were transferred from the ampoules (B) to the storage trap (A). The 5-l. reaction vessel (J) was attached in place of one of the ampoules by its side arm to the manifold, evacuated, filled with the reactants from the trap, and sealed off with a torch after the reaction charge had been frozen (−195°) into the small finger type trap. The flask J was then positioned in the furnace and resealed to the vacuum manifold as shown in Fig. 1. The reaction temperature was monitored by two chromel-alumel thermocouples. On completion of an experiment the contents of the flask J were transferred to a cold trap E (−195°) and J was removed from the system. The nature of the product mixture in E was investigated by the conventional techniques as described below.

(1) G. J. Janz and M. A. De Crescente, *J. Org. Chem.* **23**, 765 (1958); J. M. S. Jarvie, W. E. Fitzgerald, and G. J. Janz, *J. Am. Chem. Soc.* **78**, 978 (1956).

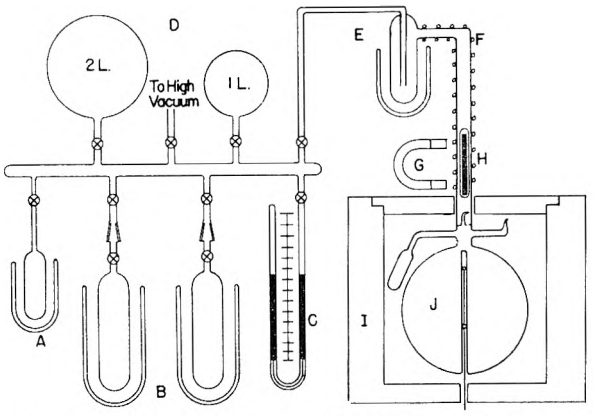


Fig. 1. Static system. A, Liquid nitrogen degassing trap. B, Input assembly. C, Closed-end Hg manometer. D, Calibrated storage volume. E, Liquid nitrogen freeze-out trap. F, Heating tape. G, Permanent magnet. H, Metal-in-glass hammer for breaker seal. I, Electric furnace. J, Reaction chamber

RESULTS

Thermal stability of pure reactants. The pyrolysis of ethylene is so well-known[2] that only a limited number of experiments were undertaken to investigate its rate of pyrolysis in the temperature range of this investigation (350°–450°). No data for trifluoroacetonitrile were known and a similar series of experiments was undertaken, the temperature range being extended to 550°. The results of these experiments may be briefly summarized as follows. Under the conditions of the experiments—*i.e.*, degassed samples, clean vessels—no appreciable pyrolysis of ethylene was observed at 400° (ethylene recovery, 99 mole %) but the presence of methane and hydrogen was detected in the products at 450°C (ethylene recovery, 75 mole %). For the trifluoroacetonitrile experiments, no traces of hexafluoroethane or cyanogen were detected in the pyrolysis products even at 550°. The gas chromatograms indicated that the limited pyrolysis corresponded to removal of the impurities in the commercial trifluoroacetonitrile (most probably trifluoroacetic acid or the amide). After twenty hours at 550°, 450°, and 400° respectively, 98.5, 99.0, and 100 mole % respectively of the initial trifluoroacetonitrile were recovered unchanged.

Addition reaction. The results for a series of experiments for equimolar mixtures of trifluoroacetonitrile and ethylene for the temperature range 350°–450° are summarized in Table I. It is significant that both reactants are gaseous at room temperature so that the liquid product must be attributed to an addition reaction or, less probably, to a selfpolymerization of one of the reactants. The evidence from the thermal stabilities of the reactants, and from the exact correspondence of the conversions of each reactant at 350° is strong support for an addition reaction. The fact that the trifluoroacetonitrile conversion does not exceed 60% at 400° suggests the possibility of thermodynamic control. The correspondingly higher conversions of ethylene may be understood in the light of a more complex process at 400° with the formation of additional products having more than one ethylene per mole of trifluoroacetonitrile as a possibility. The significance of the values calculated for K_p in the last column of Table I is discussed later.

Identification of products. The unchanged trifluoroacetonitrile and ethylene were quantitatively analyzed by gas chromatography. The liquids from the experiments all at 400° ± 3° were combined for distillation analysis. The gas chromatograph of this mixture indicated two main components, one in large excess, being present, and a number of minor peaks indicating some components of less extensive simultaneous reactions. Distillation in a semimicro Podbielniak apparatus separated two fractions, one low boiling (b.p. 139°–140°/760 mm.) and the other higher boiling (b.p. 197°–198°/760 mm.) in the approximate weight ratio of 8:1 respectively and which, within the limits of the technique, composed 90–95% of the unrefined liquid mixture.

(i) The lower boiling liquid product was identified as 4,4,4-trifluorobutyronitrile.

Anal. Calcd. for $C_4H_4F_3N$: H, 3.3; N, 11.4; F, 46.3. Found: H, 3.44, 3.48; N, 11.30, 11.07; F, 45.55, 45.83.

An aliquot was hydrolyzed in methanolic sodium hydroxide yielding an acid shown to be 4,4,4-trifluorobutyric acid (I. R. spectra, b.p. 162° lit. 166°).[3] The physical properties and infrared spectrum for 4,4,4-trifluorobutyronitrile have not been reported previously and were observed as follows: n_D^{25}, 1.565; d_4^{25}, 1.21 g./ml.; infrared spectrum (Perkin-Elmer Model 21; sodium chloride region) shows clearly that absorption at 2280 cm.$^{-1}$ confirms the nitrile group (*cf.* perfluoronitriles[4] 2275 ± cm.$^{-1}$, it is slightly shifted from the 2240–2260 region characteristic of aliphatic mono- and dinitriles[5]). Bands at 1309, 1180, and 1142 cm.$^{-1}$ are in accord with the literature values,[6] 1321 ± 9, 1179 ± 7, and 1140 ± 9 cm.$^{-1}$ for the symmetrical and antisymmetrical deformation modes of CF_3. The bands, 1230–1287 cm.$^{-1}$ and at 3000 cm.$^{-1}$ are in the regions for C—F and C—H stretching modes[7] respectively. The infrared spec-

(2) C. D. Hurd, *The Pyrolysis of Carbon Compounds*, Chem. Cat. Co., New York (1929).

(3) E. T. McBee *et al.*, *J. Am. Chem. Soc.* **70**, 2910 (1948); **76**, 3722 (1954).

(4) D. G. Weiblen, *Fluorine Chemistry*, Vol. 2, Academic Press Inc., New York, 1954.

(5) R. E. Kiston and N. E. Griffith, *Anal. Chem.* **24**, 334 (1952).

(6) R. R. Randle and D. M. Whiffen, *J. Chem. Soc.* 1371 (1955).

(7) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley and Sons, Inc., New York, 1958.

TABLE I

TRIFLUOROACETONITRILE-ETHYLENE ADDITION REACTION

Temp.	Time, hr.	C_2H_4 In (moles)	C_2H_4 Out (moles)	C_2H_4 Conversion (mole %)	CF_3CN In (moles)	CF_3CN Out (moles)	CF_3CN Conversion (mole %)	Liquid[a] Product (Total) (g.)	K_p (expt.)
348	20.3	0.0490	0.0460	6.12	0.0475	0.0446	6.12	0.359	0.03
366[b]	89.0	0.0440	—	—	0.0455	—	—	1.98	0.4
397	25.0	0.0491	0.0105	79.0	0.0475	0.0446	50.1	3.03	0.7
399	20.3	0.0486	0.0145	70.5	0.0481	0.0232	51.6	3.68	1.0
400	92.0	0.0501	0.0	100	0.0503	0.0205	59.5	3.41	1.2
401	48.0	0.0496	0.0	100	0.0499	0.02063	58.5	3.59	1.3
401	67.5	0.0503	0.0	100	0.0503	0.0232	54.2	3.34	0.9
499	46.2	0.0451	0.0	100	0.0451	0.0149	66.5	3.60	—

[a] Liquid at 25° and 1 atm. pressure. [b] Trifluoroacetonitrile was prepyrolyzed at 550° for this experiment.

trum, within the limits of the preceding analysis, is in support of the structure 4,4,4-trifluorobutyronitrile for the addition product (b.p. 140°). An NMR spectrogram relative to fluorine showed only a triplet, identifying all the fluorine atoms as equivalent, in this structure. An alternate structure 2,4,4-trifluorobutyronitrile thus is seen as most improbable. Additional support for the structure 4,4,4-trifluorobutyronitrile for this product is seen in the NMR spectrum which showed a high order splitting for the proton resonance, due to the perturbation of the trifluoromethyl and nitrile groups in the sample, these groups being quite similar in electronegativity. In the alternate structure this would not be expected as the groups FCH_2 and CF_2CN differ considerably in electronegativity and the protons are no longer all equivalent.

(ii) The higher boiling product (b.p. 190°), gained in much smaller amounts under the present conditions of reaction, has not been investigated at present except to note that the infrared spectrum showed the frequencies characteristic of CN, CF_3, and CH_2 as in the preceding compound, and that the NMR spectrum confirmed that all fluorine atoms were equivalent and, in addition, that the protons were in a more aliphatic environment, *i.e.*, less perturbed, in comparison with the results for 4,4,4-trifluorobutyronitrile. The results are in accord with the identification of this product as $CF_3(CH_2)_nCN$, where $n>2$. Comparison of the boiling point range with those of related aliphatic nitriles shows that its boiling point (190°) is as would be predicted for $n = 4$, *i.e.*, 6,6,6-trifluorocapronitrile. The product has not been investigated further.

Thermodynamic considerations. In view of the experimental results at 400° relative to the conversions of trifluoroacetonitrile, an estimate of the thermodynamics for the simple addition reaction

$$CF_3CN + C_2H_4 = CF_3CH_2CH_2CN \qquad (1)$$

seemed of interest to evaluate the yields relative to thermodynamic control for the overall process. The standard free energy change for the reaction is readily obtained from the expression:

$$\Delta F_T^\circ = \sum_{p-r} \Delta(F^\circ - H_0^\circ)_T + \Delta H_0^\circ \qquad (2)$$

where $\sum_{p-r}$ expresses the differences in the summation function for the products and the reactants, and ΔH_0° is evaluated from the relation:

$$\Delta H_0^\circ = - \sum_{p-r} \Delta(H^\circ - H_n^\circ)_{298} + \Delta H^\circ_{298} \qquad (3)$$

in which ΔH_{298} is the heat of reaction at 25° and must be known or calculated from heat of formation data. A summary of the necessary thermodynamic data over the temperature range 350°–550° is given in Table II. Relative to the estimates of data in Table II, it is sufficient to note that the thermodynamic functions for 4,4,4-trifluorobutyronitrile were calculated by the method[8] of group equations and a knowledge of the data for propane,[9] *n*-pentane,[9] and trifluoroacetonitrile.[10] The values for the heats of formation for trifluoroacetonitrile and 4,4,4-trifluorobutyronitrile were similarly calculated by the principle of additivity[8] using the values for acetonitrile[11] and propane,[9] and *n*-pentane[9] as parents and the recently reported[12] precise values of 46.5 kcal./mole for the difference in the bond energies $E(RCF_3 - RCH_3)$ where R is any hydrocarbon group. The values in Table II are reported to more significant figures than the data for the parent compounds can justify for the sake of internal consistency in the equilibrium calculations. Since ΔF° is directly propor-

(8) G. J. Janz, *Estimation of Thermodynamic Properties of Organic Compounds*, Academic Press Inc., New York, 1958.

(9) F. D. Rossini, *et al.*, Ed., *Selected Values of Physical and Thermodynamic Properties of Hydrocarbons and Related Compounds*, Carnegie Press, Pittsburgh, Pa., 1953.

(10) G. J. Janz and S. C. Wait, Jr., *J. Chem. Phys.* **26**, 1766 (1957).

(11) N. S. Kharasch, *Bur. Standards J. Research* **2**, 359 (1929).

(12) W. D. Good, D. R. Douslin, D. W. Scott, A. George, J. L. Lacina, J. P. Dawson, and G. Waddington, *J. Phys. Chem.* **63**, 1133 (1959).

TABLE II

THERMODYNAMIC DATA FOR PREDICTION OF K_p IN THE TRIFLUOROACETONITRILE-ETHYLENE ADDITION REACTION

Substance		C_2H_4		CF_3CN		$CF_3CH_2CH_2CN$		$\sum_{p-r}$
Function	Temp.	kcal./mole	Ref.	kcal./mole	Ref.	kcal./mole	Ref.	(kcal./mole)
$\Delta H_f°$	298.1°K	12.50	[a]	−126.7	[b]	−136.9	[b]	−22.70
$-\frac{(F° - H_0°)}{T}$	600°K	50.70	[a]	69.15	[c]	87.18	[b]	19.60
	800°K	54.19		74.54		96.11		26.10
$\frac{(H° - H_0°)}{T}$	298.1	8 47	[a]	12.68	[c]	19.78	[b]	−1.37

[a] See ref. 9. [b] Estimated, this work. [c] See ref. 10.

tional to the absolute temperature, the values over the temperature range of the experiments are readily gained by interpolation, and from the well known expression:

$$\Delta F° = -RT\ln K_p \quad (4)$$

the following values for equilibrium constant are predicted for the formation of trifluorobutyronitrile by the trifluoroacetonitrile-ethylene addition reaction:

T	350°	400°	450°
K_p (theor.)	4.8	1.2	0.4

These are to be compared with the values in Table I from the experimental data and the expression:

$$K_p = \frac{1}{RT}\frac{C_3}{C_1C_2} \quad (5)$$

where C_1, C_2 and C_3 are the concentrations (moles/l) of trifluoroacetonitrile, ethylene and 4,4,4-trifluorobutyronitrile at equilibrium. For this purpose it was assumed as a first approximation that the liquid was entirely 4,4,4-trifluorobutyronitrile and that the equilibrium conversion of ethylene was equal to that for trifluoroacetonitrile as the reactants contribute in this ratio to the formation of the above product. The conversions at 348° (Table I) clearly support the latter assumption. Comparison shows that thermodynamic control, *i.e.*, equilibrium yields, can be attained readily at 400°, whereas at 350° the reaction is under kinetic control even after reaction times of ninety hours. The results should be interpreted qualitatively rather than quantitatively in view of the estimates necessary for the theoretical calculations and the assumptions in the treatment of the experimental data. Indirect support for the assumption that 4,4,4-trifluorobutyronitrile is in large part the only addition product at 350°–400° is seen in the close agreement with the theoretically predicted K_p values at 400°.

DISCUSSION

The salient results may be briefly restated in that it has been shown that trifluoroacetonitrile reacts readily with ethylene in the homogeneous gas phase at moderately high temperatures (300°–500°) with the formation of 4,4,4-trifluorobutyronitrile as the main product when the reactants are mixed in equimolar ratio at atmospheric pressure. Some evidence for the formation of another product in smaller amounts, *i.e.*, 6,6,6-trifluorocapronitrile was noted. Equilibrium yields predicted from thermodynamics can apparently be readily attained at 400°, *i.e.*, thermodynamic control can be achieved. The experiments do not lend themselves to kinetic interpretation but some speculation on the mechanism is of interest and possible by analogy with related addition processes. A close correspondence in the reactivities of trifluoroacetonitrile and cyanogen in the gas phase with 1,3-dienes at moderately high temperatures has been demonstrated elsewhere.[1] That incipient formation of free trifluoromethyl radicals may occur from trifluoroacetonitrile by simple thermal dissociation or a suitable trace catalyst seems probable as this is known for cyanogen.[13] The reaction may thus be understood by a mechanism rather similar to the free radical addition of hydrogen bromide to olefins,[14] *i.e.*:

$$CF_3CN \xrightarrow{\Delta} \dot{C}F_3 + \dot{C}N \quad (6)$$

$$\dot{C}F_3 + CH_2{=}CH_2 \longrightarrow CF_3{-}CH_2{-}\dot{C}H_2 \quad (7)$$

$$CF_3{-}CH_2{-}\dot{C}H_2 + CF_3CN \longrightarrow CF_3{-}CH_2CH_2{-}CN + \dot{C}F_3 \quad (8)$$

with termination steps which need not be detailed for the present. The investigations are being extended to gain an insight on the nature of the reaction mechanism and the possible role of trifluoroacetonitrile as a telogen[15] as distinct from the thermodynamics of the overall process.

Acknowledgment. This work was made possible in part by fellowship grant support from the Monsanto Chemical Company and Union Carbide Chemical Company. Dr. C. M. Huggins (General Electric Company) is thanked for information on the NMR spectra reported in this work. The experimental contributions of C. A. Wahl and W. J. Leahy are gratefully acknowledged.

TROY, N. Y.

(13) G. J. Janz, *J. Am. Chem. Soc.* **74**, 457(1952).

(14) C. Walling, *Free Radicals in Solution*, John Wiley and Sons, Inc., New York, 1957.

(15) M. D. Petersen and A. G. Weber, U. S. patent 2,395,292, Feb. 16, 1948.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF LOYOLA UNIVERSITY]

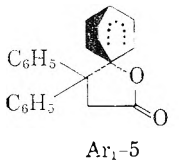
The Anomalous Hunsdiecker Reaction. II. The Scope of the Reaction[1,2]

JAMES W. WILT AND JAMES L. FINNERTY, S.J.

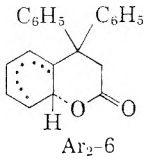
Received August 1, 1960

A number of β,β,β-triarylpropionic acids have been prepared and characterized. Their silver salts rearranged under Hunsdiecker reaction conditions to substituted acrylate esters in poor yield (under 20%) but in fair conversion (35–50%). Evidence is presented that these rearrangements proceed *via* a five-membered ring intermediate of the Ar_1-5 type. The effect of competition between phenyl and substituted phenyl groups in the rearrangement was also investigated.

The rearrangement of β,β,β-triphenylpropionic acid under Hunsdiecker reaction conditions was reported earlier from this laboratory.[2] There was found a surprising 53% carbon skeletal rearrangement[3] in addition to a 44% recovery of the original acid and 3% bromodecarboxylation, the normally expected Hunsdiecker reaction.[4] Migration of a phenyl group followed by elimination of the elements of hydrogen bromide yielded phenyl β,β-diphenylacrylate which, in the presence of excess bromine, gave largely its α-bromo derivative. The overall process, a 1,4-phenyl migration, was rationalized as occurring by an intramolecular process involving a five- or six-membered ring intermediate (Ar_1-5 or Ar_2-6 type, respectively[5]) possessing either phenonium ion or free radical characteristics, as shown below without specification as to the electronic nature of each. The earlier



Ar_1-5



Ar_2-6

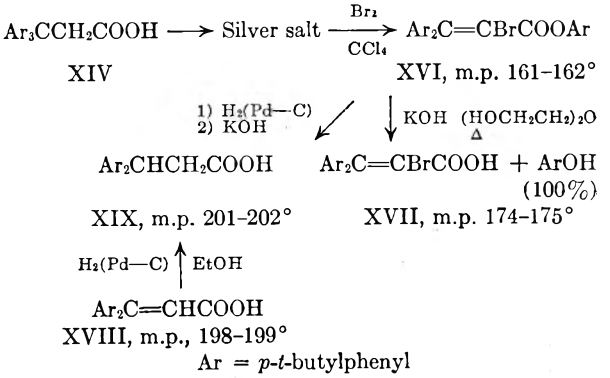
work indicated the Ar_1-5 intermediate to be the more likely, primarily from steric considerations. This instance of intramolecular ester formation by rearrangement was the first reported in the literature of the Hunsdiecker reaction, and it was felt of interest to investigate this rearrangement further, particularly to elucidate the ring size of the intermediate, the scope of the reaction, and its conditions.

RESULTS

The first points, the ring size of the intermediate and the scope of the reaction, were determined by the placement of a substituent on one (or more) of the phenyl groups in the initial acid. Reaction by way of the Ar_1-5 spiro ring would keep the substituent in the same position relative to C-1 in the aromatic ring, while reaction *via* the Ar_2-6 intermediate would in effect isomerize the substituted aromatic ring. The pathway actually involved was easily decided by the isolation and identification of the phenol obtained by saponification of the ester product. The results are given in Table I. Other experiments were performed with the tris-substituted acids I, XIII, XIV, and XV in order to investigate the course of this reaction and the effect thereon of changing the various reaction conditions. The results of these attempts are listed in Table II.

In one reaction series the ester produced was isolated and characterized. The choice of the series using the tris-*p*-*t*-butyl acid (XIV) was occasioned by two considerations. First, a tris-substituted acid was chosen since the ester mixture likely to result would be less complex. Second, an acid that gave a fair yield in the process was chosen. Other than the parent acid I, which had been already investigated only XIV seemed appropriate for this portion of the study.

The rearrangement of XIV gave rise to a single ester (XVI) that was converted by hydrogenation and saponification to β,β-bis(*p*-*t*-butylphenyl)-propionic acid (XIX). The latter material was identical with that obtained by the hydrogenation of authentic β,β-bis(*p*-*t*-butylphenyl)acrylic acid (XVIII).[6] The ester (XVI) was also saponified to the α-bromo acid (XVII).



(1) Taken from the doctoral dissertation of James L. Finnerty, S. J., Loyola University, February, 1960.

(2) Paper I, J. W. Wilt and D. D. Oathoudt, *J. Org. Chem.*, **23**, 218 (1958).

(3) Repeated attempts have not duplicated this higher yield; the rearrangement yield seems uniformly 20–23%, the recovered acid 50–70%.

(4) R. G. Johnson and R. K. Ingham, *Chem. Revs.*, **56**, 219 (1956).

(5) R. Heck and S. Winstein, *J. Am. Chem. Soc.*, **79**, 3105 (1957).

TABLE I

REARRANGEMENT OF MONOSUBSTITUTED β,β,β-TRIARYLPROPIONIC ACIDS (SILVER SALTS)

$X—C_6H_4(C_6H_5)_2CCH_2COOAg$

Code for Acid	X	Decarboxylation,[a] %	Rearrangement,[b] %	Phenol Composition[c]
I	H	3.2	22.0[d]	1.0
II	*o*-CH_3	5.9	9.5[e]	10.3
III	*m*-CH_3	2.8	12.4[e]	9.5
IV	*p*-CH_3	10.7 (5.3)[f]	8.7 (8.0)	1.9
V	*p*-$(CH_3)_3C$	6.1 (8.9)	7.6 (6.6)	0.64
VI	*p*-C_6H_5	3.5	[g]	—
VII	(C_4H_3)	Trace (6.8)	[h] (Trace)	—
VIII	*p*-CH_3O	2.2[i]	[j,k]	—
IX	*p*-F	2.4	12.3[e]	0.14
X	*m*-Cl	5.3	13.7[e]	0.55
XI	*p*-Cl	5.4	11.7[e]	0.29
XII	*p*-Br	10.4	13.7[d]	0.35

[a] Measured as carbon dioxide evolved (barium carbonate precipitation). An induction period of five to ten minutes was always noticed prior to any gas evolution. [b] Measured as total phenols produced by saponification of reaction product (infrared and v.p.c.). [c] Moles, relative to phenol; found as follows: wt.-% $X—C_6H_4OH$/wt.-% C_6H_5OH × mol. wt. C_6H_5OH/mol. wt. $X—C_6H_4OH$ × 2. [d] Average of two experiments. [e] Average of three experiments. [f] Values in parentheses were obtained when chlorine was used instead of bromine. [g] Bromination of reaction material made analytical techniques invalid. [h] Extensive degradation occurred. α-Naphthyldiphenylcarbinol (m.p. 133–138°) isolated. [i] Hydrogen chloride was evolved, so no barium carbonate was produced. [j] Only isolable product was an acid, m.p. 170–171°, presumably the monobromo derivative of VIII. Neut. equiv. Calcd. for $C_{22}H_{19}BrO_3$, 411. Found: 418. Zeisel test was positive. [k] A dichloro derivative of the initial acid VIII, presumably β-(3,5-dichloro-4-methoxyphenyl)-β,β-diphenylpropionic acid was isolated in 33% yield, m.p. (from alcohol) 207–208°. Neut. equiv. Calcd. for $C_{22}H_{18}Cl_2O_3$, 401. Found: 400, 407. *Anal.* Calcd.: C, 65.86; H, 4.52. Found: C, 65.77; H, 4.59. Only traces of phenols found on saponification of reaction product.

TABLE II

REARRANGEMENT OF TRIS-SUBSTITUTED β,β,β-TRIARYLPROPIONIC ACIDS (SILVER SALTS)

$(X—C_6H_4)_3CCH_2COOAg$

Code of Acid	X	Temp.	Time, Hr.	Solvent, Halogen	CO_2, %	Rearrangement,[a] %
I	H	25°	1 week	CCl_4,Br_2	[b]	21.7
		25–35°	2.5	CCl_4,Br_2	3.2	22.3
		25–70°	2.5	CCl_4,Cl_2	21	6.2
		25°	12	$C_6H_5NO_2,Br_2$	Trace	9.9
		0–25°	6	C_5H_5N,Br_2	7.6	Trace
XIII	*p*-CH_3	15–45°	0.75	CCl_4,Cl_2	Trace	1–2
XIV	*p*-$(CH_3)_3C$	25°	12	CCl_4,Br_2	1	21[c]
		77° (Reflux)	1.5	CCl_4,Br_2	13	7[d]
		−12–0°	3.5	CCl_4,Br_2	Trace	8[d]
XV	*p*-Cl	25°	2	CCl_4,Br_2	5	0

[a] Determined as the polybromo derivative of the phenol obtained from the reaction. [b] Not determined. [c] Based on isolated ester, see Experimental. [d] Based on *p*-*t*-butylphenol isolated upon saponification.

It is of importance that only *p*-*t*-butylphenol was isolated from the saponification of XVI as obtained directly from the reaction, *i.e.*, prior to any purification. No trace of isomeric phenols was found.

DISCUSSION

The point most clear from the present study is that *no ortho* shift results from this reaction. The isolation and/or identification of phenols solely with the position of the substituent retained was achieved in every instance where the reaction succeeded. Such a finding eliminates the Ar_2-6 mechanism and affords support for the Ar_1-5 mechanism previously put forward.[2] All attempts to increase aryl migration and the formation of ester were unsuccessful, and these experiments only indicated the reaction limits. While the complexity of these reactions and the low yield of esters obtained do not allow the phenol composition values to be regarded as meaningful "migration aptitudes," certain features seem worthy of mention. The values cover a relatively narrow range grouped about unity (0.1 to 10). Characteristically, radical proc-

(6) This acid and its methyl ester were graciously supplied by Professor E. C. Kooyman of the University of Leiden, the Netherlands. These compounds were reported by H. Breederveld and E. C. Kooyman, *cf.* footnote *b* to Table VI.

TABLE III

TRIARYLMETHYLMALONIC ESTERS, PARENT AND MONOSUBSTITUTED
$X—C_6H_4(C_6H_5)_2CCH(COOC_2H_5)_2$

X	Yield, %	M.P. Obs.	M.P. Lit.	Calcd. C	Calcd. H	Found C	Found H
H	79	134–135°	132–133°[a]				
o-CH_3	72	112–113°	112–113°[b]				
m-CH_3	83	95–97°	99–100°[c]				
p-CH_3	72	72–73°	74–75°[b]				
p-$(CH_3)_3C$	82	113–114°	107–108°[d]				
p-F	80	123–124°		74.27	5.99	74.16	5.92
m-Cl	80	93–94°		71.47	5.77	71.61	5.94
p-Cl	85	110–111°		71.47	5.77	71.30	5.53
p-Br	78	110–111°		64.86	5.24	65.10	5.32

[a] G. G. Henderson, *J. Chem. Soc.*, **51**, 225 (1887). [b] See Ref. 12a. [c] See Ref. 12b. [d] See Ref. 12c.

TABLE IV

TRIARYLMETHYLMALONIC ESTERS, TRIS-SUBSTITUTED
$(X—C_6H_4)_3CCH(COOC_2H_5)_2$

X	Yield, %	M.P.	Calcd. C	Calcd. H	Found C	Found H
p-CH_3	[a]	94.5–95°	78.35	7.26	78.55	7.11
p-Cl	76	114–115°	61.73	4.58	61.48	4.49

[a] Not determined.

esses show limited selectivity wherever evaluated.[7] In addition, the failure of nitrobenzene and pyridine (polar solvents resistant to ionic substitution) to assist the rearrangement indicated that increased solvent polarity did not facilitate the reaction, as one might expect were this process ionic. On the other hand, the known reactivity of these solvents in radical reactions[8] rationalizes their deleterious effect on this reaction if it be radical, since they could react in some fashion competitively with the rearrangement. While such considerations cast some doubt on our previous suggestion[2] that this reaction is ionic in nature, no compelling evidence was found in this study one way or the other.

The ease of rearrangement of the *o*-tolyl group in this reaction contrasts with the low migration ability obtained by McNeer[7] for this group in triarylmethyl peroxide decompositions. The difference, we feel, is primarily steric. The Wieland rearrangement is a 1,2-shift and the *o*-tolyl group usually is poor in such processes,[9] presumably because of steric crowding by the group in the transition state. The opposite situation apparently exists in this process, where the steric strain in the spiro intermediate can be shown by models to be less when the *o*-tolyl group migrates.[10] Apparently, steric features do not account for the curious values obtained for the *m*-and *p*-tolyl groups. *p*-Tolyl activation in either ionic or radical reactions is considerably greater than *m*-tolyl and the found values present an anomaly.

EXPERIMENTAL

All melting points were obtained on a calibrated Fisher-Johns block. Infrared spectra were obtained with a Perkin-Elmer model 21 Infrared Spectrophotometer, using a sodium chloride prism. The spectra of all solids were determined in potassium bromide pellets. The spectra of all phenols were determined in carbon disulfide solution.[11] The ultraviolet spectra were from a Beckman model DU instrument, manually operated. The vapor phase chromatograms were obtained with a Perkin-Elmer model 154C Vapor Fractometer with helium as the carrier gas and on a di-2-ethylhexyl sebacate column. Analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Triarylmethylmalonic esters. These compounds were synthesized by coupling the appropriate triarylmethyl chloride with ethoxymagnesiomalonic ester.[12a,b,c] The latter reagent was prepared from diethyl malonate (240 g., 1.5 moles), magnesium (36.4 g., 1.5 g.-atoms) and absolute ethanol (350 ml.). Since the reaction is highly exothermic, the magnesium and one-third of the malonic ester-ethanol solution were placed in a 1-l. reaction flask equipped with stirrer, condenser and addition funnel. A crystal of iodine and a

(7) R. M. McNeer, dissertation, University of Chicago (1953). A referee has noted that migration aptitudes in some ionic processes, such as the deamination of β,β-diarylethylamines, are also crowded very close together.

(8) D. R. Augood and G. H. Williams, *Chem. Revs.*, **57**, 123 (1957).

(9) The reaction of *o*-tolyl Grignard with benzil is such a case, the product obtained resulting from migration of phenyl rather than *o*-tolyl in a benzilic acid type rearrangement. R. Roger and A. McGregor, *J. Chem. Soc.*, 442 (1934).

(10) See the dissertation of J. L. F., pp. 30–33.

(11) The spectra and v.p.c. data for the appropriate compounds are contained in the dissertation of J.L.F.

(12)(a) G. A. Holmberg, *Acta Acad. Abo. Math. et Phys.*, **16**, 138 pp. (1948). *Cf. Chem. Abstr.*, **45**, 558c (1951). (b) G. A. Holmberg, *Acta Acad. Abo. Math. et Phys.*, **17**, 14 pp. (1950). *Cf. Chem. Abstr.*, **46**, 6114i (1952) (c) G. A. Holmberg, *Acta Acad. Abo. Math. et Phys.*, **18**, 13 pp. (1952). *Cf. Chem. Abstr.*, **49**, 228g (1955).

TABLE V

β,β,β-TRIARYLPROPIONIC ACIDS, PARENT AND MONOSUBSTITUTED

X—$C_6H_4(C_6H_5)_2CCH_2COOH$

Code	X	Yield, %	M.P. Obs.	M.P. Lit.	Calcd. C	Calcd. H	Found C	Found H
I	H	64	180–181°	180°[a]				
II	*o*-CH_3	81	174–175°	174–175°[b]				
III	*m*-CH_3	51	117–118°	118–119°[c]				
IV	*p*-CH_3	80	196–197°	195–196°[b]				
V	*p*-$(CH_3)_3C$	81	170–171°	165–167°[d]				
VI	*p*-C_6H_5[e]	31	98°	100–101°[c]				
VII	(C_4H_3)[e]	45	234–235°	236–237°[c]				
VIII	*p*-CH_3O[e]	66	141–142°[f]	155–156°[c]	79.49	6.07	79.66	6.18
IX	*p*-F	50	164–165°		78.73	5.35	79.06	5.56
X	*m*-Cl	31	142–143°		74.88	5.09	75.05	5.02
XI	*p*-Cl	71	192–193°		74.88	5.09	74.70	5.19
XII	*p*-Br	78	180–181°		66.16	4.49	66.12	4.39

[a] L. Hellerman, *J. Am. Chem. Soc.*, 49, 1738 (1927). [b] See Ref. 12a. [c] See Ref. 12b. [d] See Ref. 12c. [e] Prepared from triarylmethyl chloride without isolation of malonic ester intermediate. [f] Presumably a polymorph.

TABLE VI

β,β,β-TRIARYLPROPIONIC ACIDS, TRIS-SUBSTITUTED

$(X—C_6H_4)_3CCH_2COOH$

Code	X	Yield, %	M.P. Obs.	M.P. Lit.	Calcd. C	Calcd. H	Found C	Found H
XIII	*p*-CH_3	21[a]	233–234°		83.69	7.02	83.45	6.90
XIV	*p*-$(CH_3)_3C$[b]	58	249–250°	251–253°[b]				
XV	*p*-Cl	48[c]	192–193°		62.16	3.73	62.22	3.74

[a] Overall yield from triarylmethyl chloride. [b] Prepared by reaction of tris-(*p*-*t*-butylphenyl)carbinol with malonic acid in acetic anhydride according to the directions of H. Breederveld and E. C. Kooyman, *Rec. trav. chim.*, 76, 297 (1957). [c] Yield of crude acid, of which only a part was purified.

few drops of carbon tetrachloride were added, gentle heating was applied until reaction began, and an ice bath was used to moderate the initial hydrogen evolution. Stirring was begun and controlled addition of the remaining malonic ester–ethanol solution was sufficient to maintain reflux. When the magnesium was consumed, the excess ethanol was removed by vacuum distillation and azeotropic distillation with benzene. There remained a solution of the reagent in benzene (425 ml.) which was kept in a graduated cylinder sealed from the atmosphere, under which condition it was stable. In preparing the substituted malonic esters, a benzene solution of the halide was added rapidly to an aliquot of the organomagnesium reagent. The mixture was stirred at reflux for 5 min., then stirred at 25° for 2–3 hr., during which time a variety of color changes occurred, ending in a pale green solution. After hydrolysis with dilute (10%) hydrochloric acid, the benzene layer was separated, washed and dried. Removal of the benzene by vacuum distillation left the ester which was readily crystallized from 95% ethanol. The esters and their properties are listed in Tables III and IV. The infrared spectra of these esters showed a split ester carbonyl in every case except the tris-*p*-chlorophenyl example. The separation was about 0.05–0.1 μ, with the peaks generally at 5.7–5.8 μ and 5.8–5.9 μ. This splitting is interesting, since malonic ester has normal carbonyl absorption.[13]

β,β,β-Triarylpropionic acids. In the general procedure, a solution, or rapidly stirred emulsion, of the ester, 95% ethanol (7–10 ml./g. ester) and an excess of aqueous potassium hydroxide (50%, 6 moles/mole ester) was refluxed for 5 hr. The solution was concentrated under reduced pressure, and the potassium salt was dissolved in warm water (1 l.). The addition of this solution to dilute (5%), cold hydrochloric acid (10 moles/mole ester) liberated the free acid. Recrystallization was effected from alcohol, although before successful crystallization in some of the preparations, the crude acid required heating to 200° to complete decarboxylation. Thus, acid II was so treated and the resulting plastic material taken up in dilute sodium hydroxide, a small amount of residue was removed by filtration, and upon reprecipitation with acid a readily recrystallized product was obtained. Acid X crystallized slowly and tended to oil out first. Also, the limited solubility of acid IV made a hot wash with alcohol preferable for purification of large quantities. Benzene (with acids III and XI) and benzene-petroleum ether (b.p. 30–60°) (with acid V) were successfully employed in crystallizations. Acid XIV was obtained best by boiling its sodium salt with concentrated hydrochloric acid. The analytical sample of acid XIII was material recovered from the Hunsdiecker reaction, as a persisting trace of potassium salt accompanied the isolation by the above methods. The properties of these acids are given in Tables V and VI.

Silver β,β,β-triarylpropionates. The silver salts were generally prepared by the dropwise addition of an equivalent amount of silver nitrate (10% in distilled water) to a hot, stirred solution of the sodium salt of the acid (1–5% in distilled water, *p*H adjusted to 7–8 with dilute (1:1) nitric acid). The suspension was stirred for 3–4 hr., protected from light. The white silver salts were filtered, washed with distilled water, and oven-dried at 80° for 48 hr. Ash analyses were performed, but the yield data are not corrected for the slight lack of purity in some of these salts.

Rearrangement of the silver salts. The reaction of the silver salts with bromine was carried out essentially as described earlier.[2] Ordinarily, no attempt was made to separate the esters produced, but rather the esters were saponified directly by refluxing an alcoholic (100 ml.) solution of the esters

(13) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, Wiley, New York, 1954, p. 157.

with aqueous potassium hydroxide (50%, 5 moles/mole of initial silver salt) for 12 hr. In those instances in which chlorine was employed, the gas was bubbled slowly into the reaction mixture from a desk cylinder. These reactions were slower in starting, perhaps due to less intimate contact between reactants. Pertinent data are given in Tables I and II.[14]

Isolation and analysis of the phenols. Three methods were used to obtain the phenols quantitatively from the saponifications. Each method involved removal of the solvent (alcohol) by distillation, acidification of the phenoxides with dilute hydrochloric acid, steam distillation, or codistillation with water of the liberated phenols, and, finally, extraction of the distillate to obtain the carbon disulfide solutions of the phenols for infrared and v.p.c. analysis. No detailed examination of the rest of the saponified material was done, although the residues were soluble in base and gave initial acid (50–70% recovery) upon acidification. The identity of this recovered acid was established in all but a few runs. The distillations were continued in these isolations until negative bromine-water tests were obtained. The aqueous distillation residues were also so checked. The aqueous solutions of the phenols were then saturated with salt and extracted with an organic solvent until the water layer gave a negative bromine water test. In one method, ether was the extractant. The ethereal extract was dried, concentrated, and the ether replaced by carbon disulfide via distillation to 45°. In the other methods, the phenol solution was made alkaline again and redistilled, followed by isolation again as before, in one case by repeated extraction with small volumes of carbon disulfide or, in the other and best method, by day-long continuous extraction. Control experiments on standard solutions of various phenols, using the methods given, indicated isolation yields of better than 98%, well within the limits of accuracy of this work.

Standard mixtures of the phenols expected from each run were prepared and their infrared and v.p.c. characteristics determined. Absorbances (log 1/T) were calculated for a characteristic peak of each phenol in each standard mixture. The ratio of absorbances of the phenols were plotted against the wt.% of the phenols, giving excellent linearity in all cases. The reaction phenol mixture was then examined in the infrared and the ratio of characteristic absorbances determined. From the graph, the percentage composition was readily evaluated. The same standard-width sample cell was used throughout. Vapor phase chromatographic analyses were performed by the ratio of areas method, the peaks being integrated by both planimeter and half-width techniques. The column length was 1 meter, the temperature 180°.

Rearrangement of β,β,β-tris(p-butylphenyl)propionic acid (XIV), *silver salt.* Dry bromine (6.4 g., 0.04 mole) in dried carbon tetrachloride (10 ml.) was added in 1 hr. at 25° to a stirred suspension[15] of the silver salt of XIV (purity 93%, 23 g., 0.04 mole) in carbon tetrachloride (30 ml.), employing a nitrogen sweep as before.[2] After 30 min., a paste resulted. Carbon dioxide evolved was slight (1%). After standing overnight, the reaction was worked up as is customary,[2] giving recovered acid (13.4 g., 71.1%, m.p. 245–247°). A golden semisolid was also obtained which, on trituration with alcohol, gave a white solid (4.5 g., 21%) which was an ester (hydroxamic acid test) containing bromine (Beilstein test). A portion was recrystallized from alcohol, m.p. 161–162°, and subsequent work indicated this material to be *p-t*-butylphenyl α-bromo-β,β-bis(*p-t*-butylphenyl)acrylate (XVI).

Anal. Calcd. for $C_{33}H_{39}BrO_2$: C, 72.39; H, 7.16. Found: C, 72.85; H, 7.03.

(14) For data on the thirty-odd reactions performed, the dissertation of J.L.F. should be consulted.

(15) The silver salts of most of the acids studied were soluble in carbon tetrachloride; the salt of XIV, however, was not.

The infrared spectrum showed C=O (5.7 μ, strong), C=C (6.05 μ, very weak), and an quartet of peaks in the 11.5–12 μ region, among others. All features of the spectrum were consistent with the proposed structure. The ultraviolet spectrum showed a λ_{max}^{ale} 289 mμ (ε 8920) with λ_{min}^{ale} 282.5 μ (ε 8300). Similar spectra were noted for the compounds obtained in the earlier study.[2]

The remainder of the crude ester was saponified and worked up to give exclusively *p-t*-butylphenol (m.p. and mixture m.p. 98–99°) as the phenolic component. The acid portion was investigated as follows.

α-Bromo-β,β-bis(p-t-butylphenyl)acrylic acid (XVII). XVI (0.45 g., 0.8 mmole, m.p. 161–162°) was saponified at 130–140° for 3–4 min. with potassium hydroxide (0.6 g.) in diethylene glycol (10 ml.). Water (10 ml.) was added to the cooled mixture and the flakes of the potassium salt of XVII collected. Acidification and steam distillation of the filtrate gave *p-t*-butylphenol (0.12 g., 100%, m.p. 98°). Acidification of the potassium salt of XVII gave the acid as a white solid. Two recrystallizations from water-alcohol gave flakes, m.p. 174–175°.

Anal. Calcd. for $C_{23}H_{27}BrO_2$: C, 66.51; H, 6.55. Found: C, 66.71; H, 6.68.

The infrared spectrum was consistent with this structure. The C=O absorption was at 5.95 μ.

β,β-Bis(p-t-butylphenyl)propionic acid (XIX). XVI (0.41 g., 0.75 mmole, m.p. 161–162°) was shaken in a mixture of absolute ethanol (50 ml.), sodium hydroxide (0.5 g.) and palladium on charcoal (10%, 0.5 g.) under 1 atm. of hydrogen for 16 hr. The mixture was neutralized, freed from catalyst, and the ethanol evaporated. Extraction with ether followed. The ester remaining after removal of the ether was saponified as described for ester XVI, giving XIX as a white crystalline solid, m.p. 201–202°.

Anal. Calcd. for $C_{23}H_{30}O_2$: C, 81.61; H, 8.93. Found: C, 81.39; H, 9.03.

The infrared spectrum showed the absence of non-aromatic unsaturation, with C=O (5.8 μ, strong), OH (2.8–3.0 μ, broad), and C—CH_3 (7.3 μ) prominent. Authentic XIX was prepared by the hydrogenation of acid XVIII (palladium on charcoal, 2 atm. hydrogen, 2 hr., quantitative). The acid from this source had a m.p. 201–202° and the mixture melting point of this sample and the material from XVI was undepressed.

β-(p-t-Butylphenyl)-β-phenylacrylic acid. In the course of this work, this acid was synthesized. Since a new intermediate was prepared, the synthesis is recorded briefly at this time. *p-t*-Butylbenzophenone was prepared (75.5%, b.p. 168–170° at 2 mm., lit.[16] b.p. 132–134° at 0.1 mm.). This ketone and ethyl bromoacetate (8.35 g., 0.05 mole) with mossy zinc (3.26 g., 0.05 mole) gave, in a straightforward Reformatsky reaction, ethyl β-hydroxy-β-(*p-t*-butylphenyl)-β-phenylpropionate (flakes, m.p. 84°, 4.3 g., 29%).

Anal. Calcd. for $C_{21}H_{26}O$: C, 77.26; H, 8.03. Found: C, 77.33; H, 8.15.

The infrared spectrum possessed an OH peak at 2.9 μ (sharp, strong). Dehydration and saponification of this ester by the method of Fuson[17] gave the substituted acrylic acid in poor yield (10%, m.p. 171–173°, lit.[18] m.p. 178°).

Acknowledgment. We are grateful for the support given this work in the form of grants from the Research Corporation and a grant-in-aid from the Society of the Sigma Xi.

CHICAGO 26, ILL.

(16) F. Bergmann and J. Szmuskowicz, *J. Am. Chem. Soc.*, **70**, 2748 (1948).

(17) L. L. Alexander, A. L. Jacoby, and R. C. Fuson, *J. Am. Chem. Soc.*, **57**, 2208 (1935).

(18) F. Bergmann, M. Weizmann, E. Dimant, J. Patai, and J. Szmuskowicz, *J. Am. Chem. Soc.*, **70**, 1612 (1948).

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

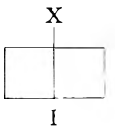
Synthesis and Deamination of 1-Aminobicyclo[2.2.1]heptan-7-one[1]

DOUGLAS E. APPLEQUIST AND JOSEPH P. KLEIMAN

Received September 27, 1960

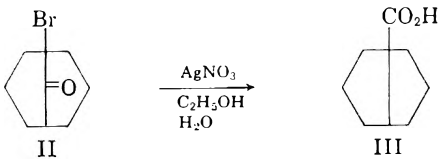
The amine of the title has been prepared by a Curtius degradation and isolated as its hydrated hydrochloride and perchlorate salts. Diazotization of the perchlorate in acetic acid followed by a hydrolytic isolation procedure has given unrearranged 1-hydroxybicyclo[2.2.1]heptan-7-one (as its hydrate) and 4-ketocyclohexanecarboxylic acid. A possible product, bicyclo[2.2.0]hexane-1-carboxylic acid, has not been obtained.

In connection with other studies in progress in this laboratory, it was desired to have a source of 1-substituted bicyclo[2.2.0]hexanes (I).



I

A route to such compounds which appeared promising was a ring contraction similar to contractions of 1-substituted bicyclo[3.3.1]nonan-9-ones which have previously been observed.[2] A typical example is the reaction of 1-bromobicyclo[3.3.1]nonan-9-one (II) with silver nitrate in aqueous ethanol to give the acid III and its ethyl ester.[2b] The possibility of



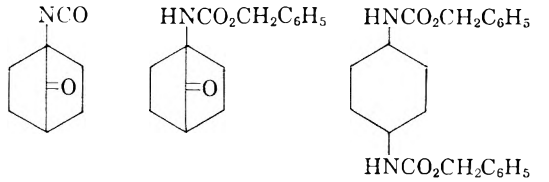
II III

analogous ring contractions in the bicyclo[2.2.1]-heptane series has been presented by a recently announced synthesis of bicyclo[2.2.1]heptan-7-one-

IV V

1-carbonyl chloride (IV).[3] In particular, it appeared probable that amine V would be readily obtainable, and that diazotization of V would be similar enough to the reaction of II with silver nitrate that contraction to the bicyclic acid (I, X=COOH) might occur.

The reaction of IV with activated sodium azide in refluxing benzene gave a product characterized as the isocyanate, VI, by its infrared spectrum, which showed typical 7-keto carbonyl absorption[4] at 1786 cm.$^{-1}$ and isocyanate absorption[5] at 2240 cm.$^{-1}$



VI VII VIII

Reaction of sodium azide with IV in acetone-water and subsequent reaction of the product with benzyl alcohol did not give the expected bicyclic ketobenzyl carbamate, VII, but gave the dibenzyl carbamate, VIII, of *trans*-1,4-diaminocyclohexane. Its identity was established by analysis, infrared spectrum (bands at 3270, 1688, 1678, and 1550 cm.$^{-1}$ which probably can be assigned to the amide group and to the aromatic ring; lack of a carbonyl absorption in the 1775 cm.$^{-1}$ region) and comparison with the literature melting point.[6] The great sensitivity of the 7-ketobicyclo[2.2.1]heptane system toward nucleophilic ring opening, when an electronegative substituent is on the bridgehead, had been observed previously.[3]

Reaction of VI with concentrated hydrochloric acid gave the hydrated amine hydrochloride, IX, rather than the expected V hydrochloride (X). The infrared spectrum of IX showed broad absorptions in the 3000–3450 cm.$^{-1}$ region (OH and NH stretching vibrations) but no carbonyl

IX X

(1) Abstracted from the Ph.D. thesis of J. P. Kleiman, University of Illinois, 1960.

(2) (a) A. C. Cope and M. E. Synerholm, *J. Am. Chem. Soc.*, **72**, 5228 (1950); (b) A. C. Cope and E. S. Graham, *J. Am. Chem. Soc.*, **73**, 4702 (1951); (c) A. C. Cope, E. S. Graham, and D. J. Marshall, *J. Am. Chem. Soc.*, **76**, 6159 (1954).

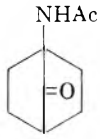
(3) W. R. Hatchard and A. K. Schneider, *J. Am. Chem. Soc.*, **79**, 6261 (1957).

(4) (a) C. F. H. Allen and J. A. VanAllan, *J. Org. Chem.*, **20**, 323 (1955); (b) P. Wilder, Jr., and A. Winston, *J. Am. Chem. Soc.*, **78**, 868 (1956).

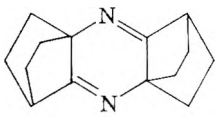
(5) R. N. Jones and C. Sandorfy in A. Weissberger, *Technique of Organic Chemistry*, Vol. IX, Interscience Publishers, Inc., New York, N. Y., 1956, p. 544.

(6) T. Curtius, *J. prakt. Chem.*, **91**, 1 (1915).

absorption, which was expected near 1775 cm.$^{-1}$ When IX was heated at 100° at reduced pressure over phosphorus pentoxide, compound X was obtained, having a strong infrared absorption at 1775 cm.$^{-1}$ and a sharp peak at 3370 cm.$^{-1}$ There was no broad absorption in the OH region. When X was treated with concentrated hydrochloric acid, IX was regenerated, as shown by the identity of the infrared spectra. Reaction of IX with acetic anhydride in pyridine gave the dehydrated amide XI, as shown by elemental analyses and the infrared spectrum (ketone C=O at 1775 cm.$^{-1}$, N—H at 3400 cm.$^{-1}$, and amide C=O at 1665 cm.$^{-1}$). Reaction of IX with aqueous sodium hydroxide gave the dihydropyrazine XII as shown by ele-



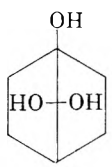
XI



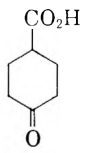
XII

mental analysis, molecular weight, and absence of OH, NH, or C=O absorptions in the infrared (C=N appeared at 1697 cm.$^{-1}$ (medium)). Reaction of XII with concentrated hydrochloric acid regenerated IX.

Hydrochloride IX was converted to the perchlorate with silver perchlorate and the perchlorate was diazotized with sodium nitrite in glacial acetic acid at room temperature. An isolation procedure which involved probable saponification of any ester products yielded the triol, XIII, and the keto acid, XIV, the yields being 38% and 21%, respectively. The structure of XIII was assigned on

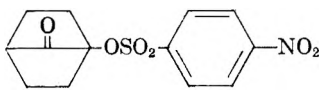


XIII



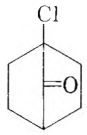
XIV

the basis of its analysis, infrared spectrum (broad OH absorption in the 3000-3500 cm.$^{-1}$ region and no carbonyl absorption), reaction with 2,4-dinitrophenylhydrazine to form a 2,4-dinitrophenylhydrazone (C=N absorption at 1685 cm.$^{-1}$ and broad OH absorption in the infrared), and reaction with *p*-nitrobenzenesulfonyl chloride to give the keto *p*-nitrobenzenesulfonate XV (C=O stretching absorption at 1788 cm.$^{-1}$). The acid XIV was identified by comparison with an authentic sample.



XV

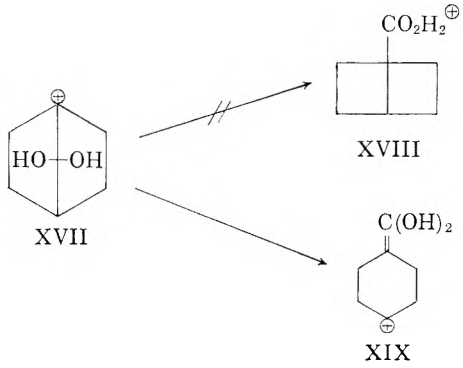
Diazotization of IX in water gave a 52% yield of crude XIII and a small amount of 1-chlorobicycloheptanone (XVI) which was characterized as its dinitrophenylhydrazone. The NMR spectrum of the latter showed signals at 2.58 p.p.m. and 1.64



XVI

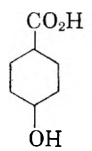
p.p.m. (from water) in a ratio of 8:1, corresponding to the methylene and bridgehead hydrogens, respectively. The infrared spectrum showed no carbonyl or hydroxyl absorptions. Some acidic material was also obtained in the aqueous diazotization, but no pure substances were isolated from it.

The formations of XIII and XVI are not without analogy in the deaminations of bridgehead amines, which normally proceed without rearrangement.[7] It was somewhat surprising that the intermediate cation XVII apparently opened up to give XIX rather than to give the contraction

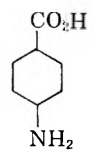


product XVIII expected from the analogies in the bicyclo[3.3.1]nonane system.[2] The less favorable locus of positive charge in XIX as compared with XVIII is presumably compensated for by the excessive strain in XVIII. The possibility exists that XVIII was actually formed first, and that ring opening, leading to XIV, took place under the conditions of the reaction or isolation procedure. This possibility lacks analogy at present and appears improbable. Another possibility is that some nonclassical cation, of which XVII, XVIII, and XIX are contributing resonance structures, gives both types of product observed.

The formation of XIX would be expected to lead to the hydroxy acid XX, or its acetate ester under the diazotization conditions reported here.



XX



XXI

(7) D. E. Applequist and J. D. Roberts, *Chem. Rev.*, **54**, 1065 (1954).

An oxidation is required to obtain the observed keto acid, XIV. Such oxidation may have been caused by some oxidizing species derived from nitrous acid in the diazotization reaction mixture, or may have been a Meerwein-Ponndorf reduction of XIII by XX during the basic extraction in the isolation procedure. That the oxidation was not simply an oxidation of XX by nitrous or perchloric acid was shown by diazotization of 4-aminocyclohexanecarboxylic acid (XXI) as its perchlorate salt in acetic acid under the same conditions of reaction and isolation to give the hydroxy acid, XX, rather than the keto acid, XIV.

EXPERIMENTAL[8]

Hexahydroterephthaloyl chloride.[9] A mixture of 43 g. (0.25 mole) of *cis*- and *trans*-hexahydroterephthalic acid (from hydrogenation of dimethyl terephthalate in acetic acid over platinum oxide at room temperature and 2500 p.s.i.) and 215 g. of thionyl chloride was stirred and heated under reflux for 24 hr. The excess thionyl chloride was removed *in vacuo* and the residue was distilled to give 48 g. of *cis*- and *trans*-hexahydroterephthaloyl chloride, b.p. 85–90° (0.5 mm.).

Bicyclo[2.2.1]heptan-7-one-1-carbonyl chloride (IV).[3] A solution of 29 g. (0.29 mole) of triethylamine in 100 ml. of anhydrous ether was added dropwise over 1 hr. to a stirred mixture of 50 g. (0.24 mole) of *cis*- and *trans*-hexahydroterephthaloyl chloride in 550 ml. of ether at reflux temperature. The reaction mixture was refluxed and stirred for an additional 20 hr. The mixture was then filtered directly into a distillation flask in small portions in an apparatus designed to exclude air and moisture. The ether was removed from each portion at reduced pressure before more ether mixture was added. On distillation of the residue, 18.8 g., b.p. 78–82° (0.5 mm.) (reported[10] b.p. 86.5–88°, 1 mm.) of IV was obtained.

Reaction of bicyclo[2.2.1]heptan-7-one-1-carbonyl chloride with sodium azide in aqueous acetone. To a cooled stirred solution of 3.7 g. (0.0214 mole) of bicyclo[2.2.1]heptane-7-one-1-carbonyl chloride in 200 ml. of reagent-grade acetone was added 1.7 g. (0.0262 mole) of sodium azide in 4.8 ml. of water. The mixture was poured into 32 ml. of water and 30 ml. of benzene. The benzene layer was separated and added to 40 ml. of benzyl alcohol. The mixture was heated to a pot temperature of 70° and then the heat source was removed. Nitrogen evolution proceeded at a steady rate and no heat was necessary to keep the reaction going. The mixture was heated to 75° for a few minutes after nitrogen evolution appeared to cease. On cooling the reaction mixture, 1.59 g., m.p. 239–243°, of a solid precipitated out. A pure sample, m.p. 245–247°, was obtained by recrystallization from benzene and was identified as the bis(benzylcarbamate) of *trans*-1,4-diaminocyclohexane (lit.[6] m.p. 244–245°). Its infrared spectrum had bands at 3270 cm.$^{-1}$, 1688 cm.$^{-1}$, 1678 cm.$^{-1}$, and 1550 cm.$^{-1}$

Anal. Calcd. for $C_{22}H_{26}N_2O_4$: C, 69.09; H, 6.85; N, 7.33. Found: C, 68.92; H, 6.76; N, 7.30.

Evaporation of the filtrate at reduced pressure gave an additional 3.5 g. of material, m.p. 204–214°, which was not identified.

7-Ketobicyclo[2.2.1]hept-1-yl isocyanate (VI). Activated sodium azide was prepared with 85% hydrazine hydrate.[11] A mixture of 1.0 g. (0.0058 mole) of bicyclo[2.2.1]heptane-7-one-1-carbonyl chloride, 0.41 g. (0.0063 mole) of activated sodium azide, and 50 ml. of benzene was refluxed and stirred for 22 hr. The reaction mixture was cooled and filtered to remove the inorganic material. The benzene was removed by freeze-drying. The infrared spectrum of the residue indicated the product was 7-ketobicyclo[2.2.1]hept-1-yl isocyanate (a carbonyl band at 1786 cm.$^{-1}$ and an isocyanate band at 2240 cm.$^{-1}$). The crude material was used directly in the next step.

7,7-Dihydroxybicyclo[2.2.1]hept-1-ylamine hydrochloride (IX); *Procedure A.* The crude isocyanate was dissolved in 25 ml. of benzene. To this was added 15 ml. of concd. hydrochloric acid and the mixture was heated under reflux for 2.5 hr. The cooled layers were separated and the benzene layer was washed with a little water. The water layers were combined and the water was removed at reduced pressure. The last traces of water were removed in a vacuum desiccator over phosphorus pentoxide to give 0.8 g. of a white solid. Its infrared spectrum had a wide absorption in the 3450–3000 cm.$^{-1}$ region, many small peaks in the 2800–2400 cm.$^{-1}$ region, and peaks at 2020, 1625, 1600, and 1531 cm.$^{-1}$

A sample was heated at 100° for 10 hr. over phosphorus pentoxide at reduced pressure to give a material with a strong carbonyl absorption at 1775 cm.$^{-1}$ and a sharp peak at 3370 cm.$^{-1}$ Addition of concentrated hydrochloric acid to the dried material and then removal of the acid at reduced pressure and drying of the residue over phosphorus pentoxide gave back the original product (IX) as shown by the infrared spectrum. The carbonyl absorption was no longer present.

Procedure B. To a solution of 5 g. (0.029 mole) of bicyclo[2.2.1]heptane-7-one-1-carbonyl chloride in 100 ml. of benzene was added 2.02 g. (0.0315 mole) of activated sodium azide. The stirred mixture was heated under reflux for 20 hr. The reaction mixture was cooled and filtered directly into another reaction flask. The precipitate was washed with about 50 ml. of benzene. To the combined benzene solutions was added 75 ml. of concd. hydrochloric acid and the mixture was heated under reflux for 6 hr. The cooled mixture was separated and the benzene layer was washed with water. The combined water layers were evaporated at aspirator pressure and the final traces of water were removed by drying over phosphorus pentoxide in a vacuum desiccator. A total of 4.8 g. of amine hydrochloride was obtained.

3,9-Diazapentacyclo[8.2.2.2.^{4,7} 0.^{2,10} 0^{4,8}]hexadecadiene-2,8 (XII). To a solution of 3.2 g. (0.0178 mole) of 7,7-dihydroxybicyclo[2.2.1]hept-1-ylamine hydrochloride in 50 ml. of water was added enough 10% sodium hydroxide to make the *p*H 12. The solution was extracted continuously with ether for 1 day to give 1.6 g. of solid, m.p. 204–208°. Its infrared spectrum had a band at 1697 cm.$^{-1}$ and no absorption in the NH or OH region (3500–3000 cm.$^{-1}$). An analytical sample, m.p. 211.5–212°, was prepared by recrystallization from cyclohexane-ether. Treatment of the condensation product with concentrated hydrochloric acid at room temperature for 10 hr. and evaporation of the acid gave back 7,7-dihydroxybicyclo[2.2.1]hept-1-ylamine hydrochloride as shown by identity of its infrared spectrum with that of an authentic sample.

Anal. Calcd. for $C_{14}H_{18}N_2$: C, 78.46; H, 8.47; N, 13.07; M. W., 214. Found: C, 78.78; H, 8.38; N, 13.18; M. W. 229.

1-Acetamidobicyclo[2.2.1]heptan-7-one (XI). To a solution of 0.2221 g. (0.00123 mole) of 7,7-dihydroxybicyclo[2.2.1]-hept-1-ylamine hydrochloride in 15 ml. of pyridine was

(8) Melting points and boiling points are uncorrected. Infrared spectra were measured by Mr. James Brader, Mr. Paul McMahon, and their associates using a Perkin-Elmer model 21B spectrophotometer with sodium chloride optics. The NMR spectra were measured by Mr. Ben Shoulders with a Varian high resolution spectrometer (model V-4300B with super stabilizer) at 40 mc. with external methylene chloride as standard. The signal of methylene chloride was taken to be at −0.65 p.p.m. from water. Microanalyses were done by Mr. Josef Nemeth and his associates.

(9) R. Malachowski, J. J. Wasowska, S. Jozkiewicz, J. Adamiczka, and G. Zimmerman-Pasternak, *Ber.*, **71B**, 759 (1938).

(10) W. R. Hatchard, private communication.

(11) P. A. S. Smith, *Org. Reactions*, **3**, 382 (1946).

added 0.413 g. (0.00405 mole) of acetic anhydride. The reaction mixture was refluxed overnight. It was cooled and then poured onto 25 ml. of concd. hydrochloric acid on cracked ice. The solution was extracted continuously with ether for 1 day to give 100 mg. of amide. Several recrystallizations from cyclohexane gave an analytical sample, m.p. 115–117°. Its infrared spectrum had a strong carbonyl band at 1775 cm.$^{-1}$ and amide bands at 3400 and 1665 cm.$^{-1}$.

Anal. Calcd. for $C_9H_{13}NO_2$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.67; H, 7.89; N, 8.47.

Reaction of 7,7-dihydroxybicyclo[2.2.1]hept-1-ylamine hydrochloride with sodium nitrite in water. To a stirred solution of 4.8 g. (0.0266 mole) of 7,7-dihydroxybicyclo[2.2.1]hept-1-ylamine hydrochloride in 50 ml. of 2.5*N* hydrochloric acid was added a solution of 7.44 g. (0.108 mole) of sodium nitrite in 25 ml. of water over a 30-min. period. The reaction mixture was heated under reflux for 6 hr., cooled, made basic with aqueous sodium hydroxide, and extracted continuously for 3 days with ether. Evaporation of the ether gave 2.5 g. of solid material. Addition of warm benzene to this solid dissolved 0.5 g. The benzene was filtered and on evaporation of the filtrate an oil was obtained that had a strong carbonyl band at 1775 cm.$^{-1}$ A 2,4-dinitrophenylhydrazone was prepared according to the method of Shriner, Fuson, and Curtin.[12] A yield of 500 mg. of crude material was obtained. On chromatography of this material on acid-washed alumina, 290 mg. of the 2,4-dinitrophenylhydrazone of 1-chlorobicyclo[2.2.1]heptan-7-one, m.p. 207.5–208.5°, was obtained. The NMR spectrum of a saturated deuterochloroform solution had signals at 2.58 and 1.64 p.p.m. relative to water, in the ratio of 8:1.

Anal. Calcd. for $C_{13}H_{13}N_4O_4Cl$: C, 48.08; H, 4.03; N, 17.25; Cl, 10.92. Found: C, 48.18; H, 4.07; N, 16.87; Cl, 11.13.

The 2.0 g. of benzene-insoluble material had an infrared spectrum quite similar to the spectrum of 1,7,7-trihydroxybicyclo[2.2.1]heptane (wide OH absorption in 3500–3000 cm.$^{-1}$ region and peaks at 938 and 967 cm.$^{-1}$).

The reaction solution was made acidic to about *p*H 2 with concentrated hydrochloric acid and extracted continuously with ether for 3 days. Evaporation of the ether gave 1.6 g. of an orange oil that had a neutralization equivalent of 94. No pure compound could be isolated. The infrared spectrum had bands at 1700 cm.$^{-1}$ and broad-OH absorption from 3500 to 3000 cm.$^{-1}$ and 2700 to 2600 cm.$^{-1}$

Diazotization of 7,7-dihydroxybicyclo[2.2.1]hept-1-ylamine perchlorate in glacial acetic acid. To a solution of 5.0 g. (0.0278 mole) of 7,7-dihydroxybicyclo[2.2.1]hept-1-ylamine hydrochloride in 100 ml. of water was added a solution of 5.75 g. (0.0278 mole) of anhydrous silver perchlorate in water. The mixture was filtered and the silver chloride cake was washed with water. The combined solution and washings were evaporated at reduced pressure and the last traces of water were removed by drying in a vacuum desiccator over phosphorus pentoxide. The yield was 4.0 g. To a stirred suspension of 4.0 g. (0.0164 mole) of the amine perchlorate in 20 ml. of glacial acetic acid cooled with an ice bath was added 3.41 g. of solid sodium nitrite over a 45-min. period. The reaction mixture was protected with a drying tube except during the addition of the sodium nitrite. The ice bath was removed and the reaction mixture was stirred for an additional 2.5 hr., after which time no sodium nitrite was present (potassium iodide-starch paper). The reaction mixture was diluted with 150 ml. of water and was extracted with 1500 ml. of ether. The ether was dried over Drierite. After removal of the ether and acetic acid at reduced pressure, the residue, 3.43 g., was dissolved in aqueous sodium hydroxide to *p*H 10 to 12 and extracted continuously for 3 days with ether. The ether was evaporated in an air stream to give 0.9 g. of solid XIII, m.p. 114–118°. An analytical sample, m.p. 121.5–122.5°, was prepared by recrystallization from acetone.

Anal. Calcd. for $C_7H_{12}O_3$: C, 58.31; H, 8.39. Found: C, 58.57; H, 8.54.

Its infrared spectrum had a broad —OH absorption at 3500–3000 cm.$^{-1}$ and no carbonyl band in the 1775 cm.$^{-1}$ region. Reaction of the compound with 2,4-dinitrophenylhydrazine gave an immediate precipitate. An analytical sample, recrystallized from ethanol, melted at 216.5–217.5°.

Anal. Calcd. for $C_{13}H_{14}O_5N_4$: C, 50.97; H, 4.61; N, 18.29. Found: C, 51.27; H, 4.38; N, 17.97.

The basic solution was then made acidic with concentrated hydrochloric acid to *p*H 1 or 2 and extracted continuously with ether for 3 days to give 1.6 g. of dark brown acidic material after evaporation of the ether. Sublimation of this material at 70°, 0.05 mm., gave 0.5 g. of solid XIV m.p. 56–63°, which, on drying *in vacuo*, melted at 66–69°. An analytical sample, m.p. 70.5–71.5°, was prepared by two more sublimations. The acid gave a precipitate with 2,4-dinitrophenylhydrazine. It was identified (see below) as 4-ketocyclohexanecarboxylic acid (lit.[13] m.p. 68°).

Anal. Calcd. for $C_7H_{10}O_3$: C, 59.12; H, 7.09; neut. equiv., 142. Found: C, 58.83 H, 7.18; neut. equiv., 143.

A semicarbazone of XIV was prepared according to directions in Shriner, Fuson, and Curtin.[14] After several recrystallizations from ethanol, it decomposed at 196–197° (lit.[13] decomposition point, about 200°).

Anal. Calcd. for $C_8H_{13}N_3O_3$: C, 48.23; H, 6.57; N, 21.10. Found: C, 48.26; H, 6.42; N, 20.96.

7-Ketobicyclo[2.2.1]hept-1-yl p-nitrobenzenesulfonate (XV). A solution of 1.12 g. (0.0078 mole) of 1,7,7-trihydroxybicyclo[2.2.1]heptane and 3.82 g. (0.0172 mole) of *p*-nitrobenzenesulfonyl chloride in 10 ml. of pyridine was stirred at room temperature for 45 hr. The reaction mixture was then poured onto 20 ml. of concd. hydrochloric acid and 50 g. of cracked ice. The solution was extracted with 2 l. of ether and the ether solution was dried over Drierite. After evaporation of the ether and recrystallization from benzene-hexane, 1.41 g. of ester, m.p. 130–132°, was obtained. An analytical sample, m.p. 131–132°, was prepared by several recrystallizations from benzene-hexane.

Anal. Calcd. for $C_{13}H_{13}NO_6S$: C, 50.15; H, 4.21. Found: C, 50.17; H, 4.37.

4-Hydroxycyclohexanecarboxylic acid (XX). A mixture of 60 g. of ethyl *p*-hydroxybenzoate, 600 ml. of glacial acetic acid, and 1.0 g. of platinum oxide was shaken with hydrogen at 1500 p.s.i. at room temperature until the theoretical amount of hydrogen was taken up. The reaction mixture was filtered and the acetic acid was removed at reduced pressure. The product showed no aromatic bands in the infrared region. The reaction mixture was distilled at reduced pressure to give two products, ethyl cyclohexanecarboxylate, b.p. 65–67° (10 mm.), 14.3 g., and ethyl 4-hydroxycyclohexanecarboxylate, b.p. 93–98° (0.3 mm.), 17.4 g. The ethyl 4-hydroxycyclohexanecarboxylate was saponified by boiling with 100 ml. of 10% aqueous sodium hydroxide for 2 hr. The solution was cooled and made acid to *p*H 2 with concentrated hydrochloric acid. The mixture was then extracted continuously with ether for 4 hr. The ether was removed by air blowing and the residue was recrystallized from benzene-ethanol-ether to give 11.7 g., m.p. 120–142°, of a mixture of *cis*- and *trans*-4-hydroxycyclohexanecarboxylic acid.

Reaction of 4-carboxycyclohex-1-ylamine perchlorate with sodium nitrite in glacial acetic acid. To a solution of 3.1 g. (0.0172 mole) of 4-carboxycyclohex-1-ylamine hydrochloride[15] in 50 ml. of water was added a solution of 3.56 g.

(12) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *The Systematic Identification of Organic Compounds*, John Wiley & Sons, Inc., New York, N. Y., 1956, p. 219.

(13) W. H. Perkin, Jr., *J. Chem. Soc.*, 85, 416 (1904).

(14) Ref. 12, p. 218.

(15) J. P. Greenstein and J. Wyman, *J. Am. Chem. Soc.*, 60, 2341 (1938).

(0.0172 mole) of silver perchlorate in 50 ml. of water. After filtration, the solution was evaporated to near dryness at aspirator pressure and last traces of water were removed by drying over phosphorus pentoxide in a vacuum desiccator to give 3.8 g. (0.0156 mole) of 4-carboxycyclohex-1-ylamine perchlorate. To a mixture of 3.8 g. of the amine perchlorate in 20 ml. of glacial acetic acid, cooled in an ice bath, was added 3.24 g. (0.047 mole) of sodium nitrite over a period of about 30 min. The ice bath was removed and the mixture stirred for an additional 6 hr. The mixture was poured into 250 ml. of water and extracted with 1.5 l. of ether. After evaporation of the ether, the residue gave a negative test with 2,4-dinitrophenylhydrazine reagent. Aqueous sodium hydroxide (10%) was added to the residue until the *p*H was 12 and the solution was extracted continuously with ether for 2 days. Evaporation of the ether gave no residue. After acidification of the basic solution with concentrated hydrochloric acid to *p*H 2 and continuous extraction for 2 days with ether, evaporation of the ether and extracted acetic acid gave 90 mg., m.p. 112–127°, of acidic material. Its infrared spectrum had bands at 3440, 2600, and 1705 cm.$^{-1}$ and was almost identical with the spectrum of a mixture of *cis*- and *trans*-4-hydroxycyclohexanecarboxylic acid.

4-Ketocyclohexanecarboxylic acid (XIV). To a stirred suspension of 3.0 g. (0.0208 mole) of 4-hydroxycyclohexanecarboxylic acid in 10 ml. of water and 3.6 g. of sulfuric acid was added 4.23 g. (0.0144 mole) of potassium dichromate in small portions over a 15-min. period, during which time the temperature rose to about 50°. After the addition was complete, the reaction mixture was stirred for 3 hr. The solution was extracted with 1 l. of ether. The ether was dried over sodium sulfate and then was evaporated to give 2.39 g. of solid material. Sublimation of 0.86 g. of this material gave 0.69 g. of 4-ketocyclohexanecarboxylic acid, m.p. 67–70°. Its infrared spectrum had a band at 1705 cm.$^{-1}$ and broad absorptions from 3500–3000 cm.$^{-1}$ and 2700–2600 cm.$^{-1}$ and was identical to the spectrum of the acid obtained from diazotization of 7,7-dihydroxybicyclo[2.2.1]hept-1-ylamine perchlorate. A mixed melting point with the acid obtained from the diazotization was 68–71°.

Acknowledgment. The authors are indebted to the Research Corp. and the Alfred P. Sloan Foundation for grants in partial support of this research, and to the Monsanto Chemical Co. for a fellowship held by J. P. K. during the year 1957–58.

URBANA, ILL.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF COLORADO]

Bridged Polycyclic Compounds. XIV. Free-Radical Addition of *p*-Toluenesulfonyl Chloride to Some Norbornenes[1]

STANLEY J. CRISTOL AND JAMES A. REEDER

Received October 26, 1960

Free-radical addition of *p*-toluenesulfonyl chloride to norbornene (I) and to aldrin (II) led to the formation of *trans* 1,2-addition products (III and IV, respectively) without skeletal rearrangement or *cis-exo* addition products being noted. Addition to norbornadiene (V) gave the rearranged product VII. The results are discussed in terms of classical radical intermediates.

The addition of sulfonyl halides to olefins *via* free-radical paths has been noted by several groups of investigators.[2,3,4] In the course of our work on the stereochemistry of addition and of rearrangements during additions to bridged polycyclic olefins,[1,5–10] we decided to investigate the free-radical additions of arenesulfonyl chlorides to norbornenes to see whether these followed the same general pattern as other free-radical addition reactions.

Exclusive *exo-cis* addition of *p*-thiocresol to 6-chloroaldrin (*endo-exo*-1,2,3,4,6,10,10-heptachloro-1,4,4a,5,8,8a-hexahydro-1,4,5,8-dimethanonaphthalene) has been reported.[7] The free-radical addition of bromine to various substituted norbornenes (and 7-oxa analogs) has also been shown to give considerable *exo-cis* products,[11] and ethyl bromoacetate is reported to give *exo-cis* addition to norbornene.[12] On the other hand, we have now found that *p*-toluenesulfonyl chloride adds to norbornene (I) and to aldrin (II) to give the *trans* addition product.

When norbornene (I) was heated at 75–90° with *p*-toluenesulfonyl chloride in the presence of

(1) Previous paper in series: S. J. Cristol and R. K. Bly, *J. Am. Chem. Soc.*, **82**, 6155 (1960).

(2) E. C. Ladd, U. S. Patent **2,521,068** (Sept. 5, 1950); U. S. Patent **2,573,580** (Oct. 30, 1951).

(3) M. S. Kharasch and R. A. Mosher, *J. Org. Chem.*, **17**, 453 (1952).

(4) P. S. Skell and R. C. Woodworth, *J. Am. Chem. Soc.*, **77**, 4638 (1955); P. S. Skell and J. H. McNamara, *J. Am. Chem. Soc.*, **79**, 85 (1956).

(5) S. J. Cristol and G. D. Brindell, *J. Am. Chem. Soc.*, **76**, 5699 (1954).

(6) S. J. Cristol, R. P. Arganbright, G. D. Brindell, and R. M. Heitz, *J. Am. Chem. Soc.*, **79**, 6035 (1957).

(7) S. J. Cristol and R. P. Arganbright, *J. Am. Chem. Soc.*, **79**, 6039 (1957).

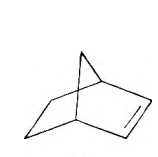
(8) S. J. Cristol, G. D. Brindell, and J. A. Reeder, *J. Am. Chem. Soc.*, **80**, 635 (1958).

(9) S. J. Cristol and R. T. LaLonde, *J. Am. Chem. Soc.*, **81**, 1655 (1959).

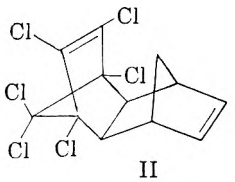
(10) S. B. Soloway and S. J. Cristol, *J. Org. Chem.*, **25**, 327 (1960).

(11) J. A. Berson and R. Swidler, *J. Am. Chem. Soc.*, **75**, 4366 (1953); **76**, 4060 (1954); J. A. Berson, *J. Am. Chem. Soc.*, **76**, 5748 (1954).

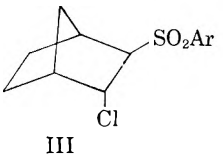
(12) J. Weinstock, Abstracts of the 128th Meeting of the American Chemical Society, Minneapolis, Minn., September 1955, p. 19-O.



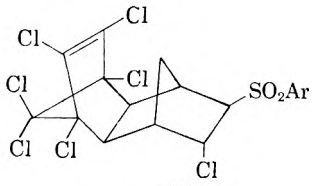
I



II



III



IV

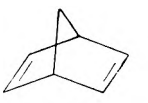
benzoyl peroxide or with ultraviolet irradiation, a substantial yield of a 1:1 addition product was obtained. The principal component of this product was shown to be *exo*-2-*p*-toluenesulfonyl-*endo*-3-chloronorbornane (III) which has been previously prepared and characterized.[6] The free-radical nature of the reaction was demonstrated by catalysis and by inhibition.

Aldrin (II) reacted with *p*-toluenesulfonyl chloride more slowly than norbornene, but addition occurred in twenty-four hours at 155° in the presence of di-*tert*-butyl peroxide to give the *trans* addition product, *endo*-3,4,5,6,7,8,9,9-heptachloro-1,2,3,4,4a,5,8,8a-octahydro-*exo*-2-*p*-toluenesulfonyl-1,4,5,8-*exo*-*endo*-dimethanonaphthalene (IV) a product of known structure.[6] The yield in this reaction was poor, considerable hydrogen chloride evolution being noted, but no other products were isolated.

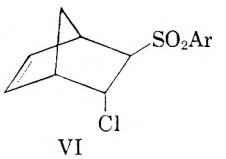
This reaction, like that with norbornene, then, is different from those previously noted in that *trans* addition is observed,[13] although similar in that no rearrangement is observed. It appears in order to rationalize the *trans* addition which occurs rather than the *cis-exo* addition previously noted. No explanation involving bridged radical intermediates appears tenable, in particular as Skell and his colleagues[4] have noted that the reactions of *p*-toluenesulfonyl iodide with *cis*- and *trans*-2-butene are not stereospecific and as we have found (*vide infra*) that *p*-toluenesulfonyl chloride adds to norbornadiene by homoconjugate addition. It seems necessary to suggest that the intermediates in these radical reactions are classical radicals,[7] and that the direction from which chain transfer occurs is controlled by steric factors.

A large steric requirement for the *p*-toluenesulfonyl group has been postulated by Bordwell and Cooper[14] to explain the inertness of chloromethyl *p*-tolyl sulfone to solvolysis, and by Weinstock, Pearson, and Bordwell[15] to explain the reduction of 2-*p*-toluenesulfonylcyclohexanone, and the corresponding cyclopentanone, with sodium borohydride to give the *cis*-substituted alcohols. A similar explanation can be advanced for the principal *trans* addition observed in the present investigation. According to this explanation, the approach of a molecule of *p*-toluenesulfonyl chloride to the 3-carbon atom of the intermediate radical is inhibited in the *exo* direction by steric interference from the large *p*-toluenesulfonyl group. Thus the occurrence of chain transfer from the *endo* direction is favored sterically.

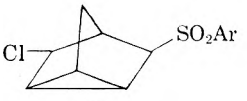
The addition of *p*-thiocresol to norbornadiene (V) has been shown to give a mixture of the products of simple 1,2- addition and 1,5-homoconjugate addition,[5] the ratio of the two modes depending upon the rate of chain transfer.[8] If *p*-toluenesulfonyl chloride added in a similar fashion to V, the products would be expected to be the *trans*-1,2-addition product VI and one or more of the isomers of the homoconjugate addition product VII. The addition of the sulfonyl chloride to V gave a product that was largely saturated,[16] and which gave upon recrystallization a 42% yield of a compound having properties anticipated for VII. This substance was inert to dilute potassium permanganate in acetone or bromine in carbon tetrachloride. The nortricyclene ring system is consistent with these data, with infrared data and with the lack of consistency of properties with the known[6] unsaturated isomer VI. The stereochemistry of the product has not yet been demonstrated. The relative completeness of the rearrangement to the nortricyclene ring system may be rationalized on the basis of the slow chain transfer of the intermediate radicals with the sulfonyl chloride allowing sufficient time for rearrangement of radical VIII to IX.[8]



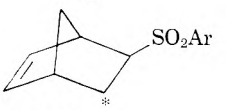
V



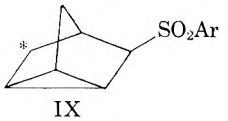
VI



VII



VIII



IX

(13) D. I. Davies, *J. Chem. Soc.*, 3669 (1960) has recently noted *trans* addition of bromotrichloromethane to aldrin, and N. A. LeBel, *J. Am. Chem. Soc.*, **82**, 623 (1960) has reported that hydrogen bromide adds to 2-bromonorbornene principally in the *cis-exo* fashion, but partly *trans*.

(14) F. G. Bordwell and G. D. Cooper, *J. Am. Chem. Soc.*, **73**, 5184 (1951).

(15) J. Weinstock, R. G. Pearson, and F. G. Bordwell, *J. Am. Chem. Soc.*, **78**, 3468 (1956).

(16) The composition of the equivalent product from benzenesulfonyl chloride has been investigated in this laboratory and will be reported later (S. J. Cristol and D. I. Davies).

EXPERIMENTAL

Addition of p-toluenesulfonyl chloride to norbornene. (*a*) *Peroxide-catalyzed reaction.* A mixture of 1.67 g. (17.73 mmoles) of norbornene and 1.82 g. (9.57 mmoles) of *p*-toluenesulfonyl chloride (Matheson, redistilled, m.p. 68–69°) was prepared in a 20-ml. flask equipped with a thermometer, reflux condenser, and mechanical stirrer. To this heterogeneous mixture was added 79 mg. (0.5 mmole) of benzoyl peroxide to act as a radical-chain initiator. The stirred mixture was heated rapidly to 100°, becoming homogeneous at about 70°. No spontaneous temperature rise attributable to the heat of reaction was noted. The temperature was maintained at 85–90° for 8 hr., and then the reaction mixture was cooled slowly with stirring. It solidified to a thick white paste at 32°.

The paste was immediately dissolved in 8 ml. of ethyl acetate and chromatographed on 60 g. of alumina. Elution with a solution of 10% ethyl acetate in petroleum ether (b.p. 60–80°) yielded 1.73 g. (64% based on starting *p*-toluenesulfonyl chloride) of white solid material in three fractions, the first melting at 95–98°, the second at 109–112°, and the third at 100–104°. Two recrystallizations of this solid from methanol gave a white solid, m.p. 114–115°.

The melting point of this solid when mixed with an authentic sample[6] of *exo*-2-*p*-toluenesulfonyl-*endo*-3-chloronorbornane (III, m.p. 114–115°) was 114–115°, showing no depression.

(*b*) *Addition initiated by ultraviolet light.* A mixture of 3.00 g. (31.8 mmoles) of norbornene and 6.06 g. (31.8 mmoles) of *p*-toluenesulfonyl chloride was prepared in a 125-ml. Vycor flask equipped with a thermometer, magnetic stirrer, and reflux condenser. The flask was irradiated for 1 hr. with ultraviolet light from a Mazda AH-4 lamp placed about 2 cm. away from the flask. Heat from the lamp was sufficient to maintain the temperature inside the flask at 120–130°. The reaction mixture was cooled overnight, and the resulting viscous oil was subjected to vacuum distillation at room temperature and 0.2 mm. pressure, to recover 0.81 g. (27%) of unchanged norbornene in a trap cooled with Dry Ice–isopropyl alcohol. The flask was heated under vacuum to remove most of the starting *p*-toluenesulfonyl chloride, which solidified in the upper part of the flask. The crude solid remaining in the bottom of the flask weighed 6.12 g. and melted at 85–97°, for a crude yield of 67.5% (92.5% based on unrecovered norbornene). One recrystallization from methanol gave 4.48 g. of a white solid melting at 109–112°, for a yield of 49.5% (67.7% based on unrecovered norbornene). One more recrystallization from methanol gave pure III, m.p. 114–115°.

Proof of free-radical nature of addition reaction. A mixture of 1.00 g. (10.6 mmoles) of norbornene and 2.02 g. (10.6 mmoles) of *p*-toluenesulfonyl chloride was prepared in a 20-ml. flask equipped with a thermometer and a reflux condenser. The temperature of the flask was maintained at 75–80° for 17 hr., after which the flask was cooled to room temperature and subjected to vacuum distillation for 1 hr. at room temperature and 0.2 mm. pressure, during which time the unchanged norbornene was collected in a trap cooled in Dry Ice–isopropyl alcohol. The trap was protected from moisture by a calcium chloride drying tube. The recovery of unchanged norbornene was 0.38 g. (38%).

Another experiment was conducted under exactly similar conditions, except that 160 mg. (1.0 mmole) of benzoyl peroxide was added to the reaction mixture before heating. In this experiment the recovery of unchanged norbornene was 0.11 g. (11%).

When a third experiment was conducted under the same conditions, but with 211 mg. (1.0 mmole) of trinitrobenzene added and no peroxide, the recovery of unchanged norbornene was 0.73 g. (73%).

The conditions under which the starting norbornene was recovered were identical in all three experiments.

Addition of p-toluenesulfonyl chloride to aldrin. A mixture of 1.82 g. (5.00 mmoles) of aldrin (II), m.p. 99–101°, 953 mg. (5.00 mmoles) of *p*-toluenesulfonyl chloride, and 61 mg. (0.5 mmole) of di-*tert*-butyl peroxide was sealed into a glass combustion tube of 10-mm. inside diameter. The tube was heated at 152–155° for a total of 24 hr. The tube was cooled to room temperature and opened, and some positive pressure inside from hydrogen chloride gas was noted. The reaction mixture inside the tube was a black glassy material. It was dissolved in glacial acetic acid and treated twice with activated charcoal (Darco G-60). Then most of the acetic acid was evaporated under a jet of dry air, and the white solid which separated was collected on a sintered glass filter funnel. After drying, the yield of this solid was 0.88 g. (32%), melting at 215–245°. Two recrystallizations from carbon tetrachloride yielded 0.36 g. (13%) of white solid, m.p. 265–268°. The infrared spectrum of this material was identical with that of a known sample[6] of IV and a mixed melting point was 265–268°, showing no depression.

In another experiment in which 1.00 g. (2.74 mmoles) of aldrin, 522 mg. (2.74 mmoles) of *p*-toluenesulfonyl chloride, and 43 mg. (0.27 mmole) of benzoyl peroxide was heated in 20 ml. of refluxing chlorobenzene for 24 hr., no product was obtained. Instead, 0.95 g. (95%) of impure aldrin was recovered which melted at 50–60°. Two recrystallizations raised the melting point to 95–98°, and a mixed melting point with pure aldrin showed no depression.

Addition of p-toluenesulfonyl chloride to norbornadiene. (*a*) *Peroxide-catalyzed addition.* A mixture of 2.00 g. (21.6 mmoles) of norbornadiene and 2.05 g. (10.8 mmoles) of *p*-toluenesulfonyl chloride was prepared in a 20-ml. flask equipped with a thermometer and reflux condenser, and 160 mg. (1.0 mmole) of benzoyl peroxide was added. The flask was heated at 75–82° for 24 hr. A white paste was obtained, which was dissolved in 10 ml. of dry chloroform and chromatographed on 60 g. of activated alumina. Elution with petroleum ether (b.p. 60–80°) yielded 988 mg. of a colorless oil with the odor of norbornadiene. This material was not investigated further. A total of 1.47 g. (47%) of white solid was eluted in thirteen 50-ml. fractions with a 10% solution of ethyl acetate in petroleum ether (b.p. 60–80°). The melting points of these fractions ranged from 100–125° to 146–152°. They were recrystallized separately to give a total of 0.95 g. of solid melting at 148–152° plus 0.33 g. of a solid melting at 152–154°. The fractions were combined to give a total yield of 1.28 g. (42%) of VII which melted at 154–155° after two more recrystallizations from methanol.

Anal. Calcd. for $C_{14}H_{15}ClO_2$: C, 59.46; H, 5.35. Found: C, 59.47; H, 5.28.

The infrared spectrum of VII showed strong absorption peaks at 11.85, 12.2, and 12.4 μ. Absorption in this region is characteristic of the nortricyclene structure.[17,18,19] Unfortunately this region overlaps that for *para* disubstituted benzenes.[20,21] A number of compounds containing a *p*-tolyl group have been examined in this laboratory, and these consistently appear to show a *single* strong absorption peak in the 12.2–12.4 μ region unless some other function is present which could be responsible for additional peaks. The infrared spectrum also showed a strong peak at 8.75 μ and a series of peaks in the 7.7 μ region, which can be attributed to the sulfone group.[21,22]

---

(17) J. D. Roberts, E. R. Trumbull, W. Bennett, and R. Armstrong, *J. Am. Chem. Soc.*, 72, 3116 (1950).

(18) R. A. Alexander, N. C. Baenziger, C. Carpenter, and J. R. Doyle, *J. Am. Chem. Soc.*, 82, 535 (1960).

(19) H. Hart and R. A. Martin, *J. Org. Chem.*, 24, 1267 (1959).

(20) R. B. Barnes, R. C. Gore, R. W. Stafford, and V. Z. Williams, *Anal. Chem.*, 20, 404 (1948).

(21) J. Cymerman and J. B. Willis, *J. Chem. Soc.*, 1332 (1951).

(*b*) *Addition initiated by ultraviolet light.* A stirred solution of 1.00 g. (10.8 mmoles) of norbornadiene and 2.05 g. (10.8 mmoles) of *p*-toluenesulfonyl chloride in 50 ml. of cyclohexane was irradiated for 24 hr. in a Vycor flask, using the ultraviolet light from a Mazda AH-4 lamp. The cyclohexane was removed by evaporation and a pasty residue was obtained, which was chromatographed on 60 g. of activated alumina. Elution with 20% ethyl acetate in petroleum ether (b.p. 60–80°) gave a total of 1.62 g. (53.2%) of a white solid, m.p. 100–125°. Two recrystallizations from methanol gave X melting at 151.5–153.5°.

(22) C. Barnard, J. M. Fabian, and H. P. Koch, *J. Chem. Soc.*, 2442 (1949).

Acknowledgment. The authors are indebted to the Shell Development Co. and the Dow Chemical Co. for fellowships in support of this work. They are also indebted to Professor Philip S. Skell for drawing this reaction of sulfonyl halides to their attention. Norbornene was obtained through the generosity of the Polychemicals Department of E. I. du Pont de Nemours & Co., Inc., and norbornadiene and aldrin through that of the Shell Chemical Co.

BOULDER, COLO.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, CASE INSTITUTE OF TECHNOLOGY]

Reactions of Free Radicals with Olefins. Reactions of *t*-Butoxy and *t*-Butyl Peroxy Radicals with 4-Vinylcyclohexene[1]

J. REID SHELTON AND J. NEIL HENDERSON[2]

Received August 1, 1960

Abstraction of hydrogen (rather than addition) is demonstrated as a preliminary step in the formation of *t*-butyl vinylcyclohexenyl peroxides from 4-vinylcyclohexene with *t*-butyl hydroperoxide in the presence of cobalt ions. The olefin is shown to be peroxidated mainly in the 6-position, with minor proportions peroxidated in the 3-position and 4-position. The ratio of isomers is taken as evidence also for a strong steric effect.

Slow photolysis of di-*t*-butyl peroxide in 4-vinylcyclohexene at 40° results in the formation of four times as much dehydrodimer as any other olefin-derived product, showing that the *t*-butoxy radical prefers abstraction under these conditions. In contrast, there is as much *t*-butoxylation as dehydrodimerization of the olefin when di-*t*-butyl peroxide is decomposed at 120° in 4-vinylcyclohexene in the presence of cupric ion. These variations may be explained by differences in the nature and relative concentrations of free radicals produced.

The work described in this paper is a part of a continuing study of the reactions of free radicals with olefins. The objective of the program is to provide additional information regarding the relative reactivity of different types of free radicals with a variety of unsaturated compounds, and to determine the point of attack and the nature of the products formed. The study is particularly aimed at providing information with model compounds which relates to free-radical processes involved in polymerization, in certain cross linking reactions, and in both thermal and oxidative degradation of polymers.

In hydroperoxide decompositions induced by cobalt ions or similar metal ions, the work of the late Professor M. S. Kharasch and his colleagues[3] suggested the presence of both peralkoxy and alkoxy radicals: for example, in butadiene, *t*-butyl hydroperoxide decomposed to give *t*-$C_4H_9OOCH_2$-$CH{=}CHCH_2OOt$-C_4H_9 and isomeric peroxide along with about one-half equivalent of *t*-butyl alcohol. The roles of these radical species were originally misunderstood. It was proposed that peroxidation of olefins with a hydroperoxide (Equation 1) proceeded by addition of the peroxy radical to the

$$2\,ROOH + R'H \longrightarrow ROOR' + ROH + H_2O \quad (1)$$

double bond, followed by loss of a hydrogen atom to give, for example, 1-peralkoxyoctene-2 from octene-1. However, the untenability of this mechanism has recently been acknowledged.[4] The peroxidation of such compounds as cumene and cyclohexanone[4,5] showed that hydrogen abstraction must occur in these cases because an initial addition of $RO_2\cdot$ was not a reasonable possibility. Reexamination of the octene-1 example disclosed the presence of 3-peralkoxyoctene-1, certainly a product of hydrogen abstraction rather than of peroxy radical addition.

We had meanwhile applied the peroxidation technique to 4-vinylcyclohexene and independently concluded that the reaction must involve initial hydrogen abstraction in this case also.

The experimental work reported here involves the reaction of *t*-butoxy and *t*-butyl peroxy radicals with 4-vinylcyclohexene. This olefin provides both

(1) Presented before the Division of Organic Chemistry, 137th Meeting, American Chemical Society, Cleveland, April 1960.

(2) Present address: Research Division, Goodyear Tire and Rubber Company, Akron, Ohio.

(3) M. S. Kharasch, P. Pauson, and W. Nudenberg, *J. Org. Chem.*, 18, 322 (1953).

(4) M. S. Kharasch and A. Fono, *J. Org. Chem.*, 24, 72 (1959).

(5) M. S. Kharasch and A. Fono, *J. Org. Chem.*, 23, 324 (1958).

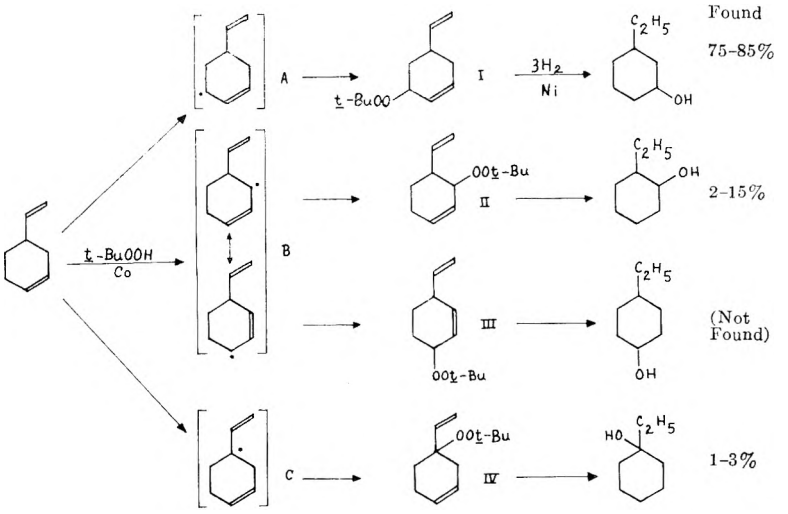


Fig. 1. Products by a hydrogen-abstraction mechanism in the *t*-butyl peroxidation of 4-vinylcyclohexene and subsequent hydrogenation

vinyl and internal unsaturation together with possible sites for hydrogen abstract from *alpha* methylene groups. The free radicals were generated by decomposition of *t*-butyl hydroperoxide and *t*-butyl peroxide as described later.

DISCUSSION

The *t*-butyl peroxidation was carried out in an excess of 4-vinylcyclohexene so as to favor monosubstitution. After the resulting peroxides were fully hydrogenated to the corresponding ethylcyclohexanols, infrared examination and preparation of derivatives showed that peroxidation had occurred predominantly in the 6-position of 4-vinylcyclohexene and that a minor proportion was peroxidated in the 3-position as illustrated in Fig. 1. These are the two positions *alpha* to the internal double bond. No 1-ethylcyclohexanol was isolated, but infrared spectra indicated that a trace quantity was present. Therefore, it may also be concluded that peroxidation occurred rarely in the 4-position of 4-vinylcyclohexene, although this is a tertiary carbon and alpha to the vinyl double bond. There was no evidence of peroxidation in the 1-position of 4-vinylcyclohexene, which might have been expected to occur *via* resonance stabilization of the radical, B, as shown in Fig. 1.

The occurrence of the peroxides I and II in the products shows that the first step of the peroxidation was hydrogen abstraction rather than addition to a double bond. The isomer ratios indicate considerable selectivity in the over-all substitution and probably in the hydrogen abstraction.

A likely agent for hydrogen abstraction in peroxidation is the alkoxy radical. Using *t*-butyl hydroperoxide with cyclohexene and octene-1, Kharasch and co-workers obtained at least as much *t*-butyl alcohol on a molar basis as peroxide,[3] and the same is true in *t*-butyl peroxidation of 4-vinylcyclohexene. While the formation of an equivalent amount of *t*-butyl alcohol does not prove that the abstraction was performed by *t*-butoxy radical, it certainly supports that interpretation.

Farmer and Moore[6] showed that cyclohexene yielded cyclohexene dehydrodimer when heated with di-*t*-butyl peroxide at 140°, showing that the *t*-butoxy radical does indeed abstract hydrogen from cyclohexene. We find that when a solution of di-*t*-butyl peroxide and 4-vinylcyclohexene at about 40° under nitrogen is irradiated, (2537 Å), at least 80% of the very small conversion of olefin results in the formation of vinylcyclohexene dehydrodimer, confirming the ability of *t*-butoxy to abstract hydrogen from this olefin, and demonstrating its reluctance to add to either of the double bonds under these conditions.

The *t*-butyl peroxidation of 4-vinylcyclohexene may be summarized as in Equation 2.

$$2\ t\text{-}C_4H_9OOH + C_8H_{12} \xrightarrow[\text{cobalt ions}]{45°-55°} t\text{-}C_4H_9OOC_8H_{11} + t\text{-}C_4H_9OH + H_2O \quad (2)$$

If this reaction were to have proceeded by the addition of *t*-butyl peroxy radical to 4-vinylcyclohexene, a major product would have been an unsaturated peroxide lacking a vinyl group, as the addition would have occurred preferentially at the vinyl double bond.[7] One evidence for hydrogen abstraction is therefore the fact that the product was mainly a mixture of doubly unsaturated peroxides which reduced to ethylcyclohexanols rather than to cyclohexylethanol. A second evidence is the presence of 2-ethylcyclohexanol among the reduction products (Fig. 1) which could not have arisen from an addition to 4-vinylcyclohexene. Finally, addition to the internal double bond followed by loss of hydrogen, should have afforded approxi-

(6) E. H. Farmer and C. G. Moore, *J. Chem. Soc.*, 131 (1951).

(7) M. S. Kharasch and M. Sage, *J. Org. Chem.*, 14, 537 (1949).

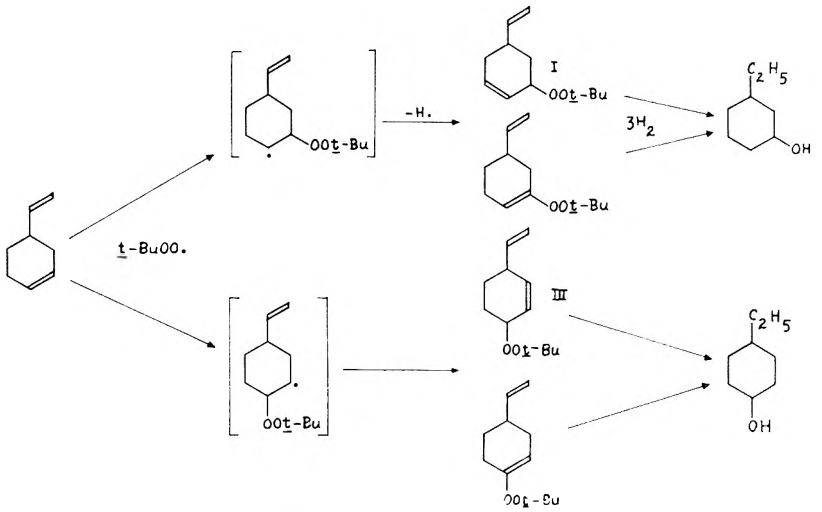


Fig. 2. Supposed products of *t*-butyl peroxy radical added to the internal double bond of 4-vinylcyclohexene

mately equal amounts (after hydrogenation) of 3-ethylcyclohexanol and 4-ethylcyclohexanol, as shown in Fig. 2. Actually, the amounts of these alcohols were not equal. The 3-ethylcyclohexanols accounted for most of the product and no infrared peaks characteristic of 4-ethylcyclohexanol were observed. By the abstraction route also (Fig. 1) both alcohols could be formed but they would not be expected to be in equal amount. For these reasons, the peroxidation of 4-vinylcyclohexene is concluded to proceed *via* abstraction of hydrogen to produce vinylcyclohexenyl radicals. Induced decomposition of the hydroperoxide by reaction with free radicals would merely produce more $RO_2\cdot$ which could in turn abstract hydrogen to reform the hydroperoxide and a free radical. Consequently, the observed vinylcyclohexenyl peroxide may be considered to result from a coupling of the appropriate free radicals:

$$2\,ROOH \xrightarrow[\text{cobalt ions}]{} RO\cdot + RO_2\cdot + H_2O \quad (3)$$

$$RO\cdot + R'H \longrightarrow ROH + R'\cdot \quad (4)$$

$$RO_2\cdot + R'\cdot \longrightarrow RO_2R' \quad (5)$$

Kharasch and Fono[4,5] have recently postulated in detail further reaction steps to account for substitutive peroxidations by the action of alkoxy and peralkoxy radicals produced by hydroperoxide decomposition induced by ions of metals such as cobalt. The substituted product R'OOR is attributed in the later papers to reaction of the metallic ion with a hydrogen-bonded complex:

$$R'\cdot + ROOH \longrightarrow R'\cdot H{:}OOR \quad (6)$$

$$Me^{++} + R'\cdot H{:}OOR \longrightarrow R'OOR + Me^{+} + H^{+} \quad (7)$$

An alternative interpretation is available which accounts for the formation of peroxides, ethers, and dehydrodimers under varying conditions. In substitutive peroxidations (where both RO· and $RO_2\cdot$ are present) the peroxide R'OOR could be formed by initial abstraction of hydrogen by RO· and coupling of ROO· with R'· as in reactions 4 and 5. In alkoxylations with ROOR, (where $RO_2\cdot$ is absent) ROR' could be formed similarly by coupling of RO· with R'· to produce ROR', when the concentration of RO· is sufficiently large. Where RO· is in very small concentration, as in the slow photolysis of di-*t*-butyl peroxide in 4-vinylcyclohexene, the coupling of R'· is favored, to give R'_2, in this case the dehydrodimer of vinylcyclohexene. The much more rapid, copper-induced decomposition of the same mixture at 120° gave a mixture of ROR', R'_2, and tars:

$$ROOR + R'H \xrightarrow[CuCl_2]{} R'_2 + ROR' + ROH, \text{ etc.} \quad (8)$$

The method used to accomplish the alkoxylation of 4-vinylcyclohexene was adapted from a preliminary communication of Kharasch and Fono[5] on radical reactions modified by the presence of copper salts. In a more complete recent report,[8] these authors suggest that unstable copper organic complexes are intermediates. However, they stress that decompositions of peroxides and related compounds are appreciably faster when copper induced, a circumstance which leads us to suppose that concentration effects resulting from different rates of radical generation may also play a part in the modifications which are observed.

In view of the recent report of Brill[9] that 4-vinylcyclohexene is oxidized primarily (though probably not exclusively) to 4-hydroperoxy-4-vinylcyclohexene, the selective avoidance of this position in peroxidation, and the preferred orientation toward the 6-position, is particularly striking. It suggests the operation of a strong steric factor. The availability of only one tertiary hydrogen at the 4-position as compared to two abstractable hydrogens at each of the methylenes in the 3- and

(8) M. S. Kharasch and A. Fono, *J. Org. Chem.*, **24**, 606 (1959).

(9) W. F. Brill, *J. Org. Chem.*, **24**, 257 (1959).

6-positions would favor reaction at these positions as observed in our work.

The effect of polar factors should also be considered as alkoxy radicals and peralkoxy radicals should be strongly electron-seeking, and this characteristic could affect their selectivity.[1c] The greater electronegativity of $RO_2\cdot$ would tend to make it less selective than RO·. The variations in electron density at the carbon-hydrogen bonds of 4-vinylcyclohexene is probably small, however, and the fact that initiation by molecular oxygen and propagation by $RO_2\cdot$ gives a different selectivity from that of RO· again lends more weight to a steric argument.

It nevertheless seems to us that in understanding reactions of alkoxy and peralkoxy radicals, their electrophilic nature should be considered. The observations of McBay and colleagues[11] regarding the competitive coupling of radicals are pertinent: whether it be because of field repulsion of like substituents or the electron availability at radical sites (or both), coupling will tend to occur between the unlike radicals. If we may assume that with respect to electrophilic character, $RO_2^{2}\cdot > RO\cdot >> R'\cdot$, then it is to be expected that in the presence of comparable concentrations of all three radicals, in systems where other reactions are minimized, the major product will be RO_2R' and not ROR' or R'R'. Similarly, ROR' will form when $RO_2\cdot$ is absent, and R'R' when both $RO_2\cdot$ and RO· are in short supply.

SUMMARY

Hydrogen abstraction (rather then radical addition) appears to be the initial step leading to the formation of peroxides and other substitution products in the reactions reported here. The marked selectivity in 4-vinylcyclohexene peroxidation may be attributed to steric effects. 4-Vinylcyclohexene was alkoxylated with di-*t*-butyl peroxide in the presence of a cupric salt, but slow photolysis (in the absence of cupric ion) produced only the dehydrodimer. The difference may be attributed to the more rapid generation of radicals occurring in the metal-catalyzed decomposition of the peroxide. In both alkoxylations and peroxidations it is proposed that variations in the relative concentrations of the free radicals, together with some contribution from polar and steric factors, provide an adequate explanation of the observed behavior.

EXPERIMENTAL

Reagents. The 4-vinylcyclohexene was supplied by Phillips Petroleum Company, pure grade, 99 mole percent minimum purity. It was distilled at reduced pressure in a 20-plate Oldershaw column under nitrogen, within 48 hr. of use: n_D^{20}, 1.4635. The *t*-butyl hydroperoxide was of 99% purity,[12] obtained from Lucidol reagent by fractionation at reduced pressure in the Oldershaw column. The di-*t*-butyl peroxide was Lucidol reagent, redistilled, n_D^{20}, 1.3877. Cobalt naphthenate was used in the form of Nuodex cobalt catalyst 6% cobalt.

Reaction of t-butyl hydroperoxide with 4-vinylcyclohexene. The reaction was carried out according to the method of Kharasch and co-workers[3,4] in either of two ways:

A. The cobalt catalyst was added at intervals to the magnetically stirred mixture, for example, 0.8 mole of *t*-butyl hydroperoxide in 2.9 moles 4-vinylcyclohexene under nitrogen. Total catalyst concentration was varied from 0.2 mole percent based on initial hydroperoxide, to 2 mole percent. The larger amount of catalyst led to a higher proportion of tarry material, accounting at the maximum for as much olefin as was monoperoxidated. With 0.2 mole percent of catalyst, the amount of higher-boiling materials accounted for less than 60% as much olefin as was monoperoxidated. The yield of *t*-butyl vinylcyclohexenyl peroxides was 51–52% in either case, based on initial *t*-butyl hydroperoxide.

B. The cobalt catalyst (0.1 mole percent) was added all at once, by capsizing through magnetic stirring a floating glass boat containing the catalyst, under a nitrogen atmosphere. The continuously stirred reaction mixture, for example, 0.59 mole of *t*-butyl hydroperoxide in 3.8 moles 4-vinylcyclohexene was then allowed to warm and was maintained at 50–55° for 3 hr. by external heating. In this case the yield of *t*-butyl vinylcyclohexenyl peroxides was 0.164 mole, 56% of the theoretical yield based on the initial *t*-butyl hydroperoxide. Higher-boiling and tarry material amounted to 7.9 g., accounting for less than 40% as much olefin as was peroxidated.

In either method, low-boiling materials were removed by distillation at reduced pressure. The *t*-butyl vinylcyclohexenyl peroxide mixture was separated and purified by vacuum distillation; or alternatively, the entire peroxide mixture after removal of low-boiling materials was hydrogenated over Raney nickel.

Identification of t-butyl vinylcyclohexenyl peroxides. Infrared spectra showed absorption indicating the retention of vinylcyclohexenyl unsaturation—*i.e.*, vinyl and *cis*-internal double bonds respectively: 3.25, 3.30, 5.5, 6.08, 10.06, 11.0, 15.2; 3.30, 6.1, 13.6 μ. The presence of the *t*-butyl group was indicated primarily by the absorptions at 7.21, 7.33 μ; carbon-oxygen bond by strong absorption at 8.36 μ. A band at 11.4 μ was attributed to O—O stretching. Physical properties were consistent with a mixture of monovinylcyclohexenyl compounds: b.p. 26–33° at 0.02 mm; n_D^{20}, 1.461–1.463; pungent odor.

Anal. Calcd. for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27; mol. wt., 196. Found[13]; C, 73.4; H, 10.2; mol. wt., 152 (Rast).

Decomposition is presumed to have lowered the molecular weight. Peroxide fractions became contaminated, on standing, with conjugated ketone (5.93 μ) and hydroxyl (2.9 μ) presumed to be *t*-butyl alcohol.

Over reduced platinum oxide (Adam's catalyst) in ethanol[14] at room temperature and atmospheric pressure of hydrogen, 3.62 g. of *t*-butyl vinylcyclohexenyl peroxides absorbed 959 ml. of hydrogen (S.T.P.) or 2.3 moles per mole of peroxide. From the reaction mixture both *t*-butyl ethylcyclohexyl peroxide (2 g.) and a mixture of ethylcyclohexanols (0.6 g.) were isolated, confirming partial hydrogenation of the peroxide bond. The *t*-butyl ethylcyclohexyl peroxide (boiling 49–50° at 0.7 mm; n_D^{20}, 1.4405) was identified by its infrared spectrum, analysis, and further reduction.

(10) E. C. Kooyman, R. Van Helden, and A. F. Bickel, *Kon. Ned. Akad, Weten*, **46**, 75 (1959).

(11) H. C. McBay, O. Tucker, and P. T. Groves, *J. Org. Chem.*, **24**, 536 (1959).

(12) Iodometric analysis: V. R. Kokatnur and M. Jelling, *J. Am. Chem. Soc.*, **63**, 1432 (1941).

(13) Elemental analyses and molecular weight determinations by Drs. Weiler and Strauss, Oxford, England.

(14) R. P. Linstead, J. A. Elvidge, and M. Whalley, *A Course in Modern Techniques of Organic Chemistry*, Butterworth's, London, 1955, p. 84.

Absorptions due to unsaturation are absent in its spectrum; the *t*-butyl, C—O and O—O bonds remain.

Anal. Calcd. for $C_{12}H_{24}O$: C, 71.95; H, 12.08; mol. wt. 200. Found[14]: C, 72.12; H, 12.09; mol. wt., 236.

Reduced by a sodium dispersion in xylene,[15] 1.25 g. of *t*-butyl ethylcyclohexyl peroxide yielded 0.25 g. of *t*-butyl alcohol and 0.6 g. of mixed ethylcyclohexanols.

Over Raney nickel[16] in ethanol at room temperature and 4 atm. of hydrogen in the Parr hydrogenation apparatus, 22.7 g. of *t*-butyl vinylcyclohexenyl peroxide produced a pressure drop of 28 p.s.i. Under these conditions the theoretical pressure drop was 27 p.s.i. for 3 moles of hydrogen per mole peroxide.

Identification of ethylcyclohexanols. The individual ethylcyclohexanols in fractionally distilled hydrogenation mixtures were identified through preparation of alcohol derivatives by standard procedures, and by infrared analysis. A similar infrared analysis of a mixture of ethylcyclohexanols has been reported.[17] Authentic 1-ethylcyclohexanol in crystalline form was supplied by Dr. K. W. Scott of Goodyear Tire and Rubber Co.; authentic 2-ethylcyclohexanols and 3-ethylcyclohexanols, respectively, were prepared by hydrogenation of 2-ethylphenol and 3-ethylphenol in ethanol over Raney nickel[16] at 150° in hydrogen at 1400 p.s.i., under the direction of Dr. A. P. Arnold at Cleveland Industrial Research, Inc. 4-Ethylcyclohexanols were prepared similarly from 4-ethylphenol by Dr. T. P. Yen and S. T. Quigley at Goodyear Tire and Rubber Company. The hydrogenation mixtures were fractionated by distillation at reduced pressures but the pure isomers were not generally separable in this manner. All seven of the isomeric ethylcyclohexanols were thus available pure or in *cis-trans* mixtures to enable comparisons with authentic derivatives and spectra. The purity of each ethylphenol isomer, redistilled Eastman Organic Chemicals 4514, P4520, and P4503, was assured by infrared examination.

Ethylcyclohexanol mixtures from hydrogenation of the peroxides were also oxidized to the corresponding ketones, using chromic acid.[18] Derivatives were prepared and isolated: *cis*-3-ethylcyclohexyl phenylurethan, m.p., 100°.

Anal. Calcd. for $C_{15}H_{21}NO$: C, 72.8; H, 8.56; N, 5.67; Found[13]: C, 73.3; H, 8.45; N, 5.80;

cis, or *trans*-2-Ethylcyclohexyl naphthylurethan, m.p., 153.5° (range, two degrees).

Anal. Calcd. for $C_{19}H_{23}NO$: C, 76.7; H, 7.80; N, 4.71. Found: C, 77.2; H, 8.04; N, 4.62.

2,4-*D*initrophenylhydrazone, m.p., 126° .

Anal. Calcd. for $C_{14}H_{18}N_4O_4$: C, 54.9; H, 5.92; N, 18.29. Found: C, 55.0; H, 6.05; N, 18.15.

3-Ethylcyclohexanone semicarbazone, m.p., 161.5°.

Anal. Calcd. for $C_9H_{17}ON_3$: C, 58.9; H, 9.35. Found: C, 58.5; H, 9.28.

In each case the derivative when mixed with the corresponding authentic derivative failed to depress the melting point. (Melting points are not corrected.)

Using Perkin-Elmer spectrophotometers, Model 21 and/or Model 137, infrared spectra were made of all peroxide hydrogenation products, which were in all cases mixtures of ethyl cyclohexanols imperfectly separated by distillation and occassionally contaminated with ethylcyclohexanones and *t*-butyl ethylcyclohexyl peroxides. Semiquantitative estimates were made of the proportions of each isomer in each fraction by selecting the peaks having a minimum of interference from other isomers and assuming Beer's law to hold. As indicated in Fig. 1, considerable latitude is allowed for the error in this procedure. In the case of 2-ethylcyclohexanol *cis-trans* mixtures,[19] absorption at 11.37, 11.82, and 12.2 μ served to indicate the presence of 2-isomers, but each of these peaks occurs close to absorptions for 3-isomers, which are the major components in these solutions, so that our accuracy is probably poorest for 2-ethylcyclohexanols. Based on the 11.82 band, the proportion was estimated to be 5%. 1-Ethylcyclohexanol may be recognized by absorptions at 8.57, 8.90, 10.56, and 11.09 μ; based on the absorption at 8.57 μ, the concentration was calculated to be 2%. *trans*-3-Ethylcyclohexanol, the low-boiling isomer,[18,20] has characteristic absorptions, e.g., at 9.65, 9.86, 10.33, 11.66, 12.27 μ; *cis*-3-ethylcyclohexanol: 9.00, 9.53, 10.45, 11.92 μ. In *cis-trans* 3-ethylcyclohexanol mixtures the absorbance-concentration plots were linear at 11.92, 12.27 μ. using these, the proportion of *cis*-3-ethylcyclohexanol in all fractions of one peroxidation run was estimated to be 31%; *trans*-3-ethylcyclohexanol, 46%.

4-Ethylcyclohexanols have strong or moderate absorptions at 8.74, 10.10, 10.50, 11.15 μ, probably *cis*; and 9.17, 9.50, 10.36, 11.15 μ, probably *trans*. The peaks least likely to show interference from other components of these mixtures are those at 10.10, 10.50, 11,15 μ. In undiluted, hydrogenated product mixtures in 0.02 to 0.045-mm. infrared cells, none of these absorptions was detected unequivocally in any fraction. Carbonyl absorption at 5.84 μ persisted in the spectra of the hydrogenated products, lower-boiling fractions. Very small absorptions in these fractions near 7.45, 7.62, 10.35, and 11.55 μ were attributed to 3-ethylcyclohexanone.

Ethylcyclohexyl peroxides contribute few distinctive absorptions but the presence of peroxides is indicated in some runs by a broad band at 11.4 μ.

Mixtures of ethylcyclohexanols were not found to be separable on the gas chromatograph, using a two-foot column, silicone grease on celite, F and M Scientific Corp., Model 124. The carrier was helium gas at 50 ml. per minute. Column temperatures 115° and 140° were used.

Photolysis of di-t-butyl peroxide in 4-vinylcyclohexene. A magnetically stirred mixture of 300 g. of di-*t*-butyl peroxide and 180 g. of 4-vinylcyclohexene was irradiated 24 hr. with a quartz-jacketed 8 watt germicidal lamp (General Electric G8T5, 2537 Å) partially immersed in the solution, the entire system under a nitrogen atmosphere. Under these conditions the temperature of the mixture was maintained by the lamp at 39–40° without external heating or cooling. By distillation of the reaction mixture, under reduced pressure, *t*-butyl alcohol (about 3 g.), and unchanged di-*t*-butyl peroxide and 4-vinylcyclohexene were removed. The residue, 3.8 g, representing 2.1% conversion of the 4-vinylcyclohexene, was a slightly tarry liquid. Of this vinylcyclohexene-derived material, 3.0 g. (80%)[21] was separated by distillation (on redistillation, boiling at 59° at 0.12 mm.; n_D^{29}, 1.5190) and identified as vinylcyclohexene dehydrodimer. The infrared spectrum showed the presence of practically all of the absorptions characteristic of 4-vinylcyclohexene, the only marked exception being the moderately strong 4-vinylcyclohexene peak at 8.77 μ, (unassigned), absent in the dehydrodimer. A sample, 0.4695 g., absorbed 191 ml. hydrogen (S.T.P.; 4.0 moles hydrogen per mole) over Adam's catalyst at one atmosphere.

Anal. Calcd. for $C_{16}H_{22}$: C, 89.65; H, 10.35. Found[13]: C, 89.72; H, 10.38.

t-Butoxylation of 4-vinylcyclohexene with di-t-butyl peroxide.

(15) N. A. Miles and D. M. Surgenor, *J. Am. Chem. Soc.*, **68**, 205 (1946).

(16) H. Adkins, *Reactions of Hydrogen with Organic Compounds over Copper-Chromium Oxide and Nickel Catalysts*, The University of Wisconsin Press, 1937, p. 20.

(17) J. Hoffman and C. E. Boord, *J. Am. Chem. Soc.*, **78**, 4973 (1956).

(18) J. J. Lamneck and P. H. Wise, *J. Am. Chem. Soc.*, **76**, 5108 (1954).

(19) J. Entel, C. H. Rouf, and H. C. Howard, *J. Am. Chem. Soc.*, **73**, 4152 (1951).

(20) Assignment based on work with analogous compounds: E. L. Eliel, R. G. Haber, *J. Org. Chem.*, **23**, 2041 (1958). W. Huckel, M. Meier, E. Jordan, and W. Seeger, *Ann.*, **616**, 46 (1958).

(21) The remaining 20% was a higher-boiling tarry mixture.

A magnetically stirred mixture of 165 g. of 4-vinylcyclohexene, 36 g. of di-*t*-butyl peroxide and 0.3 g. of cupric chloride hydrate was gently refluxed 5 hr. under nitrogen, the pot temperature varying from 115–125°. The reaction vessel was fitted with a six-inch glass-helix-packed column and distilling head with controlled take-off. Effluent vapors were trapped and oxygen excluded by a liquid-nitrogen cooled trap and a mercury check-valve which also served to maintain the system pressure slightly above atmospheric pressure. During the course of the reaction, 27 g. of *t*-butyl alcohol and 7 g. of di-*t*-butyl peroxide were collected as distillate. After filtration of the mixture and fractionation of the filtrate, a further 0.5 g. of *t*-butyl alcohol was recovered and 2 g. of di-*t*-butyl peroxide; 110 g. of 4-vinylcyclohexene was recovered. Identification of products was not complete but 4 g. of *t*-butyl vinylcyclohexenyl ether (boiling 30° at 0.2 mm.; n_D^{25}, 1.462) and 4 g. of vinylcyclohexene dehydrodimer were isolated. The infrared spectrum of the *t*-butyl vinylcyclohexenyl ether contains the major olefinic absorptions of 4-vinylcyclohexene; the absorptions at 7.21 and 7.34 μ, assigned to *t*-butyl; a strong band at 8.40 μ, C—O stretching; and a very strong, broad band at 9.4 μ, typical of ethers. A 0.36-g. sample absorbed 85 ml. hydrogen (S.T.P.; 2.0 moles hydrogen per mole) over Adam's catalyst in ethanol at one atmosphere at room temperature.

Anal. Calcd. for $C_{12}H_{20}O$: C, 79.9; H, 11.2; mol. wt., 180. Found[13]: C, 78.4; H, 11.2; mol. wt., 192. Subsequent gas chromatographic analysis showed the presence of two as yet unrecognized impurities, totalling possibly 7% of the sample.

Acknowledgment. The authors wish to acknowledge the contribution of Dr. Lieng-huang Lee (Present address: Dow Chemical Company), who helped to establish the direction of this study and began the experimental work. This paper is based on the Ph.D. thesis of J. Neil Henderson and is a part of a research program supported by The Goodyear Tire and Rubber Co.

CLEVELAND 6, OHIO

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

The Structure of 2,6-Dibenzalcyclohexanone Dimer

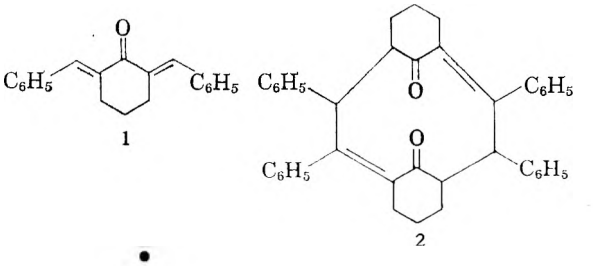
HERBERT O. HOUSE AND ALFRED G. HORTMANN

Received November 21, 1960

A solution of 2,6-dibenzalcyclohexanone in boiling toluene is converted to an equilibrium mixture of the starting ketone and its dimer. Subsequent transformations have established the structure 9 for this dimer.

Solutions of 2,6-dibenzalcyclohexanone (1) in boiling acetic anhydride, acetic acid benzene and ethanol have been reported[1] to yield a colorless dimer, m.p. 187–188°. The dimer was reported[1] to exhibit an ultraviolet maximum at 292 mμ (ϵ 42,500) with infrared bands at 1695, 1608, 754, and 697 cm.$^{-1}$ and to form a dioxime, m.p. 197–198°, and a tetrahydro derivative, m.p. 217–218°. From these observations, as well as the failure to isolate benzoic acid from a permanganate oxidation, the structure II was tentatively suggested for this dimer.

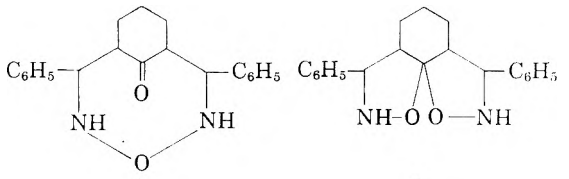
As it was not apparent why the reaction conditions described should convert the unsaturated ketone 1 to structure 2 or to any other dimer containing two carbonyl groups,[2] the formation and constitution of the dimer have been reinvestigated. Our attempts to prepare the dimer by refluxing an ethanol solution of 1 for 120 hours, a process reported to form the dimer in 90% yield, were uniformly unrewarding. In one instance in which an ethanol solution of 17.7 g. of the dimer had been refluxed for 121 hours, chromatography of the mother liquors remaining after separation of the starting material afforded 10 mg. of the crude dimer, m.p. 184–187°. However, the use of the higher-boiling solvents acetic anhydride, bromobenzene and toluene permitted formation of the dimer in reasonable yield. Use of boiling toluene with a reaction period of two days was found most convenient and permitted the isolation of the dimer, m.p. 192–193° dec., in 21% yield. The dimerization proceeded equally well when the reaction mixture was protected from light indicating that the dimerization was not a photochemical transformation. After a solution of the dimer in bromobenzene had been refluxed for twenty hours, the pure, monomeric unsaturated ketone 1 was isolated in 60% yield. Solutions of the ketone 1 and the dimer in boiling toluene were heated until equilibrium was established. In these toluene solutions, containing the equivalent of 0.30*M* 2,6-dibenzalcyclohexanone (1), equilibrium was established when 50–55% of the dimer was present.



(1) (a) P. Y. Yeh, *J. Taiwan Pharm. Assoc.*, **5**, 2 (1953); (b) P. Y. Yeh, C. T. Chen, S. Y. Ro, and C. H. Wang, *J. Am. Chem. Soc.*, **77**, 3415 (1955).

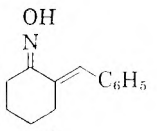
(2) Although the formation of photodimers containing cyclobutane rings is well known [A. Mustafa, *Chem. Revs.*, **51**, 1 (1952)], there was no indication (ref. 1) that light was required to transform the ketone 1 to its dimer.

The spectra of our product exhibited the features previous noted[1] with an ultraviolet maximum at 293 mμ (ε 43,500) and infrared absorption at 1685 cm.$^{-1}$ but no band in the 3 μ region attributable to a hydroxyl function. Since the previously reported[1] dimer dioxime, m.p. 197–198°, had been obtained in poor yield after a long reaction period and the reported analytical values (C, 82.65; H, 6.34) did not agree with the values calculated for the molecular formula $C_{40}H_{38}N_2O_2$ (C, 83.01; H, 6.62), we were led to consider other structures for this derivative. The reported[3,4] reaction of 2,6-dibenzalcyclohexanone (**1**) with hydroxylamine to form a substance $C_{20}H_{22}N_2O_2$, m.p. 199–200° dec., suggested that the reported[1] dimer dioxime may have been the substance $C_{20}H_{22}N_2O_2$ formed by partial dissociation of the dimer to 2,6-dibenzalcyclohexanone (**1**) followed by reaction with hydroxylamine. The substance $C_{20}H_{22}N_2O_2$, which has been formulated as **3**[3] or **4**[4], exhibits an ultraviolet maximum at 267 mμ (ε 15,500) with broad infrared absorption at 3300 cm.$^{-1}$ as well as a weak band at 1600 cm.$^{-1}$ and, consequently, cannot have either structure **3** or **4**. The close resemblance of the ultraviolet spectrum of the substance $C_{20}H_{22}N_2O_2$ to the spectrum of 2-benzalcyclohexanone oxime (**5**), λ_{max} 272 mμ (ε 15,100), permits the substance $C_{20}H_{22}N_2O_2$ to be assigned either structure **6** or **7**, structure **6** being more probable.

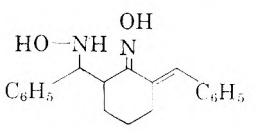


3

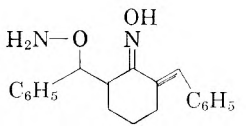
4



5



6



7

Reaction of the dimer with hydroxylamine in either ethanol or pyridine afforded a product, m.p. 198–199.5° dec., which proved not to be identical with the 2,6-benzalcyclohexanone-hydroxylamine product **6**, but rather had the composition $C_{40}H_{37}NO_2$ corresponding to the monoxime of the dimer. This monoxime has an ultraviolet maximum at 287 mμ (ε 31,500) with broad infrared absorption at 3350 cm.$^{-1}$ as well as weak bands at 1640, 1615 and 1600 cm.$^{-1}$ The infrared spectrum lacks absorption in the 6μ region attributable to a carbonyl function indicating that the dimer is a monocarbonyl compound rather than a dicarbonyl compound as had previously[1] been supposed.

We were unable to duplicate the previously reported[1] catalytic hydrogenation of an ethanol solution of the dimer over platinum to form a tetrahydro derivative because of the insolubility of the dimer in alcohol. However, hydrogenation of an ethyl acetate solution of the dimer over platinum resulted in a relatively rapid uptake of one equivalent of hydrogen followed by a slower absorption of additional hydrogen. As the mixtures obtained after absorption of more than one and one-half molar equivalents or more proved to be extremely complex, subsequent hydrogenation reactions were stopped after approximately one and one-half equivalents of hydrogen had been absorbed. From a representative experiment of this type the materials isolated were the unchanged dimer (14.8%), a dihydrodimer A, m.p. 161.5–163° (24.5%), a second crystalline form of dihydrodimer A, m.p. 173.5–175° (6.4%), and a dihydrodimer B, m.p. 212.5–214° dec. (4.9%). The dihydrodimer A has infrared absorption at 1720 cm.$^{-1}$ with no band in the 3μ region attributable to a hydroxyl function and an ultraviolet maximum at 293 mμ (ε 28,500); similarly, the dihydrodimer B has a band at 1718 cm.$^{-1}$ in the infrared with an ultraviolet maximum at 292 mμ (ε 23,600).

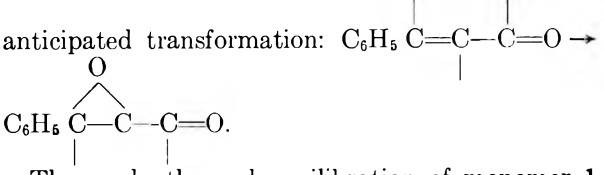
These data are compatible with the presence of the chromophores

$$C_6H_5C{=}CC{=}C \text{ and } C_6H_5C{=}CC{=}O$$

in the dimer and of the chromophores

$$C_6H_5C{=}CC{=}C \text{ and } C_6H_5CHCHC{=}O$$

in the dihydrodimers A and B.[5] Because of the similarity in analytical values for the dimer, the dihydrodimer, and the tetrahydrodimer, additional evidence for these assignments was obtained by reaction of the dimer with alkaline hydrogen peroxide in order to convert the α,β-unsaturated ketone present in the dimer to an α,β-epoxy ketone. The resulting epoxide of the dimer exhibits infrared absorption at 1725 cm.$^{-1}$ but no absorption in the 3 μ region attributable to a hydroxyl group and an ultraviolet maximum at 291 mμ (ε 27,800). These data are in accord with the anticipated transformation:

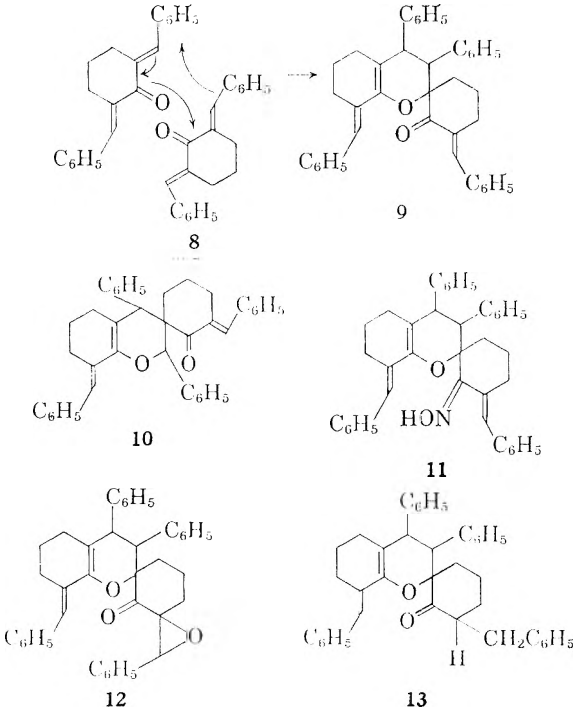


The ready thermal equilibration of monomer **1** and dimer in an inert medium is reasonably accommodated only if one supposes that the dimer is formed by a redistribution of multiple bonds in two molecules of the monomer. Utilizing this

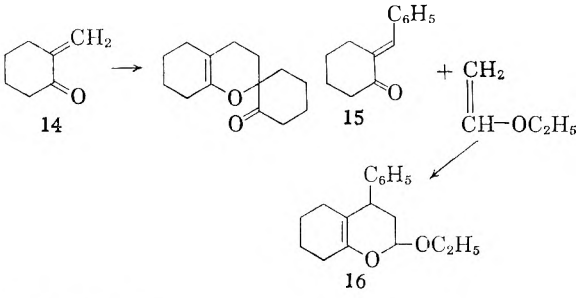
(3) R. Poggi and P. Saltini, *Gazz. chim. ital.*, **64**, 189 (1934).

(4) P. Dreyfuss, *Rend. seminario facolta sci. univ. Cagliari*, **4**, 55 (1934); *Chem. Zentr.*, **106 II**, 46 (1935); *Chem. Abstr.*, **30**, 6340 (1936).

principle (e.g., 8), only two rational structures 9 and 10 for the dimer can be drawn which contain the necessary functional groups. Either structure explains satisfactorily the remaining chemical transformations. For example, if the dimer has structure 9, the oxime would be 11, the epoxide would be 12, and the dihydrodimers A and B would be epimers of structure 13.



The dimerization of ketones possessing an adjacent vinylidene group to form dihydropyran derivatives is well known,[6] the dimerization of methylenecyclohexanone 14 being a typical example. However, we are not aware of previous examples of this type of dimerization of α,β-unsaturated ketones such as 1 which do not possess a terminal methylene group. However, the Diels-Alder reaction of 2-benzacyclohexanone (15)



with ethyl vinyl ether to form the dihydropyran 16 has been reported.[7]

Although previous analogies[6,7] suggest that the dimer should be formulated as structure 9 rather than 10, we considered additional evidence to be desirable. Accordingly, a solution of the dihydrodimer A 13 in boiling acetic acid was treated with zinc dust in an effort to reductively cleave the carbon-oxygen bond *alpha* to the carbonyl function in structure 13. However, the only compounds which could be isolated from this reaction were the unchanged dihydrodimer A and the dihydrodimer B. While these results confirm the epimeric nature of the two dihydrodimers, they provide no evidence to distinguish between structures 9 and 10 for the dimer. The question has been resolved by measuring the NMR spectrum of the dimer (Fig. 1). This spectrum (60 mc.) ex-

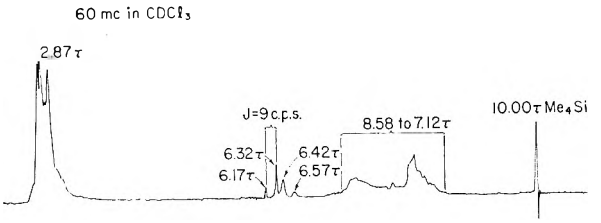


Fig. 1. NMR spectrum of 2,6-dibenzalcyclohexanone dimer

hibits a series of partially resolved peaks in the region of 2.87 τ (60% of total area) attributable to the twenty-two vinyl and aryl protons present in the dimer, a series of partially resolved peaks in the region 7.12 to 8.58 τ (35% of total area) attributable to the twelve methylene protons present in the dimer, and two doublets (5% of total area, J = 9 c.p.s.) located at 6.57 and 6.42 τ and at 6.32 and 6.17 τ attributable to the two benzylic protons present in the dimer. The splitting pattern observed is consistent with the presence of adjacent C_6H_5CH groupings as in structure 9 but not with the location of these groupings as shown in structure 10.

From the mode of formation of the dimer 9, its stereo chemistry may be ascertained by the application of Alder's rules (represented in structure 17) as previously discussed,[6c] as the ultraviolet absorption [λ_{max} 232 mμ (ϵ 15,600) and 323 mμ (ϵ 20,200)] of the starting 2,6-dibenzalcyclohexanone leaves no doubt that the material possesses the *trans, trans*-configuration[8] indicated in structure 1. Consequently, the stereochemistry of the dimer is represented by structure 18. It should be noted that the magnitude of the coupling con-

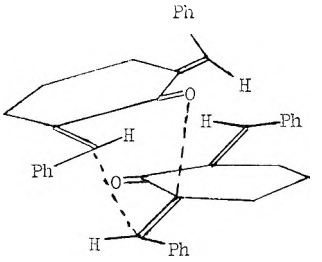
(5) The ultraviolet spectra of 2-benzalcyclohexanone [H. O. House and R. L. Wasson, *J. Am. Chem. Soc.*, 78, 4394 (1956)] and *trans*-1-phenyl-1,3-butadiene [E. A. Braude, E. R. H. Jones, and E. S. Stern, *J. Chem. Soc.*, 1087 (1947); O. Grummitt and F. J. Christoph, *J. Am. Chem. Soc.*, 73, 3479 (1951)] have maxima at 290 mμ (ϵ 16,200) and 280 mμ (ϵ 28,300), respectively.

(6) For example, see (a) C. Mannick, *Ber.*, 74, 557 (1941); (b) H. Fiesselmann and J. Ribka, *Chem. Ber.*, 89, 40 (1956); (c) E. Romann, A. J. Frey, P. A. Stadler, and A. Eschenmoser, *Helv. Chim. Acta*, 40, 1900 (1957).

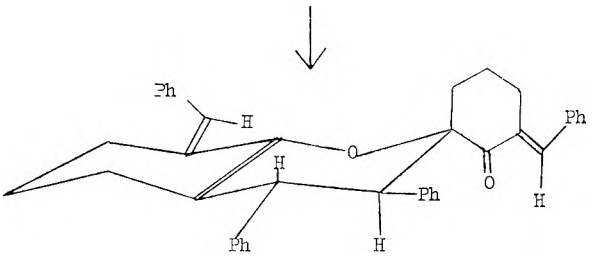
(7) W. S. Emerson, G. H. Birum, and R. I. Longley, Jr., *J. Am. Chem. Soc.*, 75, 1312 (1953).

(8) For a discussion see P. Yates, N. Yoda, W. Brown and B. Mann, *J. Am. Chem. Soc.*, 80, 203 (1958).

stant (J = 9 c.p.s.) observed in the NMR spectrum of the dimer is consistent with the location of the two benzylic hydrogen atoms in a *trans*, diaxial conformation[9] as shown in structure **18**.



17



18

EXPERIMENTAL[10]

2,6-Dibenzalcyclohexanone dimer (**9**). A solution of 45 g. (0.16 mole) of 2,6-dibenzalcyclohexanone, m.p. 116.5–118° (lit.[11] m.p. 117–118°), λ_{max} 232 mμ (ε 15,600) and 323(mμ, (ε 20,200),[12] in 75 ml. of toluene was refluxed for 72 hr. and then concentrated under reduced pressure. The residual solid was extracted with 350 ml. of boiling ethanol to leave the crude dimer which was recrystallized from ethyl acetate. The dimer separated as white, cotton-like needles, m.p. 192.3–193.3° dec., yield 9.5 g. (21%). An additional crystallization afforded to dimer as white needles, m.p. 194.3–195° dec. (lit.[1] m.p. 187–188°), which exhibit infrared absorption[13] at 1685 cm.$^{-1}$ (conj. C=O) with no absorption in the 3 μ region attributable to a hydroxyl function and an ultraviolet maximum[12] at 293 mμ (ε 43,500).

Anal. Calcd. for $C_{40}H_{36}O_2$: 87.56; H, 6.61; mol. wt. 549. Found: C, 87.69; H, 6.70; mol. wt. (Rast), 528.

A solution of 200 mg. of the dimer in 15 ml. of bromobenzene was refluxed for 20 hr. and then concentrated under reduced pressure. Recrystallization of the residue from ethanol afforded 120 mg. (60%) of 2,6-dibenzalcyclohexanone, m.p. 117–118.5°. To study the equilibration of the monomer and dimer solutions of 2.0712 g. (0.00756 mole) of the monomer and 2.0869 g. (0.00379 mole) of the dimer in 25-ml. portions of toluene were boiled under reflux, aliquots being removed from the solutions periodically for analysis by ultraviolet spectroscopy. After 213.5 hr., the solution originally containing pure monomer contained 55% of the monomer and the solution originally containing pure dimer contained 46% of the monomer. Extrapolation of the composition *vs.* time curves for the two solutions indicated that at equilibrium 50–55% of the dimer would be present.

Reaction of 2,6-dibenzalcyclohexanone (**1**) *with hydroxylamine.* A solution of 4.0 g. (0.015 mole) of 2,6-dibenzalcyclohexanone, 8.0 g. (0.12 mole) of hydroxylamine hydrochloride and 16 g. of sodium acetate in a mixture of 55 ml. of ethanol and 34 ml. of water was refluxed for 1.75 hr. and allowed to cool. The cold solution deposited 2.44 g. (54%) of the crude derivative, m.p. 177–181.5° dec. Recrystallization from ethanol afforded the pure derivative as white needles, m.p. 198.7–199.7° dec. (lit.[3] m.p. 199–200°), which exhibit infrared absorption[14] at 3300 cm.$^{-1}$ (broad, OH and NH) with no absorption in the 6 μ region attributable to a carbonyl function and an ultraviolet maximum[12] at 267 mμ (ε 15,500).

Anal. Calcd. for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69; mol. wt., 322. Found: C, 74.26; H, 7.08; N, 8.58; mol. wt. (Rast), 312.

For comparison, the *oxime of 2-benzalcyclohexanone* was prepared. The product, which crystallized from aqueous ethanol as colorless plates melting at 127–128.5° (lit.[15] m.p. 126.5°), has infrared bands[13] at 3600 cm.$^{-1}$ (unassoc. OH), 3300 cm.$^{-1}$ (assoc. OH), and 1640 cm.$^{-1}$ (very weak, C=N) with an ultraviolet maximum[12] at 272 mμ (ε 15,100).

Anal. Calcd. for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.48; H, 7.45; N, 6.71.

Monoxime of the dimer **9**. A mixture of 0.275 g. (0.5 mmole) of the dimer, 0.278 g. (2.0 mmoles) of hydroxylamine hydrochloride, and 5 ml. of pyridine was heated on a steam bath for 90 min. and then concentrated. Fractional crystallization of the crude product from ethanol and aqueous ethanol separated 0.137 g. (50% recovery) of the dimer and 0.50 g. (18%) of the crude oxime, m.p. 196.5–201° dec. Two additional crystallizations from ethanol–ethyl acetate mixtures afforded the pure oxime as white needles, m.p. 198–199.5° dec. The product has broad infrared absorption[14] at 3350 cm.$^{-1}$ with weak bands at 1640 cm.$^{-1}$ (C = N) and 1615 cm.$^{-1}$ (conj. C=C) and no absorption in the 6 μ region attributable to a carbonyl function; the material has an ultraviolet maximum[12] at 287 mμ (ε 31,500).

Anal. Calcd. for $C_{40}H_{37}NO_2$: C, 85.22; H, 6.62. Found C, 85.05; H, 6.78.

In another experiment a solution of 0.550 (1.0 mmole) of the dimer and 0.420 g. (6 mmoles) of hydroxylamine hydrochloride in ethanol was refluxed for 28 hr. and then concentrated. A series of fractional crystallizations from ethanol separated 8 mg. (1%) of the oxime, m.p. 198.7–199.7°, which was shown to be identical with the previously described derivative by comparison of the infrared spectra of the two samples.

Epoxidation of the dimer. To a solution of 2.22 g. (0.004 mole) of the dimer in 320 ml. of acetone was added 4.0 ml. (0.024 mole) of 6*N* aqueous sodium hydroxide and 6.0 ml. (0.063 mole) of 30% hydrogen peroxide. After the resulting mixture had been stirred at room temperature for 36 hr., an additional 2.0 ml. (0.021 mole) of 30% hydrogen peroxide, and 1.5 ml. (0.009 mole) of 6*N* aqueous sodium hydroxide were added. Stirring was continued for a total reaction time of 144 hr. at which time the reaction mixture was diluted with water and filtered to leave 2.010 g. of crude material, m.p. 184–197°. A 1.556-g. portion of this residue was subjected to a series of fractional crystallizations from ethanol to separate 1.10 g. (70% recovery) of the unchanged dimer and 0.186 g. (11.6%) of the crude epoxide, m.p. 182.5–185.6°. Additional recrystallization from ethanol afforded the pure

(9) H. Conroy in R. A. Raphael, E. C. Taylor, and H. Wynberg, ed., *Advances in Organic Chemistry, Methods and Results*, Vol. 2, Interscience, New York, 1960, pp. 265–328.

(10) All melting points are corrected. The infrared spectra were determined with either a Baird, Model B, or a Perkin Elmer Model 21, infrared recording spectrophotometer fitted with a sodium chloride prism. The ultraviolet spectra were determined with a Cary recording spectrophotometer, Model 11MS. The microanalyses were performed by Dr. S. M. Nagy and his associates and by the Scandinavian Microanalytical Laboratory. The NMR spectrum was determined in deuterochloroform by LeRoy F. Johnson of Varian Associates.

(11) D. Vorlander and K. Kunze, *Ber.*, **59**, 2078 (1926).

(12) Determined in ethanol solution.

(13) Determined in chloroform solution.

(14) Determined as a Nujol mull.

(15) R. Poggi and V. Guastalla, *Gazz. chim. ital.*, **61**, 405 (1931).

epoxide as colorless plates, m.p. 185.6–186.1°. The product exhibits infrared absorption[13] at 1725 cm.$^{-1}$ (unconj. C=O) with an ultraviolet maximum[12] at 291 mμ (ε 27,800).

Anal. Calcd. for $C_{40}H_{36}O_3$: C, 85.07; H, 6.43. Found: C, 84.96; H, 6.52.

Catalytic hydrogenation of the dimer. A solution of 5.97 g. (0.0108 mole) of the dimer in 200 ml. of ethyl acetate was hydrogenated at room temperature and atmospheric pressure over the catalyst obtained from 0.315 g. of platinum oxide. The reaction was stopped after the absorption of 354 ml. (1.58 equiv.) of hydrogen. After the catalyst had been removed by filtration, the filtrate was concentrated under reduced pressure. A combination of fractional recrystallization from ethanol and chromatography on Merck acid-washed alumina separated 0.8872 g. (14.8% recovery) of the unchanged dimer, 1.4615 g. (24.5%) of one crystalline modification of the dihydrodimer A, m.p. 159–162°, 0.3796 g. (6.4%) of a second crystalline modification of the dihydrodimer A, m.p. 171–172.5°, and 0.2914 g. (4.9%) of the dihydrodimer B, m.p. 208–211°.

One pure crystalline modification of the dihydrodimer A was obtained as white needles, m.p. 161.5–163°, by recrystallization from an ethanol-ethyl acetate mixture. The product exhibits infrared absorption[13] at 1720 cm.$^{-1}$ (unconj. C=O) with no absorption in the 3 μ region attributable to a hydroxyl function; the ultraviolet spectrum[12] exhibits a maximum at 293 mμ (ε 28,500).

Anal. Calcd. for $C_{40}H_{38}O_2$: C, 87.23; H, 6.96. Found: C, 86.91; H, 6.87.

The dihydrodimer A occasionally separated in a second crystalline modification as white prisms, m.p. 173.5–175°, which exhibit the same infrared and ultraviolet absorption as the crystalline form melting at 161.5–163°.

Anal. Calcd. for $C_{40}H_{38}O_2$: C, 87.23; H, 6.96. Found: C, 86.96; H, 6.98.

The pure dihydrodimer B crystallized from an ethanol–ethyl acetate mixture as colorless prisms, m.p. 212.5–214° dec., which exhibit infrared[13] absorption at 1718 cm.$^{-1}$ (unconj. C=O) with no absorption in the 3 μ region attributable in a hydroxyl function and an ultraviolet maximum[12] at 292 mμ (ε 23,600).

Anal. Calcd. for $C_{40}H_{38}O_2$: C, 87.23; H, 6.96. Found: C, 87.16; H, 6.84.

Treatment of the dihydrodimer **13** *with zinc and acetic acid.* A mixture of 0.8292 g. (0.0015 mole) of the dihydrodimer A, m.p. 161–163°, and 1.078 g. (0.019 g.-atom) of zinc dust in 20 ml. of acetic acid was refluxed with stirring for 1 hr. and then poured into cold water and filtered. Fractional crystallization of the residue from ethanol–ethyl acetate mixtures separated 0.6225 g. (75% recovery) of unchanged dihydrodimer A and 0.0557 g. (6.7%) of dihydrodimer B, m.p. 211–213° dec., identified by a mixed melting-point determination.

CAMBRIDGE 39, MASS.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STANFORD UNIVERSITY]

Asymmetric Induction

MOTHER MARY J. KUBITSCHECK AND WILLIAM A. BONNER

Received September 6, 1960

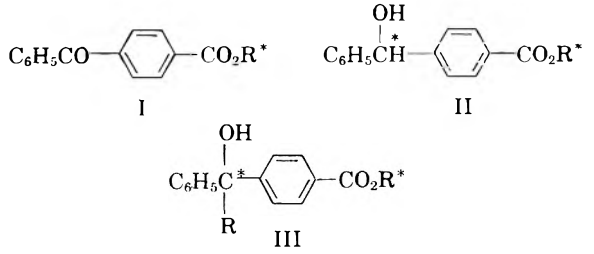
(−)-Menthyl *p*-benzoylbenzoate, a vinylog of an optically active α-keto ester has been subjected to the action of reducing agents and Grignard reagents to see if optical activity appears at the new asymmetric center produced at the benzoyl group after subsequent removal of the (−)-menthyl moiety. If asymmetric induction operates as do ordinary inductive forces through an aromatic nucleus, the ultimate products of such reactions should be optically active. If purely steric effects are responsible for asymmetric synthesis the products of such reactions should be optically inactive. In none of our experiments were we able to detect optical activity in the final reaction products, indicating that asymmetric induction if it exists is incapable of transmission through an aromatic nucleus.

Two distinct concepts of the mechanism of asymmetric synthesis are to be found in the literature. The first, that of "Asymmetric Induction," based on early suggestions of LeBel[1] and Erlenmeyer,[2] was developed in the hands of Kortum,[3] Lowry,[4] Ritchie,[5] Turner,[6] and Phillips[7] to explain not only McKenzie's classic asymmetric syntheses in the α-keto ester series[8,9] but also certain mutarotation[8,10] and anomalous rotatory dispersion[5,7] phenomena. This concept, in brief, postulates the asymmetric polarization of a symmetrical center in a molecule, under the influence of a nearby preexisting center of asymmetry. Such polarization is assumed to produce differing quantities of two diastereomeric "activated species," which ultimately react chemically to yield unequal amounts of diastereomeric products, and which are also responsible for anomalous mutarotation or rotatory dispersion properties. The second and more recent mechanism rationalizing asymmetric synthesis is one in which purely steric interactions between the symmetrical and asymmetric reactants lead to a stereochemically favored reaction path and to the ultimate production of unequal amounts

(1) J. A. LeBel, *Bull. soc. chim.* (iii), **8**, 613 (1892).
(2) E. Erlenmeyer, Jr., *Biochem. Z.*, **35**, 149 (1911).
(3) G. Kortum, *Samml. chem. u. chem.-tech. Vortrage*, 10 (1932).
(4) T. M. Lowry and co-workers, *Nature*, **113**, 565 (1924); *Bull. soc. chim.* (iv), **39**, 203 (1926).
(5) P. D. Ritchie, *Asymmetric Synthesis and Asymmetric Induction*, Oxford University Press, London, 1933. *Cf.* also J. Kenyon and S. M. Partridge, *J. Chem. Soc.*, 1313 (1936).
(6) E. E. Turner and M. M. Harris, *Organic Chemistry*, p. 653, Longmans, Green and Co., London, 1952.
(7) H. Phillips, *J. Chem. Soc.*, **127**, 2552 (1925).
(8) A. McKenzie and co-workers, *J. Chem. Soc.*, **85**, 1249 (1904); **95**, 544 (1909); *Biochem. Z.*, **208**, 456 (1929); **231**, 412 (1931); **237**, 1 (1931); **250**, 376 (1932).
(9) E. E. Turner and co-workers, *J. Chem. Soc.*, 3219, 3223, 3227 (1951).
(10) E. E. Turner and co-workers, *J. Chem. Soc.*, 538 (1941); S-169 (1949).

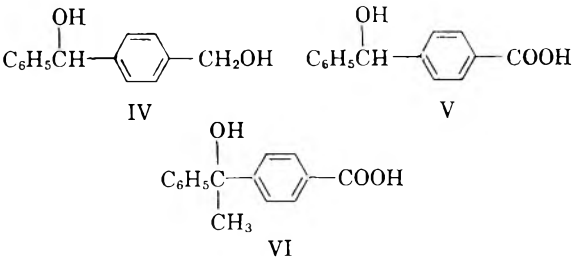
of diastereomeric products.[11-17] While the latter steric rationalization appears now generally accepted, there has been little experimental basis for a decision as to which of the two conflicting hypotheses is correct. We have attempted to design a series of semicritical experiments which might provide the basis for such a decision.

(−)- Menthyl *p*-benzoylbenzoate (I,R = (−)-menthyl) constitutes a vinylog of the optically active α-keto ester system used by McKenzie in his studies on asymmetric synthesis. Reduction of I to produce the secondary alcohol II, as well as reaction of RMgX with I to give the tertiary alcohol



III involve the introduction of a new asymmetric center at the formerly symmetrical benzoyl function in I. A true induced asymmetry by the (−)-menthyl moiety of I might, like other inductive effects, be reasonably supposed capable of transmission through the aromatic nucleus to the *p*-keto group, thus affording unequal quantities of the diastereomers of II and III. If, on the other hand, such asymmetric syntheses are due to steric interactions alone, the separation of the preexisting asymmetric center and the reacting keto function of I, as well as the linear structure of I, should preclude the unequal production of the diastereomers of II and III and the appearance of optical activity in the products resulting on removal of the (−)-menthyl moiety from II and III.

(−)-menthyl *p*-benzoylbenzoate (I), prepared either by direct esterification or *via* the corresponding chloride, proved to be an oil, and was accordingly characterized through its crystalline oxime. The action of excess lithium aluminum hydride upon I led ultimately to a sample of crystalline *p*-(α-hydroxybenzyl)benzyl alcohol (IV) which



proved to be optically inactive, indicating the failure of "asymmetric induction" to be transmitted through the phenyl nucleus of I. Reduction of I with sodium borohydride led smoothly to high yields of crystalline (−)-menthyl *p*-(α-hydroxybenzyl)benzoate (II). Alkaline or acidic hydrolysis of II yielded optically inactive, crystalline *p*-(α-hydroxybenzyl)benzoic acid (V). Since direct reduction of II with lithium aluminum hydride was incomplete due to the formation of an insoluble complex, the ester II was converted to its acetate and the latter smoothly reduced with lithium aluminum hydride to produce crystalline *p*-(α-hydroxybenzyl)benzyl alcohol (IV). The optical inactivity of the latter again indicated that no asymmetric induction had been transmitted through the phenyl nucleus of ester I during reduction of I.

In order to parallel McKenzie's successful asymmetric syntheses using Grignard reagents on α-keto esters, methylmagnesium iodide was allowed to react in benzene solvent with ester I. An excellent yield of crystalline (−)-menthyl *p*-(α-hydroxy-α-methylbenzyl)benzoate (III. R = CH_3, R* = (−)-menthyl) resulted, which on alkaline hydrolysis produced optically inactive *p*-(α-hydroxy-α-methylbenzyl)benzoic acid (VI). Reduction of ester III with lithium aluminum hydride yielded a sirupy product, presumably *p*-(α-hydroxy-α-methylbenzyl)benzyl alcohol which, though uncharacterized, proved to be optically inactive. These data again indicate the failure of asymmetric induction to be transmitted through the aromatic ring of ester I on reaction of its keto group.

As a control to the above experiments we have repeated some of the classical asymmetric syntheses of McKenzie[8] under our reaction conditions. The action of methylmagnesium iodide on (−)-menthyl phenylglyoxylate led to results comparable to those described by earlier workers,[8,9,11] while the reduction of this ester with lithium aluminum hydride or with sodium borohydride gave asymmetric synthesis to the extent of 4 to 12% preponderance of one enantiomer.[18]

The above experimental evidence clearly indicates that asymmetric induction of the sort postulated by Ritchie and others, if it indeed exists, is incapable of being transmitted across the *para* positions in an aromatic nucleus, and strongly

(11) V. Prelog and co-workers, *Helv. Chim. Acta*, **36**, 308, 320, 325, 1178 (1953); **38**, 303 (1955); **39**, 1086 (1956); *Bull. soc. chim.*, 987 (1956).

(12) W. Klyne, *Progress in Stereochemistry*, Butterworths Scientific Publications, London, 1954, p. 198 ff.

(13) D. J. Cram and co workers, *J. Am. Chem. Soc.*, **74**, 5829 (1952); **75**, 2293, 6007 (1953); **76**, 22 (1954).

(14) B. M. Benjamin, H. J. Schaeffer, and C. J. Collins, *J Am. Chem. Soc.*, **79**, 6160 (1957).

(15) H. S. Mosher and E. La Combe, *J. Am. Chem. Soc.*, **72**, 3994, 4991 (1950).

(16) W. von E. Doering and R. W. Young, *J. Am. Chem. Soc.*, **72**, 631 (1950).

(17) *Cf.* also L. M. Jackson, J. A. Mills, and J. S. Shannan, *J. Am. Chem. Soc.*, **72**, 4814 (1950); A. Streitwieser and co-workers, *J. Am. Chem. Soc.*, **75**, 5014 (1953); **77**, 1117 (1955); **78**, 5597 (1956); **79**, 903 (1957).

(18) V. Prelog, M. Wilhelm, and D. B. Bright, *Helv. Chim. Acta*, **37**, 221 (1954).

confirms the current assignment of asymmetric bias to purely steric interactions.

EXPERIMENTAL

(−)-*Menthyl phenylglyoxylate* was prepared from phenylglyoxylic acid[19] according to the general procedure of McKenzie,[8] m.p. 72–73°, $[\alpha]_D^{26}$ − 45.7° (*c*, 4.85; ethanol). Its 2,4-dinitrophenylhydrazone, shining, golden platelets, had m.p. 161–162°.

Anal. Calcd. for $C_{24}H_{28}O_6N_4$: C, 61.53; H, 6.02. Found: C, 61.57; H, 6.29.

Reaction of methylmagnesium iodide with (−)-menthyl phenylglyoxylate. The Grignard solution, prepared from magnesium turnings (0.58 g.) and excess methyl iodide in anhydrous ether (55 ml.), was added dropwise over a period of 45 min. to a stirred solution of (−)-menthyl phenylglyoxylate (2.88 g.) in ether (4 ml.). The mixture was stirred for an additional 45 min. and allowed to stand overnight, then decomposed with dilute sulfuric acid containing crushed ice. The ether layer was washed twice with sodium bisulfite solution and with water, then evaporated to yield a yellow oil. This was dissolved in 6% alcoholic potassium hydroxide solution (30 ml.) and heated under reflux for 1 hr., whereupon the alcohol was distilled and water was added to the oily residue. The menthol so precipitated was filtered and the filtrated was clarified with Norit, then heated on the steam bath to remove the last traces of menthol. The filtered solution was treated with hydrochloric acid (20 ml.) and extracted with ether. The extracts were clarified with Norit and stripped of solvent, affording 0.5 g. (30%) of atrolactic acid, m.p. 83–85, $[\alpha]_D^{22}$ − 11.1° (*c*, 5.02; ethanol). After one recrystallization the acid had m.p. 90–91.5° and $[\alpha]_D^{22}$ − 11.6°. McKenzie[8] reports a yield of 79% of an acid having $[\alpha]_D^{18}$ −9.5°.

Reduction of (−)-menthyl phenylglyoxylate with lithium aluminum hydride. The above menthyl ester (5.0 g.) in anhydrous ether (50 ml.) was added dropwise with stirring to a slurry of lithium aluminum hydride (1.47 g.) in ether (50 ml.). The reaction mixture was stirred for an additional hour and the complex was decomposed by the cautious addition of saturated ammonium chloride solution. The ether layer was stripped of solvent and the residue subjected to steam distillation, yielding the theoretical amount of menthol. The residue was saturated with sodium chloride and extracted four times with ether. The extract was dried and stripped of solvent to yield 73% of phenylglycol, m.p. 57–64°, $[\alpha]_D^{27}$ − 3.2° (*c*, 6.03; ethanol). The dibenzoate derivative of this product had m.p. 93.5–95° in good agreement with the value recorded in the literature.[20] Prelog[18] obtained from the same reaction an 85% yield of phenylglycol having $[\alpha]_D$ − 2.95°.

Reduction of (−)-menthyl phenylglyoxylate with sodium borohydride. Finely powdered sodium borohydride (0.42 g.) was added slowly with cooling to a solution of (−)-menthyl phenylglyoxylate (6 g.) in methanol (100 ml.). The solution was allowed to stand at room temperature for 2.5 hr. then poured into cold water (250 ml.). The milky mixture was extracted four times with ether, and the extracts were dried and stripped of solvent *in vacuo*, affording 5.54 g. (91.7%) of white solid having m.p. 82.5–84° and $[\alpha]_D^{26}$ − 75.8° (*c*, 6.04; ethanol). The physical properties reported[8,11] for (−)-menthyl (±)-mandelate (XVI) are m.p. 85–86° and $[\alpha]_D$ −74°.

Since acid hydrolysis of the above (−)-menthyl mandelate preceded with unsatisfactory results, the above product was subjected to further reduction with lithium aluminum hydride. The product (4.94 g.) from the above sodium borohydride reduction in anhydrous ether (50 ml.) was added dropwise to a stirred, slurry of lithium aluminum hydride (0.6 g.) in ether (50 ml.). After completion of the addition the mixture was stirred for 15 min., then processed as above, affording ultimately a pale yellow liquid which crystallized on standing in a desiccator, 1.52 g. (64.7%), $[\alpha]_D^{19}$ − 2.64° (*c*, 6.07; ethanol). This sample of phenylglycol afforded a dibenzoate having m.p. 93.5–94° after one recrystallization. In a duplication of the above experiment a sample of phenylglycol having $[\alpha]_D^{30}$ − 3.44° was obtained in 81% yield.

(−)-*Menthyl p-benzoylbenzoate.* *p*-Benzoylbenzoic acid (27.48 g.), (−)-menthol (74.39 g.) and *p*-toluenesulfonic acid (*ca.* 1 g.) were heated on the steam bath for 2.5 days. The crude product was dissolved in a 1:1 mixture of ether and benzene and the solution was washed well with a saturated solution of sodium carbonate, then with water. The solution was steam distilled for 3.5 hr., after which time the odor of menthol was substantially removed. The aqueous residue was extracted with benzene and the extracts were dried and passed through a column of alumina. The effluate was evaporated *in vacuo* to yield 23.5 g. (53%) of pale yellow sirup, b.p. 203–204° (1 mm.), $[\alpha]_D^{28}$ − 54.1° (*c*, 2.24; ethanol). No attempts to crystallize this ester were successful and it was accordingly characterized through its oxime. The latter crystallized from ethanol as feathery, colorless needles having m.p. 160–161° and $[\alpha]_D^{30}$ − 49.2° (*c*, 2.13; chloroform).

Anal. Calcd. for $C_{24}H_{28}O_3N$: C, 75.96; H, 7.70; N, 3.69. Found: C, 75.98, 76.04; H, 7.61. 7.72; N, 3.48, 3.53.

Reduction of (−)-menthyl p-benzoylbenzoate with lithium aluminum hydride. (−)-Menthyl *p*-benzoylbenzoate (5 g.) in anhydrous ether (60 ml.) was added dropwise over a 15-min. period to a slurry of lithium aluminum hydride (1.17 g.) in ether (60 ml.). The mixture was stirred for an additional 30 min., then decomposed by the cautious addition of excess 15% hydrochloric acid. The aqueous layer was salted and extracted with ether and the combined ether solution was evaporated and subjected to steam distillation. When the odor of menthol was no longer apparent the mixture was cooled, treated with sodium chloride, and extracted four times with ether. The ethereal extract was dried and evaporated under reduced pressure leaving 3.39 g. (117.7%) of yellow sirup. This high yield as well as the low yield of recovered menthol (67.3%) suggested that reduction of the starting material had been incomplete. Accordingly the sirupy product was dissolved again in ether and its solution added dropwise to a slurry of lithium aluminum hydride (1.17 g.) over a 1.3-hr. period. The mixture was stirred under reflux for an additional 2 hr. then processed as before, affording a yellow, viscous oil which was optically inactive in chloroform. Crystallization from ethanol followed by three recrystallizations from benzene yielded pure *p*-(α-hydroxybenzyl)benzyl alcohol, m.p. 103–105°.

Anal. Calcd. for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 79.16; H, 6.86.

Reduction of (−)-menthyl p-benzoylbenzoate with sodium borohydride. The ester (5 g.) in ethanol (50 ml.) was added to sodium borohydride (0.13 g.) in methanol (50 ml.). The latter solution had been treated with 10% sodium hydroxide solution until approximately *p*H 9 to prevent effervescence. After 3 hr. the mixture was poured into 10% hydrochloric acid (200 ml.) and the milky mixture was extracted with ether. The extracts were washed with water, dried, and evaporated *in vacuo* to yield 4.57 g. (91%) of solid having m.p. 103–125° $[\alpha]_D^{25}$ − 58.6° (*c*, 2.27; ethanol). Five recrystallizations of the product from methanol gave pure (−)-menthyl *p*-(α-hydroxybenzyl)benzoate, m.p. 144–145°, $[\alpha]_D^{27}$ − 43.3° (*c*, 2.7; ethanol).

Anal. Calcd. for $C_{24}H_{30}O_3$: C, 78.65; H, 8.25. Found: C, 78.39, 78.22; H, 7.89, 7.87.

p-(α-Hydroxybenzyl)benzoic acid. The above crude ester (3.42 g.) was treated with ethanol (25 ml.) and 2.5*M* potassium hydroxide solution (20 ml.). The solution was heated under reflux for 4 hr., whereupon the ethanol was

(19) D. B. Corson, R. A. Dodge, S. A. Harris, and R. K. Hazen, *Org. Syntheses*, Coll. Vol. I, 241 (1944).

(20) A. Perret and R. Perrot, *Helv. Chim. Acta*, 28, 558 (1945).

removed by distillation and the residue was extracted six times with 20-ml. portions of ether. The last extract was optically inactive, indicating complete removal of the menthol. The alkaline solution was acidified and the abundant precipitate was extracted into ether. The extracts were dried and stripped of solvent to yield 1.80 g. (84.5%) of white solid, m.p. 153–161°. The crude acid was optically inactive. Recrystallization from dilute methanol raised the m.p. to 164–165.5°, unchanged by further crystallization.

Anal. Calcd. for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30. Found: C, 73.39, 73.44; H, 5.13, 5.23.

When an attempt was made to hydrolyze the above (−)-menthyl *p*-(α-hydroxybenzyl)benzoate in dilute acetic acid containing sulfuric acid, the crude acidic product was obtained in 43.5% yield and proved to be optically inactive in ethanol.

Acetylation and lithium aluminum hydride reduction of (−)-menthyl p-(α-hydroxybenzyl)benzoate. Crude (−)-menthyl *p*-(α-hydroxybenzyl)benzoate (2 g.) was dissolved in pyridine (20 ml.). Acetic anhydride (4 ml.) was added and the solution was heated under reflux for 8 min., then poured onto chopped ice. The oily product was extracted into ether, and the extract was washed thoroughly with 6*N* hydrochloric acid, water, and sodium carbonate solution. Drying and solvent removal yielded 1.87 g. (83.9%) of cream-colored sirup. The crude sirupy acetate was dissolved in anhydrous ether (30 ml.) and the solution was added dropwise with stirring to a slurry of lithium aluminum hydride (0.51 g.) in ether (30 ml.). After 2 hr. of reflux, the mixture was hydrolyzed and processed in the usual way, yielding 0.94 g. (95.9%) of *p*-(α-hydroxybenzyl)benzyl alcohol which crystallized spontaneously. The sample was optically inactive in chloroform (*c*, 6.37) and showed no mixed melting point depression with the *p*-(α-hydroxybenzyl)benzyl alcohol obtained by the above lithium aluminum hydride reduction of (−)-menthyl *p*-benzoylbenzoate.

The reaction of methylmagnesium iodide with (−)-menthyl p-benzoylbenzoate. Methylmagnesium iodide from magnesium turnings (0.83 g.) and methyl iodide (4.87 g.) in anhydrous ether (50 ml.) was added dropwise during 1 hr. to a stirred solution of (−)-menthyl *p*-benzoylbenzoate (10 g.) in anhydrous benzene (100 ml.), causing gentle refluxing. After addition the ether component was distilled and the remaining benzene solution was stirred under reflux for 5 hr., chilled in ice, and treated gradually with 6*N* hydrochloric acid (50 ml.). Customary processing yielded 10.6 g. (101%) of an amber sirup which solidified in a vacuum desiccator.

A sample of this crude (−)-menthyl *p*-(α-hydroxy-α-methylbenzyl)benzoate (5 g.) was dissolved in anhydrous ether and the solution was added dropwise to a slurry of lithium aluminum hydride (1.11 g.) in anhydrous ether over a 30-min. period. Glass beads were then introduced into the mixture, stirring under reflux was continued for an additional 5 hr. and the excess hydride was destroyed by cautious addition of water and 6*N* hydrochloric acid. Customary work-up, including steam distillation for menthol removal yielded 2.72 g. (90.7%) calculated as *p*-(α-hydroxy-α-methylbenzyl)benzyl alcohol) of yellow sirup which proved to be optically inactive in ethanol solution.

The above crude (−)-menthyl *p*-(α-hydroxy-α-methylbenzyl)benzoate (4.95 g.) was dissolved in ethanol (40 ml.) containing 2.5*N* aqueous potassium hydroxide (20 ml.). The mixture was refluxed for 4 hr., the ethanol was distilled and the residue was cooled and extracted thoroughly with ether until the extracts were optically inactive, indicating menthol removal. The alkaline layer was acidified, at which point a heavy amber oil separated. This was extracted into ether and the dried extracts were evaporated *in vacuo*, yielding 2.59 g. (82.2%) of cream-colored solid which proved optically inactive in ethanol. The latter was recrystallized four times from benzene to yield pure *p*-(α-hydroxy-α-methylbenzyl)benzoic acid, m.p. 135–139°.

Anal. Calcd. for $C_{15}H_{14}O_3$: C, 74.36; H, 5.83. Found: C, 74.22, 74.16; H, 5.71, 5.60.

STANFORD, CALIF.

[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

Conformational Studies. I. The Relative Stabilities of the *cis*-2-Decalols[1]

O. R. RODIG AND L. C. ELLIS[2]

Received September 22, 1960

Equilibration of the isomeric *cis*-2-decalols in refluxing decalin in the presence of approximately 5 mole per cent of sodium showed that their free energies are about equal. A reinvestigation of the equilibration in the presence of excess sodium showed that the *cis-cis* isomer is present in 66 ± 2% in an equilibrated mixture rather than the previously reported 80%. The equilibria were approached from both sides and the isomer ratios determined by infrared intensity measurements and by the binary melting point diagram method. The results are briefly discussed in the light of conformational analysis concepts.

The flexibility of the *cis*-decalin system permits the existence of two interconvertible chair-chair conformations, so that in passing from one to the other an axial substituent becomes equatorial and *vice versa*. Thus, the situation is similar to that existing with cyclohexane derivatives except that the *cis*-decalins would be expected to have additional non-bonded interactions imposed by the second ring. Present conformational concepts as applied to *cis*-decalins seem to hold quite well and have aided greatly in stereochemical studies.[3]

It is possible for the *cis*-2-decalols to exist in four conformations having the most stable double-chair ring system. These are shown in Fig. 1 where Ia and Ib represent the two possible conformations of *cis-cis*-2-decalol, and IIa and IIb those for the *cis-trans*-isomer.[4]

(1) Presented in part at the Southeastern Regional Meeting of the American Chemical Society in Richmond, Va., November, 1959.

(2) Taken in part from a dissertation submitted by L. C. Ellis in partial fulfillment of the requirements of the degree of Doctor of Philosophy, University of Virginia, 1961.

(3) For example, see (a) W. G. Dauben, R. C. Tweit, and C. Mannerskantz, *J. Am. Chem. Soc.*, **76**, 4420 (1954); (*b*) J. A. Mills, *J. Chem. Soc.*, 260 (1953).

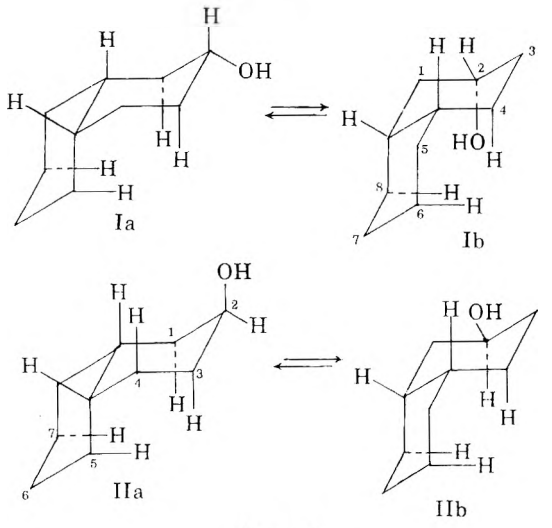


Figure 1

Dauben and Pitzer[5] have advanced the argument that of these four conformations, Ia and IIb should have comparable free energies since the interactions are similar. However, in the two conformations where the hydroxyl groups are axial, Ib can be expected to have a higher free energy than IIa because the hydroxyl group in the former is in a position similar to a skew butane conformation and should thus give rise to a steric interaction of larger magnitude than the normal $H_{(3)}$–$H_{(5)}$ interference found in IIa. The validity of this reasoning is supported by rate studies on esters of the two *cis*-2-decalols[6] and by equilibration studies on the isomeric *cis*-5-hydrindanols.[7]

Furthermore, at equilibrium there should be a larger number of molecules in form IIa than Ib while the populations of forms Ia and IIb should be about equal. The overall effect should give a higher concentration of *cis-trans*-2-decalol (II) over the *cis-cis*-isomer (I) in an equilibrated mixture.[5]

Hückel and Naab[8] carried out the equilibration of the *cis*-2-decalols in refluxing decalin in the presence of excess sodium and reported obtaining 80% of the *cis-cis*-2-decalol and 20% of the *cis-trans*-isomer when equilibrium was approached from either side. These results are in direct contrast to those expected from the conformational principles outlined above. Since these authors determined the percentages of isomers formed by direct isolation of the products and reported no overall yields, a reexamination of this equilibration seemed desirable.

In order to lessen the sources of error, direct isolation of the products was avoided in preference for an analytical method which would enable a direct determination of the isomer ratios in mixtures.[9] Direct infrared analysis was found to give acceptable results (well within ±1%) in the range of the equilibrated mixtures (Table I).[10]

TABLE I

PERCENT *cis-cis*-2-DECALOL IN KNOWN MIXTURES FROM INFRARED INTENSITY MEASUREMENTS AT 10.52 AND 11.03 μ

Mixture	Actual, %	Found, %	Deviation, %
1	45.8	47.0	+1.2
2	47.3	47.3	0.0
3	52.5	53.1	+0.6
4[a]	54.4	54.3	−0.1
5[a]	57.1	57.4	+0.3
6[a]	60.5	60.0	−0.5
7	70.2	69.7	−0.5
8	80.7	79.1	−1.6

[a] Cavity cells used.

In the preparation of the *cis*-decalols from 2-naphthol it was found that hydrogenation using a ruthenium oxide catalyst gave better yields than previously reported catalytic reduction methods.[11,22a] The equilibrations were carried out using the same conditions reported by the previous workers,[8] starting with both the *cis-cis*- and the *cis-trans*-isomers to insure that equilibrium had been reached. As these conditions employ an excess of sodium, the equilibrated alcohols are undoubtedly completely in the forms of their sodium salts, and under the experimental conditions employed, these salts were completely miscible in the reaction solvent. Actually, it is of just as great interest here to know the free energy difference between the isomeric free alcohols; therefore, the equilibration was also studied using only a few mole percent of sodium. It is interesting that the amount of sodium affects the position of equilibrium quite markedly (Table II). When excess sodium was used the

(4) The nomenclature for the decalols described in this paper follows that proposed by W. G. Dauben, R. C. Tweit, and C. Mannerskantz, *J. Am. Chem. Soc.*, **76**, 4420 (1954). Conformational assignments are made relative to the positions of the hydrogen atoms at C_9, C_{10} and C_9, C_2. For the establishment of the configurations of these epimeric decalols, see W. G. Dauben and E. Hoerger, *J. Am. Chem. Soc.*, **73**, 1504 (1951).

(5) W. G. Dauben and K. S. Pitzer, *Steric Effects in Organic Chemistry*, M. S. Newman, ed., Wiley, New York, 1956, pp. 27–30.

(6) Ref. 3a and b and references cited therein; W. Hückel, *Ber.*, **67 A**, 129 (1934).

(7) Ref. 5, p. 38, and references cited therein.

(8) W. Hückel and H. Naab, *Ber.*, **64**, 2137 (1931).

(9) An obvious method of choice here is vapor phase chromatography. Attempts to separate quantitatively the two isomers on Apiezon L, Dow Corning Silicone Grease, Carbowax 20 M and Silicone GE SE-30 using columns up to six and a half feet were unsuccessful. A major problem was the decomposition of the *cis-trans*-isomer at the temperatures (140–200°) required for practical retention times. At higher temperatures the *cis-cis* was also found to decompose. The feasibility of employing this analytical method in the present and similar cases is being explored further.

(10) Outside of this range (already evident in mixtures 1 and 8) the accuracy of the method diminishes rapidly. This is because the peaks become too weak in intensity for accurate calculations or begin to overlap seriously.

(11) D. M. Musser and H. Adkins, *J. Am. Chem. Soc.*, **60**, 664 (1938). S. G. Kulikov, *Uchenye Zapieki Moskov. Gosudarst. Univ. im. M.V. Lomonosova* No. **131**, 101–64 (1950) [*Chem. Abstr.*, **47**, 1171a (1953)].

TABLE II

EQUILIBRATION OF *cis*-2-DECALOLS IN REFLUXING DECALIN

Run	Starting Material			Solvent, Ml.	Sodium		Reflux Time, Hr.	% *cis-cis* Isomer at Equilibrium
	Isomer	Grams	Moles		Grams	Moles		
1	*cis-cis*	10.0	0.065	160	2.4	0.104	7	64.5
2	*cis-trans*	0.45	0.0029	30	0.25	0.0108	8	65.5
3	*cis-trans*	5.3	0.034	100	2.0	0.087	8	66.1
4	*cis-cis*	5.0	0.032	100	0.04	0.0017	7	53.5
5	*cis-cis*	5.0	0.032	100	0.04	0.0017	24	54.2 (52.5[a])
6	*cis-trans*	2.0	0.013	50	0.016	0.0007	8	52.0

[a] Not steam distilled (see Experimental).

TABLE III

ANALYSIS OF *cis*-2-DECALOL MIXTURES BY CONVERSION TO THEIR *p*-NITROBENZOATES

Mixture	Source	Reflux Time[a]	*p*-Nitrobenzoate		M.P. Diagram		Infrared	
			% Yield	M.P.[b]	% *cis-cis*	% deviation	% *cis-cis*	% deviation
1	Known: 80.3[c]		93	61.5–92.0	78.5	−1.8	82.2	+1.9
2	Known: 81.3[c]		87	61.5–92.5	79.5	−1.8	83.5	+2.2
3	Known: 63.3[c]		82	60.5–85.5	64.5	+1.2		
4	Known: 70.0[d]						70.0	0.0
5	Equil.: *cis-cis*[e]	7	85	61.5–86.5	67.0		69.2	
6	Equil.: *cis-cis*[e]	7	90	60.0–86.0	66.0		68.8	
7	Equil.: *cis-trans*[e]	8	84	52.5–84.5	63.0		68.6	

[a] During equilibration. [b] Determined to the nearest 0.5°. [c] Amount of *cis-cis*-isomer. [d] A mixture of the pure esters containing 70.0% of *cis-cis*-2-decalyl *p*-nitrobenzoate. [e] Starting isomer.

equilibrated mixtures contained about 66% of the *cis-cis*-isomer, while the concentrations of the two isomers were about equal with the lesser amounts of sodium.[12,13] The recovery of alcohols was 90–95%.

The use of binary melting point diagrams for the analysis of isomer mixtures is frequently found in the literature and the present work provided an opportunity to compare this technique with the infrared method. Accordingly, we prepared the *p*-nitrobenzoates and 3,5-dinitrobenzoates of the two *cis*-2-decalols and plotted the melting point diagrams for these derivatives. The curves are shown in Fig. 2, and the data used in Table V. Mixtures 1–3 of Table III and 1–2 of Table IV, prepared using known amounts of the pure isomers, give an indication of the accuracy of the method. In the present case, the agreement is good between the isomer ratio values for the equilibrated mixtures as determined by the melting point diagram method and infrared analysis of the free alcohols.

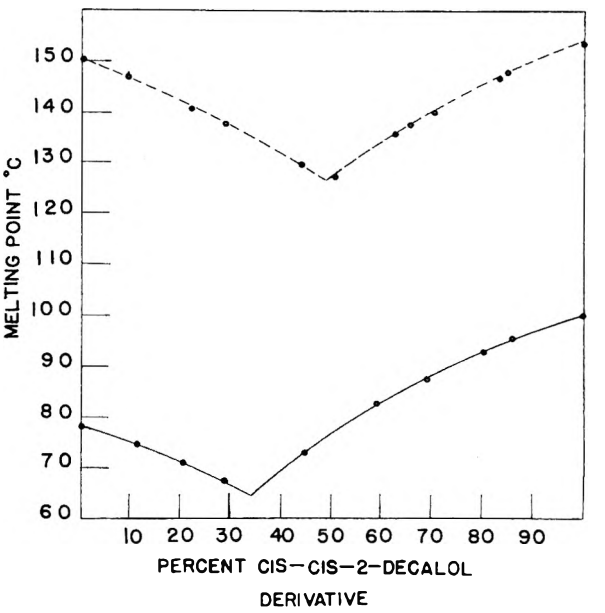


Fig. 2. Binary melting point diagrams of *cis*-2-decalol derivatives: (———) *p*-nitrobenzoates; (- - - -) 3,5-dinitrobenzoates

It is interesting that although the yield of derivative differed somewhat for the various runs (column 4 in Tables III and IV), this seemed to have little effect on the results. Several bands in the infrared spectra of the *p*-nitrobenzoates were found suitable to allow quantitative isomer ratio determinations in the *p*-nitrobenzoate mixtures. However, the best bands were not as well defined as

(12) Controls consisting of mixtures of known amounts of the two isomers when carried through the work-up procedure used in the equilibration runs, gave percentage values for the *cis-cis*-isomer which were consistently 2–4% higher than the true values. This error arises because the *cis-trans*-isomer has a relatively high vapor pressure and therefore a small amount is unavoidably lost during removal of the decalin solvent. Thus, the values given for Runs 4–6 in column 9 of Table II are several percent too high and actually represent a maximum value rather than the true value. This is not the case in Runs 1–3 where the alcohols are in the forms of their sodium salts during the decalin removal (see Experimental).

(13) Equilibration with aluminum isopropoxide in acetone–isopropyl alcohol appears to give still a different equilibrium constant. [W. Hückel, M. Maier, E. Jordan, and W. Seeger, *Ann.*, **616**, 81 (1958); personal observation].

TABLE IV

ANALYSIS OF *cis*-2-DECALOL MIXTURES BY CONVERSION TO THEIR 3,5-DINITROBENZOATES

Mixture	Source	Reflux Time[a]	3,5-Dinitrobenzoate Yield, %	3,5-Dinitrobenzoate M.P.[b]	M.P. Diagram *cis-cis*, %	M.P. Diagram Deviation, %
1	Known: 83.3[c]		59	126.0–147.0	84.0	+0.7
2	Known: 63.3[c]		91	124.5–136.0	62.7	−0.5
3	Equil.: *cis-cis*[d]	7	71	127.5–138.0	66.5	
4	Equil.: *cis-cis*[d]	7	81	126.5–139.5	68.0	
5	Equil.: *cis-cis*[d]	7	60	128.0–139.0	67.5	
6	Equil.: *cis-trans*[d]	8	81	121.5–137.5	66.0	

[a] During equilibration. [b] Determined to nearest 0.5°. [c] Amount of *cis-cis*-isomer. [d] Starting isomer.

TABLE V

THE MELTING POINTS OF MIXTURES OF *cis-cis*- AND *cis-trans*-2-DECALYL *p*-NITROBENZOATES AND 3,5-DINITROBENZOATES

p-Nitrobenzoates % *cis-cis*-	*p*-Nitrobenzoates M.P.	3,5-Dinitrobenzoates % *cis-cis*-	3,5-Dinitrobenzoates *M.P.*
0.00	77.5– 78.0	0.00	149.5–150.0
11.24	62.5– 74.5	8.99	127.0–147.0
20.40	61.5– 71.0	28.82	125.5–137.5
28.60	61.5– 67.5	22.20	126.5–140.5
44.44	61.5– 73.0	43.68	126.5–129.5
58.79	61.5– 82.5	62.46	126.5–135.5
68.99	61.5– 87.5	65.48	126.5–137.5
80.19	61.5– 93.0	70.64	126.5–139.5
85.95	63.0– 95.5	83.26	126.5–146.5
100.00	98.0–100.0	85.09	126.5–147.0
		100.00	153.0–153.5

those used with the free alcohols and so the percentages found are slightly less accurate (Table III, columns 8 and 9). The spectra of the *cis*-2-decalyl 3,5-dinitrobenzoates were found unsuitable for infrared analysis.

DISCUSSION

The data given in Tables II–IV clearly show that when the *cis*-2-decalols are equilibrated in decalin in the presence of excess sodium, the mixture contains a decided predominance of the *cis-cis*-isomer (I); whereas when only a few mole percent of sodium are used, the two isomers are present in approximately equal amount. In the latter case, the isomeric alcohols exist almost entirely in the free state, and, thus would appear to have approximately equal free energies under the present conditions of equilibration. These results are in much better agreement with present conformational views[5] than those reported previously.[8]

The question as to why the isomeric *cis*-2-decalols should have approximately equal free energies is an intriguing one which cannot be fully answered at present. Two possible explanations immediately present themselves; namely, that the two forms Ib and IIa are either present in too small amount to have any effect on the equilibrium or that their free energies are comparable. On the basis of findings concerning free energy differences between axial and equatorial hydroxyl groups in substituted cyclohexanols,[14] the contributions of these forms would not be expected to be insignificant. However, the two cases are not strictly comparable because of additional interring interactions which appear in the decalins and which probably cannot be neglected.[5]

Likewise, Ib and IIa would not be expected to have comparable free energies, as the O_2—H_8 interatomic distance in Ib of 1.7 Å (center to center) should give rise to considerable steric interference.[15] However, by a slight spreading of the valence angles of the hydroxyl containing ring, this interference can be largely alleviated with apparently little additional strain on the system.[16,17] A similar flattening of one of the rings apparently occurs in *cis*-decalin-2α,3α,-diol.[16]

With an excess of sodium, the data in Tables II–IV indicate an equilibrium ratio consisting of 66 ± 2% of the *cis-cis*-isomer. To explain the higher stability of the *cis-cis*-isomer it is tempting to consider bonding of the type shown in III as playing perhaps a minor, but important, role. To our knowledge such bonding has never been conclusively demonstrated, but a similar type of interaction has been suggested as an explanation for the greater stability of *cis*-1-hydrindanone over the *trans*-isomer.[18]

Because the free energy difference between the isomeric *cis*-2-decalols is small (approximately 0.6 kcal. in the case of the sodium salts and much smaller for the free alcohols, as calculated from the equilibrium constants) intermolecular interac-

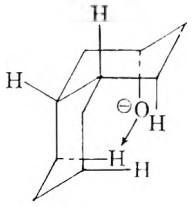
(14) For a lead reference, see R. A. Pickering and C. C. Price, *J. Am. Chem. Soc.*, 80, 4931 (1958).

(15) The energy difference between the diaxial and diequatorial conformations of *cis*-3-methylcyclohexanol has been determined as 3.3 kcal./mole from esterification rates in pyridine at 25°. [E. L. Eliel and C. A. Lukach, *J. Am. Chem. Soc.*, 79, 5986 (1957)]. If one assumes that the energy difference between Ia and Ib is of a comparable order of magnitude, the concentration of Ib would be reduced practically to zero.

(16) M. E. Ali and L. N. Owen, *J. Chem. Soc.*, 2119 (1958).

(17) Little information is available for the variation of energy with bond angle in alicyclic systems; however, it is probably quite small for moderate angle increases; see R. Pauncz and D. Ginsburg, *Tetrahedron*, 9, 51 (1960).

(18) L. F. Fieser and M. Fieser, *Organic Chemistry*, 3rd ed., D. C. Heath and Co., Boston, 1956, p. 309; however, see also N. L. Allinger, *J. Org. Chem.*, 21, 915 (1956).



III

tions and solvent effects cannot be assumed to be negligible. The evaluation of the importance of such factors must await additional and preferably more accurate equilibration data. Work along these lines is in progress and will be presented in a subsequent publication.

EXPERIMENTAL[19]

cis-cis-2-Decalol (I) *and cis-trans-2-decalol* (II). A mixture of 100 g. (0.69 mole) of 2-naphthol,1. 5 g. of ruthenium oxide,[20] and enough absolute ethanol to make a total volume of 400 ml. was hydrogenated at 1160–995 p.s.i. while slowly increasing the temperature to 91°. After 4 hr. the hydrogen uptake had ceased. The mixture was cooled, filtered, and the catalyst washed well with ethanol. As much of the ethanol as possible was removed from the filtrate by distillation *in vacuo* at 27–30°, and the residue dissolved in ether and washed with dilute aqueous sodium hydroxide. Removal of the ether left 98.0 g. of semisolid material which after several recrystallizations from petroleum ether (b.p. 90–110°) yielded 52.9 g. (0.34 mole) of *cis-cis*-2-decalol, m.p. 104–104.5° (lit.,[21] m.p. 105°).

The mother liquors were combined and the solvent removed *in vacuo*, leaving 44.8 g. of a sirupy mixture of *cis-cis*- and *cis-trans*-2-decalols. These were converted to the hydrogen phthalates[22] by refluxing for 17 hr. in 150 ml. of dry toluene with 70.0 g. (0.47 mole) of phthalic anhydride. The toluene was removed under reduced pressure, 200 ml. of water added and the mixture heated at 80–85° for 4 hr. After cooling, the solid was separated by filtration, dried, and dissolved in chloroform. The solution was refiltered, and the solvent removed. Repeated fractional crystallization of the residue from benzene-petroleum ether yielded 32.0 g. of pure *cis-trans*-2-decalyl hydrogen phthlate, m.p. 151–152° (lit.,[22a] m.p. 153°), and 30.0 g. of a mixture of *cis-trans*- and *cis-cis*-2-decalyl hydrogen phthalate.

The 30.0 g. of hydrogen phthalate mixture was hydrolyzed by refluxing with 100 ml. of 25% aqueous sodium hydroxide for 3 hr. After the solution had cooled, the decalols were extracted with ether and dried over sodium sulfate. Removal of the solvent under reduced pressure and crystallization of the residue from petroleum ether (b.p. 90–110°) gave an additional 5.6 g. of *cis-cis*-decalol, m.p. 103.5–104.5°, making the total yield of this isomer 58.5 g. (55%).

The solvent was removed from the mother liquors and the residue refluxed for 4 hr. with 16.0 g. (0.11 mole) of phthalic anhydride in 35 ml. of dry toluene. When worked up as previously described, this reaction yielded an additional 4.4 g. of *cis-trans*-2-decalyl hydrogen phthalate, m.p. 151–152°.

The 36.4 g. of *cis-trans*-2-decalyl hydrogen phthalate was hydrolyzed by refluxing overnight with 15.0 g. of sodium hydroxide in 150 ml. of water. After cooling, the product was extracted with ether and dried over sodium sulfate. Removal of the ether under reduced pressure left a sirupy residue which was distilled at 130–132° (16–17 mm.) giving 18.0 g. (17%) of *cis-trans*-2-decalol.[22]

Equilibration of the cis-2-decalols with sodium. The following procedure is typical of that followed in carrying out the equilibrations. In all runs, the sodium salts of the decalols were completely soluble in the decalin solvent under the conditions of equilibration.

A mixture of 5.3 g. (0.034 mole) of *cis-trans*-2-decalol and 2.0 g. (0.087 mole) of sodium was refluxed in 100 ml. of dry decalin for 8 hr. by immersion of the reaction flask in a Woods metal bath at 232–234°.[8] Upon cooling, the excess sodium was removed, and the decalin was removed by distillation at 90–93° (33–35 mm.) using a capillary attached to a nitrogen source. A 50% aqueous ethanol solution was added to the honey-colored residue and the mixture steam distilled. The distillate was extracted with ether, the combined ether extracts dried over sodium sulfate, and aliquots evaporated to dryness for the infrared analyses and the preparation of derivatives.

The solution remaining in the steam distillation flask was extracted with ether, and the ether then removed, leaving a small amount of oily residue which showed no bands characteristic of either of the decalols in its infrared spectrum. The total recovery of the *cis*-2-decalols was 4.95 g. (93%).

The cis-2-decalyl p-nitrobenzoates and 3,5-dinitrobenzoates were prepared by the standard procedure,[23] using a 1 to 3-hr. heating period. In recrystallization of the crude derivatives from ethanol, the mother liquors were tested by infrared analysis to insure that all of the desired products had been recovered.

The cis-2-decalyl p-nitrobenzoate and cis-2-decalyl 3,5-dinitrobenzoate binary melting point diagrams shown in Fig. 2 were prepared from the melting points of mixtures containing known percentages of the isomeric *cis*-2-decalyl derivatives. The mixtures were prepared by mixing known amounts of pure esters with an agate mortar and pestle. The melting points were determined to the nearest 0.5° in a Hershberg melting point apparatus, using Arthur H. Thomas total immersion thermometers. The temperature at which the last trace of material melted was then plotted against the percent of *cis-cis*-2-decalyl ester. Data used constructing the diagrams are shown in Table V.

Mixtures 1–3 of Table III and 1–2 of Table IV were prepared using known amounts of pure decalols. These were then converted to the *p*-nitrobenzoates or 3,5-dinitrobenzoates and their compositions analyzed from the melting point diagrams (and infrared spectra in the case of the *p*-nitrobenzoates).

Infrared analyses. The infrared analyses were made on a Perkin-Elmer model 21 spectrophotometer, using either 0.05-mm. sodium chloride, fixed-thickness, mounted cells or 0.1 mm. Type C sodium chloride cavity cells.[24] The settings on the instrument were as follows: pen speed 10.5, resolution 9.27, intensity 0.3 amps., autosuppression 5, response 1, gain 5, speed approximately 4 min. per μ. Chloroform was used as a solvent in all cases with a concentration of 202 mg. of sample per ml. of solvent for the free alcohols and 190 mg. per ml. for the *p*-nitrobenzoates.

The percentage compositions of the mixtures were calculated using the base line method of Wright[25] and the equation

$$\frac{C_{mc}}{C_{mt}} = \frac{A_t \log (I^\circ/I)_{mc}}{A_c \log (I^\circ/I)_{mt}}$$

which is easily derived from the Lambert-Beer Law.

(19) All melting points are uncorrected except those concerned with the binary melting point diagrams.

(20) American Platinum Works, Newark, N. J.

(21) W. Hückel, *Ann.*, 441, I, 15, 28 (1925).

(22)(a) W. Hückel, *Ann.*, 451, 109 (1927); (b) G. Tsatsas, *Ann. chim.*, [11], 19, 217 (1954).

(23) S. M. McElvain, *The Characterization of Organic Compounds*, revised ed., The Macmillan Co., New York, 1953, p. 199.

(24) Connecticut Instrument Corporation, Wilton, Conn.

(25) N. Wright, *Anal. Chem.*, 13, 1 (1941).

C_{mc} and C_{mt} are the relative amounts of *cis-cis-* and *cis-trans*-isomer in the mixture, respectively. $(I^0/I)_{mc}$ and $(I^0/I)_{mt}$ are the peak heights of the *cis-cis-* and the *cis-trans*-isomer, respectively, as measured from the infrared spectrum of the mixture.

$A_t = \frac{1}{C_t} \log (I^0/I)_t$ and $A_c = \frac{1}{C_c} \log (I^0/I)_c$ where C_t = concentration of pure *cis-trans*-isomer, C_c = concentration of pure *cis-cis*-isomer, $(I^0/I)_t$ = the peak height of the *cis-trans*-isomer measured from the base line, and $(I^0/I)_c$ = the peak height of the *cis-cis*-isomer. Thus A_t and A_c represent constants which are determined from the spectra of the pure isomers. The peaks found best suited[25,26] for the infrared analysis of mixtures were the following: *cis-cis-*, 10.52 μ; *cis-trans-*, 11.03 μ; *cis-cis-p*-nitrobenzoate, 10.74 μ; *cis-trans-p*-nitrobenzoate, 10.54 μ.

Preparation of the samples for infrared analysis. The *cis-trans*-isomer is relatively volatile at room temperature and noticeable amounts are lost if unstoppered samples are exposed to the air for several days. For this reason, considerable care had to be exercised in preparing samples of the free alcohols for analysis. Reproducible results could be consistently obtained by allowing an aliquot ether portion of the equilibrated mixtures to evaporate overnight from an open, tared test tube. The last traces of solvent were removed by applying vacuum (water pump) for several minutes, and enough chloroform was then added to make a solution of the desired concentration for infrared analysis.

Preparation of the *cis*-2-decalyl *p*-nitrobenzoate samples required no special precautions.

CHARLOTTESVILLE, VA.

(26) J. J. Heigl, M. F. Bell, and J. U. White, *Anal. Chem.*, 19, 293 (1947).

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY, TOKYO INSTITUTE OF TECHNOLOGY]

Studies on the Beckmann Rearrangement. I. Dehydrations of Aldoximes with Methylketene Diethylacetal

TERUAKI MUKAIYAMA, KAZUYOSHI TONOOKA, AND KENJI INOUE

Received September 8, 1960

Dehydrations of aldoximes into isonitriles or nitriles by means of methylketene diethylacetal have been studied. Addition compounds of aromatic-*syn*-aldoximes and methylketene diethylacetal decompose, in the presence of a catalytic amount of boron trifluoride and mercuric oxide, into corresponding isonitriles in good yields. On the other hand, adducts of methylketene diethylacetal and aromatic-*anti*-aldoximes, as well as of methylketene diethylaeetal and an aliphatic aldoxime, decompose to give corresponding nitriles under the same conditions.

The decomposition of an adduct of *p*-tolu-*syn*-aldoxime in the presence of Lewis acids other than boron trifluoride, of mercuric salts and of protonic acid has been investigated. Except in the case of one equivalent of zinc chloride, however, there cannot be found any other effective catalyst for the rearrangement. Further, an intermediate, presumably methylketene monoethyl monoaldiminoacetal, is obtained during the course of decomposing the adduct of *p*-tolu-*syn*-aldoxime. The mechanism of this reaction can be described in view of these results.

Dehydration reactions of primary nitroparaffins and aldoximes by means of organic reagents have been described in preceding papers.[1-4] It was shown there[2] that benzaldoxime is dehydrated with a ketene acetal in the presence of a catalytic amount of boron trifluoride and mercuric oxide to give benzonitrile and benzisonitrile, both of these dehydrated products being nearly equal in amount. The course of this reaction involves two stages, namely the initial formation of an addition compound (I) of an aldoxime and a ketene acetal, and the decomposition of the adduct which yields the dehydrated products along with an alcohol and a carboxylic ester.

$$\mathrm{R{-}CH{=}NOH + RCH{=}C(OR)_2 \longrightarrow}$$

$$\mathrm{RCH_2C(OR)_2 \longrightarrow}$$

$$\mathrm{I}\quad \begin{matrix} \mathrm{O} \\ | \\ \mathrm{N{=}CHR} \end{matrix}$$

$$\mathrm{RCH_2COOR + ROH + RCN + R{-}N{=}C}$$

It has been confirmed that the initial formation of the adduct (I) is carried out readily in the absence of catalysts and it is believed that such catalysts as a mixed catalyst of boron trifluoride and mercuric oxide used in the experiment are effective in the decomposition of the adduct.

Since the formation of an isonitrile by the reaction is considered to be the simplest model of the Beckman rearrangement, the dehydration of various aldoximes with methylketene diethylacetal has been studied in order to clarify the mechanism of this reaction.

The Beckman rearrangement has been demonstrated to occur by the process in which the migrating group approaches the migrating terminus, the nitrogen atom of oximes, from the side *trans* to the leaving group. Aldoximes exist in two forms, *syn* and *anti*, in which the hydroxyl group is respectively *cis* or *trans* to the aldehydic hydrogen. In order to know the stereochemical course of this reaction, the dehydration of *syn-* and *anti*-aldoximes with methylketene diethylacetal was tried first. Adducts were prepared from *syn-* and *anti*-al-

(1) T. Mukaiyama and T. Hoshino, *J. Am. Chem. Soc.*, 82, 5339 (1960).

(2) T. Mukaiyama and T. Hata, *Bull. Chem. Soc. of Japan*, 33, 1382 (1960).

(3) T. Mukaiyama and T. Hata, *Bull. Chem. Soc. of Japan*, 33, 1712 (1960).

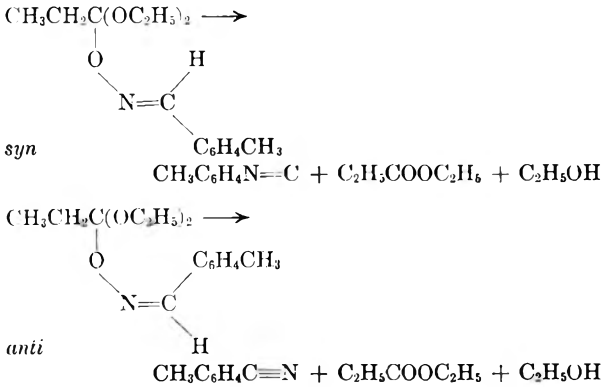
(4) T. Mukaiyama and T. Hata, *Bull. Chem. Soc. of Japan*, 34, 99 (1961).

TABLE I

THE YIELDS, PHYSICAL PROPERTIES AND ANALYSES FOR ADDUCTS OF ALDOXIMES AND METHYLKETENE DIETHYLACETAL

Aldoxime	Yield, %	M.P.	B.P. (mm.)	n_D^{25}	Formula of Adduct	Analyses, % Calcd.	Found
Benz-*syn*-	83		123 (4.8)	1.4890	$C_{14}H_{21}NO_3$	C, 66.90 H, 8.42 N, 5.57	C, 66.75 H, 8.25 N, 5.75
p-Tolu-*syn*-	95		122–123 (0.55)	1.4825	$C_{15}H_{23}NO_3$	C, 67.89 H, 8.74 N, 5.28	C, 68.29 H, 8.69 N, 5.49
p-Nitro-*syn*-	52	89–90.5			$C_{14}H_{20}N_2O_5$	C, 56.74 H, 6.80 N, 9.45	C, 56.78 H, 6.81 N, 9.63
Benz-*anti*-	61		117–118 (2)	1.4850	$C_{14}H_{21}NO_3$	C, 66.90 H, 8.42 N, 5.28	C, 66.89 H, 8.33 N, 5.40
p-Tolu-*anti*-	61		113 (0.4)	1.4865	$C_{15}H_{23}NO_3$	C, 67.89 H, 8.74 N, 5.28	C, 68.18 H, 8.71 N, 5.40
Heptan-	74		107–108 (4)	1.4338	$C_{14}H_{29}NO_3$	C, 64.82 H, 11.27 N, 5.40	C, 65.06 H, 11.37 N, 5.69

doximes and methylketene diethylacetal. The yields, physical properties, analyses, and infrared absorption bands for these adducts are listed in Tables I and II. The adducts were subjected to decomposition in the presence of a catalytic amount of boron trifluoride and mercuric oxide in dry ether. It was observed that adducts of *syn*-aldoximes decomposed into the corresponding isonitriles in yields ranging from 50 to 75% (see Table III). On the other hand, adducts of *anti*-aldoximes decomposed to yield only the corresponding nitriles under the same conditions but no isonitriles were obtained. Nitriles and isonitriles thus obtained were identified by their boiling points and the characteristic infrared absorption bands of benzonitrile and benzisonitrile at 4.48 μ and 4.72 μ, *p*-tolunitrile and *p*-toluisonitrile at 4.48 μ and 4.71 μ, respectively.



The formation of nitriles along with isonitriles by the decomposition of adducts of *syn*-aldoximes as shown in Table III is regarded as resulting from the rearrangement of the initially formed isonitriles during distillation. This is confirmed by the fact that, whereas only *p*-toluisonitrile was obtained by decomposing an adduct of *p*-tolualdoxime and distilling it at a lower temperature, *p*-tolunitrile was obtained in addition if the same decomposition products were distilled at an elevated temperature.

TABLE II

RECURRING BANDS IN INFRARED SPECTRA OF ADDUCTS OF ALDOXIMES AND METHYLKETENE DIETHYLACETAL

Aldoxime	8 μ (S)[a]	8 μ (MS)	9 μ (S)	10 μ (M)[b]
Benz-*syn*-	8.12	8.69	9.41	9.99
p-Toly-*syn*-	8.11	8.69	9.40	9.76
p-Nitro-*syn*-	8.21[c]	8.68[c]	9.40[c]	9.92[c]
Benz-*anti*-	8.11	8.70	9.42	9.85[d]
p-Tolu-*anti*-	8.10	8.71	9.40	9.76
Heptan-	8.10	8.68	9.40	9.78

[a] Strong. [b] Medium. [c] Weak. [d] Broad.

Further, it was observed that the decomposition of an adduct of an aliphatic aldoxime, heptanaldoxime, and methylketene diethylacetal gave heptanenitrile alone under the same conditions but no isonitrile was obtained. Accordingly, the formation of isonitrile by the present type of rearrangement seems to be characteristic of aromatic-*syn*-aldoximes in which *trans* migration of the phenyl group is involved in the process. The adducts of *anti*-aldoximes undergo decomposition by *trans* elimination of proton to yield nitriles.

In general, an aromatic-*syn*-aldoxime reacts with methylketene diethylacetal to form an initial adduct, which in turn decomposes to give an isonitrile. However, *p*-anis-*syn*-aldoxime did not react as readily with methylketene diethylacetal as the other aromatic aldoximes and, on prolonged heating, gave monoethyl di-*p*-anisaldimino orthopropionate instead of the expected adduct. No dehydrated product was obtained.

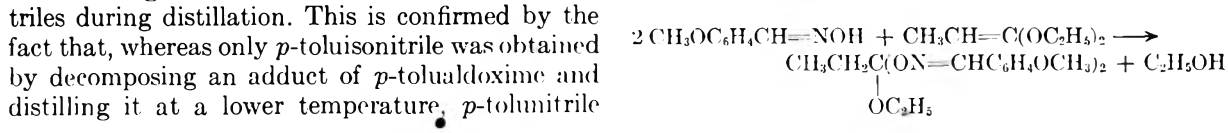


TABLE III

THE DECOMPOSITION OF ADDUCTS OF *syn*- AND *anti*-ALDOXIMES AND METHYLKETENE DIETHYLACETAL IN THE PRESENCE OF A CATALYTIC AMOUNT OF BORON TRIFLUORIDE AND MERCURIC OXIDE IN DRY ETHER

	Isonitrile			Nitrile		
Aldoxime	Yield, %	M.P.	B.P. mm.	Yield, %	M.P.	B.P. (mm.)
Benz-*syn*-	50		64 (22)[a]	45		70 (9)[b]
p-Tolu-*syn*-	73	20–21	62 (6)[c]	23	27–28	52 (4)[d]
p-Nitro-*syn*-	70	119–120				
Benz-*anti*-				60		95–96 (35)
p-Tolu-*anti*-				80	27–28	60 (2)
Heptan-				67		59–60 (21)

[a] The infrared spectrum showed a characteristic absorption peak[13] at 4.72 μ. [b] The infrared spectrum showed an absorption peak at 4.48 μ. [c] The infrared spectrum showed an absorption peak at 4.71 μ. [d] The infrared spectrum showed an absorption peak at 4.48 μ.

TABLE IV

THE DECOMPOSITION OF AN ADDUCT OF *p*-TOLU-*syn*-ALDOXIME AND METHYLKETENE DIETHYLACETAL IN THE PRESENCE OF VARIOUS ACID CATALYSTS

Catalyst	Amount	Reaction Time, Hr.	Yield, % Isonitrile	Yield, % Nitrile	Recovered Adduct, %
Mercuric acetate	0.01 g.	3	—	—	55
Mercuric chloride	0.01 g.	3	—	—	47
Mercuric sulfate	0.01 g.	3	—	—	57
Mercuric oxide	0.02 g.	3	—	—	88
Titanium tetrachloride	5 drops	3	—	75	—
Zinc chloride	0.01 g.	3	Trace	—	53
Zinc chloride	0.05 g.	14	Trace	60	—
Zinc chloride	1.55 g.	3	20	38	—
Ferric chloride	0.05 g.	3	Trace	—	33
Aluminum chloride	0.05 g.	3	—	15	40
Boron trifluoride	3 drops	1	48	38	—
Boron trifluoride and mercuric oxide	3 drops 0.01 g.	3	70	25	—
p-Toluenesulfonic acid	0.05 g.	3	—	—	50[a]
Hydrogen chloride	5 bubbles	3	—	15	40
Hydrogen chloride	Saturated	—	—	40	—[c]
Hydrogen bromide	5 bubbles	3	—	23	33
Boric acid	0.01 g.	3	—	—	57[b]

[a] A crystalline product, monoethyl dialdoximino orthopropionate, m.p. 111.5–113° was obtained. [b] Monoethyl dialdoximino orthopropionate was obtained in 30% yield. [c] *p*-Tolualdoxime hydrochloride, m.p. 146–150° dec. was obtained in 60% yield.

As shown above, isonitriles were obtained in high yields when the adducts of aromatic-*syn*-aldoximes were decomposed in the presence of a catalytic amount of boron trifluoride and mercuric oxide. However, only a 30% yield of isonitrile was obtained when the adduct of *p*-tolualdoxime was decomposed in the presence of a catalytic amount of boron trifluoride and mercuric acetate. In addition, it was found that the decomposition of the adduct of *p*-tolu-*syn*-aldoxime in the presence of a catalytic amount of boron trifluoride alone gave *p*-toluisonitrile in 38% yield along with tarry products. On the other hand, when the adduct was refluxed in the presence of a catalytic amount of mercuric oxide in dry ether, no reaction occurred and the adduct was recovered quantitatively.

In order to examine the possibility of using some other catalysts than those utilized in the above experiment, the decomposition of the adduct of *p*-tolu-*syn*-aldoxime in the presence of similar Lewis acids, such as aluminum chloride, titanium tetrachloride, zinc chloride and ferric chloride, and of mercuric salts, such as mercuric acetate and mercuric chloride, has been investigated. The results are summarized in Table IV. In view of these results, it is concluded that a mixed catalyst of boron trifluoride and mercuric oxide is the most effective for decomposition of the adduct to form *p*-toluisonitrile.

Besides, it was found that a hygroscopic crystalline product which readily decomposes on heating to give isonitrile was obtained when the adduct of *p*-tolu-*syn*-aldoxime was treated in the presence of a catalytic amount of boron trifluoride in dry ether at 10° for three hours. This crystalline product decomposed, when refluxed in the presence of a

catalytic amount of boron trifluoride and mercuric oxide in dry ether, to give a 60% yield of *p*-toluisonitrile, but only a 30% of *p*-toluisonitrile was obtained if the same product was refluxed in dry ether with boron trifluoride alone as the catalyst. It is noteworthy that these results are similar to those obtained when the adduct of *p*-tolu-*syn*-aldoxime and methylketene diethylacetal was decomposed under the same conditions as in the above mentioned experiments. Accordingly, it is reasonable to consider the compound as an intermediate in the dehydration reaction. Since this was hydrolyzed readily to give oxime, however, this compound cannot be analyzed.

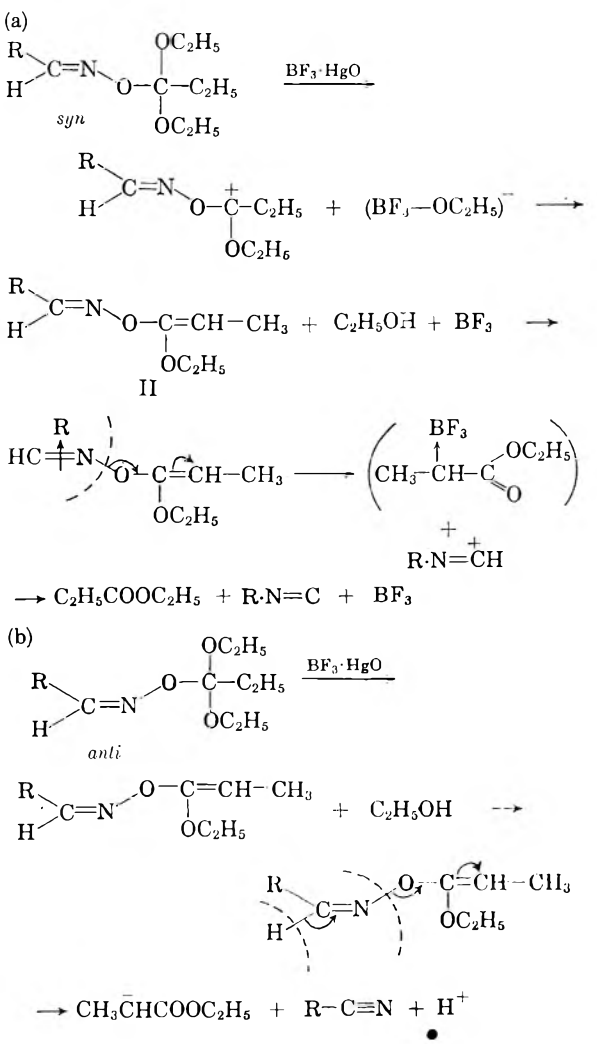
It is now established that the intermediate was hydrolyzed to give *p*-tolu-*syn*-aldoxime in 80% yield along with ethyl propionate, and that it reacted with *p*-tolualdoxime to give monoethyl dialdoximino orthopropionate in 95% yield.

$$[\text{Intermediate}] + H_2O \longrightarrow CH_3C_6H_4CH{=}NOH + C_2H_5COOC_2H_5$$

$$[\text{Intermediate}] + CH_3C_6H_4CH{=}NOH \longrightarrow C_2H_5C(ON{=}CHC_6H_4CH_3)_2(OC_2H_5)$$

[Adduct]

(a)



(b)

Materials. Methylketene diethylacetal was prepared by the method of Walters and McElvain.[5] Aldoximes used in this experiment were prepared from corresponding aldehydes and hydroxylamine hydrochloride.[6-11]

Preparation of the addition compound of benz-syn-aldoxime and methylketene diethylacetal. A solution of 4.7 g. (0.038 mole) of benz-*syn*-aldoxime[6] and 5.0 g. (0.038 mole) of methylketene diethylacetal in 20 ml. of dry ether was refluxed for 4 hr., and the solvent was then distilled. The residue was further distilled under reduced pressure and 8.0 g. (83% of theoretical), b.p. 123° (4.8 mm), n_D^{25} 1.4890, of an addition compound was obtained. The infrared spectrum of the adduct showed bands similar to those of an orthoester[12] at 8.12 μ, 8.69 μ, 9.41 μ, and 9.99 μ.

When benz-*anti*-aldoxime[7] *p*-tolu-*syn*-aldoxime,[8] *p*-tolu-*anti*-aldoxime,[9] and heptanaldoxime[11] were used in the place of benz-*syn*-aldoxime in the above experiment, adducts corresponding to each of them were obtained. The yield, physical properties, analyses, and infrared absorption bands for these adducts are listed in Table I and Table II.

When *p*-nitro-benz-*syn*-aldoxime[10] was used in the place of benz-*syn*-aldoxime in the above experiment, a crystalline product was obtained after the solvent was distilled. It was recrystallized from ligroin and 2.2 g. (52%) m.p. 89–90.5°, of adduct was obtained.

When *p*-anis-*syn*-aldoxime was used in the place of benz-*syn*-aldoxime in the above experiment, *p*-anis-*syn*-aldoxime was recovered quantitatively. When a solution of 2.5 g. (0.016 mole) of *p*-anis-*syn*-aldoxime and 1.96 g.

(5) P. M. Walters and S. M. McElvain, *J. Am. Chem. Soc.*, **62**, 1482 (1940).
(6) E. Beckmann, *Ber.*, **23**, 1684 (1890).
(7) E. Beckmann, *Ber.*, **23**, 1685 (1890); *Ann.*, **365**, 202 (1909).
(8, 9) A. Hantzsch, *Z. Physik. Chem.*, **13**, 510, 523 (1894).
(10) S. Gabriel and M. Herzberg, *Ber.*, **16**, 2000 (1883).
(11) E. W. Bousquest, *Org. Syntheses*, Coll. Vol. II, 313 (1943).
(12) S. M. McElvain and R. E. Starn, Jr., *J. Am. Chem. Soc.*, **77**, 4571 (1955).

(0.016 mole) of methylketene diethylacetal in 20 ml. of dry ether was refluxed for 15 hr., and treated in the same manner, 2.2 g. of monoethyl di-*p*-anisaldoximino orthopropionate, b.p. 122–125° (1 mm.) was obtained.

Anal. Calcd. for $C_{21}H_{26}N_2O_5$: C, 65.27; H, 6.78; N, 7.25. Found: C, 67.91; H, 7.07; N, 7.51.

Decomposition of the adducts. A solution of 8.0 g. (0.03 mole) of the adduct of *p*-tolu-*syn*-aldoxime and methylketene diethylacetal in 20 ml. of dry ether was refluxed in the presence of a mixed catalyst of 2 drops of boron trifluoride (40% ether solution) and 0.01 g. of mercuric oxide for 3 hr. and the solvent was then distilled. The residue was distilled further under reduced pressure, and ethanol, 0.5 g. of ethyl propionate, 2.5 g. (73%) of *p*-toluisonitrile, b.p. 52° (4 mm.), and 0.8 g. (23%) of *p*-tolunitrile, b.p. 79–80° (6 mm.), were obtained. The infrared spectra of *p*-toluisonitrile and *p*-tolunitrile showed the characteristic bands[12] at 4.71 μ and 4.48 μ, respectively.

The same reaction mixture, when distilled below 100° under reduced pressure, yielded ethanol, ethyl propionate, and 1.7 g. (57%) of *p*-toluisonitrile, b.p. 42–43° (2 mm.).

When adducts of benz-*syn*-aldoxime and *p*-nitro-benz-*syn*-aldoxime with methylketene diethylacetal were used in the place of the adduct of *p*-tolu-*syn*-aldoxime and methylketene diethylacetal in the above experiment, corresponding isonitriles and nitriles were obtained. The yields and boiling points are listed in Table III.

When adducts of benz-*anti*-aldoxime, *p*-tolu-*anti*-aldoxime, and heptanaldoxime with methylketene diethylacetal were used in the place of the adduct of *p*-tolu-*syn*-aldoxime and methylketene diethylacetal in the above experiment, ethanol, ethyl propionate, and corresponding nitriles were obtained. The yields and boing points are listed in Table III.

Decomposition of the adduct of p-tolu-syn-aldoxime and methylketene diethylacetal with the other catalysts. A solution of 3 g. (0.011 mole) of the adduct in 3 ml. of dry ether was refluxed in the presence of 0.05 g. of aluminum chloride for 3 hr., and the solvent was then distilled. The residue was further distilled under reduced pressure and ethanol, ethyl propionate, 0.2 g. (15%) of *p*-tolunitrile, b.p. 79–80° (6 mm.), were obtained, and 1.2 g. (40%) of the adduct was recovered.

When other Lewis acids, such as 5 drops of titanium tetrachloride, 0.01 g. of zinc chloride, or 0.05 g. of ferric chloride, protonic acids, such as 5 bubbles of hydrogen chloride, hydrogen bromide, 0.01 g. of boric acids, or 0.05 g. of *p*-toluenesulfonic acid, and mercuric salts, such as 0.01 g. of mercuric acetate, 0.01 g. of mercuric chloride, or 0.01 g. of mercuric sulfate, were used in the place of aluminum chloride in the above experiment, ethanol, ethyl propionate, and the corresponding nitriles were obtained, or the adduct was recovered. The yields are summarized in Table IV.

When one equivalent of zinc chloride (1.55 g.) was used in the place of the above catalysts in the above experiments, ethanol, ethyl propionate, 0.26 g. (20%) of *p*-toluisonitrile, b.p. 53–54° (4 mm.), and 0.5 g. (38%) of *p*-tolunitrile, b.p. 58–59° (2 mm.), were obtained.

When a solution of 5 g. (0.019 mole) of the adduct of *p*-tolu-*syn*-aldoxime and methylketene diethylacetal in dry ether was saturated with hydrogen chloride, at room temperature, 0.8 g. (40%) of *p*-tolunitrile, b.p. 86° (8 mm.), and 2.0 g. (60%) of *p*-tolualdoxime hydrochloride, 146–150° dec., were obtained.

Isolation of the intermediate (II). A solution of 5.0 g. (0.019 mole) of the adduct of *p*-tolu-*syn*-aldoxime and methylketene diethylacetal in 5 ml. of dry ether was stirred in an ice bath in the presence of 1 drop of boron trifluoride (40% ether solution) for 3 hr., and the solvent was then distilled under reduced pressure at room temperature to yield 4.5 g. of a crystalline product.

Thermal decomposition of the intermediate (II). A crystal of 4.5 g. of the intermediate (II) was heated at 120° for 5 min. or 95° for 30 min. and distilled under reduced pressure. Ethyl propionate 1.0 g. (45%), 0.9 g. (41%) of *p*-toluisonitrile, b.p. 53–54° (4 mm.), 1.0 g. (40%) of *p*-tolu-*syn*-aldoxime, b.p. 89–90° (0.4 mm.), m.p. 78°, 1.0 g. were obtained.

Reactions of the intermediate (II). A 0.9-g. sample of the intermediate (II) and 0.3 g. of water were mixed and the reaction mixture was left standing at room temperature for 12 hr. A crystalline product was obtained after water and ethyl propionate were distilled under reduced pressure. When it was recrystallized from ligroin, 0.65 g. (80%) of *p*-tolu-*syn*-aldoxime, m.p. 78°, was obtained.

Reaction of the intermediate (II), *with p-tolu-syn-aldoxime.* A solution of 4.6 g. (0.019 mole) of the intermediate (II) and 2.5 g. (0.019 mole) of *p*-tolu-*syn*-aldoxime in 3 ml. of dry ether was left standing at room temperature for 5 hr. A crystalline product was obtained after the solvent was distilled under reduced pressure. It was recrystallized from ligroin, and 6.4 g. (95%) of monoethyl di-*p*-tolualdoximino orthopropionate, m.p. 111.5–113°, was obtained.

Anal. Calcd. for $C_{21}H_{26}N_2O_5$: C, 71.16; H, 7.39; N, 7.90. Found: C, 71.00; H, 7.53; N, 7.70.

Acknowledgment. The authors wish to express their hearty thanks to Mr. Asaji Kondo for the microanalyses.

OOKAYAMA, MEGURO-KU
TOKYO, JAPAN

(13) I. Ugi and R. Meyr, *Ber.*, **93**, 239 (1960).

[CONTRIBUTION FROM THE EASTERN LABORATORY OF E. I. DU PONT DE NEMOURS & CO.]

Some Reactions of Adamantane and Adamantane Derivatives

GEORGE W. SMITH AND HARRY D. WILLIAMS

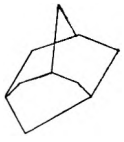
Received October 20, 1960

Reactions of adamantane, including bromination, chlorination, sulfonation, hydroxymethylation, nitration, and air oxidation were investigated. A rather high selectivity for attack in the tertiary position was observed for bromination and nitration. Some selectivity for tertiary substitution was demonstrated in the chlorination reaction when the proper solvent was employed. Monochloroadamantane, 1-bromoadamantane, 1-nitroadamantane, 1,3-dinitroadamantane, trinitroadamantane, 1,3-diaminoadamantane, adamantanone, 1-hydroxyadamantane, 2-aminoadamantane, hydroxymethyladamantane, and adamantanesulfonic acid monohydrate were among the compounds prepared in this study.

Until recently, very few reactions of adamantane were reported in the literature, probably because of the unavailability of the hydrocarbon itself. In the past, adamantane was obtained in small amounts from either petroleum naphtha[1] or by synthetic methods, the best of which afforded over-all yields of only a few per cent. An excellent review of the literature on the chemistry of adamantane ring systems appeared in 1954.[2] Recently, a two-step preparation of adamantane from dicyclopentadiene was reported.[3] In view of this new source of adamantane and an interesting report on the bromination and iodination of adamantane,[4] we were prompted to investigate some reactions of this unique hydrocarbon. After the work described herein was completed, the preparation of certain 2-substituted derivatives of adamantane by a hydroxylation process was reported.[5]

RESULTS AND DISCUSSION

The highly symmetrical molecule of adamantane (I) possesses six secondary carbons and four



I

tertiary (bridgehead) carbons. It was of interest to determine the relative ease of attack at the secondary and tertiary positions in various reactions. The results reported for the bromination of adamantane indicated that the product isolated was the tertiary monobromo derivative.[4] Recently, more evidence including NMR data was offered to show that the monobromo derivative was the bridgehead compound.[6] Our work on the bromination of adamantane indicated the same conclusion. When the bromination of adamantane was carried out in a manner similar to that described by Landa and co-workers,[4] almost the entire product was monobromoadamantane. Vapor chromatography showed that only one major product and a trace amount (<1%) of a minor product (probably a dibromo derivative) of higher retention time were present. Resolution of the monobromo peak was not realized even at lower column temperatures and reduced helium rates. This fact and the sharp melting point of the product indicated that a single isomer was present. Furthermore, NMR studies indicated that the single isomers obtained was the tertiary derivative. Such a high selectivity of attack by bromine was previously observed in other bromination reactions.[7] Bromination of monobromoadamantane afforded low conversions to a dibromo derivative. When the reaction temperature was increased from 100° to 125° the attack of bromine was less selective as evidenced by the presence of additional peaks in the dibromo region of the vapor chromatograms.

In contrast to the reaction of bromine, chlorine attacked the hydrocarbon in a random manner to yield a complex mixture of chloro derivatives. The separation of individual isomers was not easily accomplished. According to a report of some recent work on the photochlorination of 2,3-dimethylbutane, certain aromatic solvents caused an increased selectivity for attack at the tertiary positions.[8] Even more recently, additional information concerning solvent effects in chlorination reactions was reported.[9,10] Because of the random attack observed in the photochlorination of adamantane in carbon tetrachloride, other solvents were substituted which were reported to increase the selec-

(1) S. Landa and V. Machaček, *Coll. Czech. Chem. Comm.*, **5**, 1 (1933).

(2) H. Stetter, *Angew. Chem.*, **66**, 217 (1954).

(3) P. von R. Schleyer, *J. Am. Chem. Soc.*, **79**, 3292 (1957).

(4) S. Landa, S. Kriebel, and E. Knobloch, *Chem. Listy*, **48**, 61 (1954); *Chem. Abstr.*, **49**, 1598 (1955).

(5) P. von R. Schleyer, Abstracts of Papers, Third Delaware Valley Regional Meeting, American Chemical Society, Philadelphia, Pa., Feb. 25, 1960.

(6) H. Stetter, M. Schwary, and A. Hirschhorn, *Ber.*, **92**, 1629 (1959).

(7) A. V. Grosse and V. N. Ipatieff, *J. Org. Chem.*, **8**, 438 (1943).

(8) G. A. Russell, *J. Am. Chem. Soc.*, **79**, 2977 (1957).

(9) (a) *J. Am. Chem. Soc.*, **80**, 4987 (1959); (b) *J. Am. Chem. Soc.*, **80**, 4997 (1958); *J. Am. Chem. Soc.*, **80**, 5002 (1958).

(10) C. Walling and M. F. Mayahi, *J. Am. Chem. Soc.*, **81**, 1485 (1959).

tivity of attack. Indeed, in photochlorination experiments identical in every detail except for the solvent employed, a change in the product composition occurred. Carbon tetrachloride, benzene, and carbon disulfide were employed as the solvents in these experiments. Both monochloroadamantane isomers were formed in these reactions, but the ratio of these two isomers varied with the solvent used. Table I illustrates the ratio change as estimated from vapor chromatographic results. Monochloro isomer A, which had the shortest retention time, is believed to be 1-chloroadamantane. After isolation and purification, this isomer gave a melting point which corresponded to that reported for the 1-chloro derivative prepared by an independent route.[6] Also of interest is the fact that vapor chromatography showed that no polychlorination of adamantane occurred in carbon disulfide under the conditions employed and only a very minor amount occurred in benzene. However, when carbon tetrachloride was employed as solvent, a fair amount of polychlorination did occur.

TABLE I

EFFECT OF SOLVENT ON RATIO OF MONOCHLOROADAMANTANE ISOMERS

Solvent	Monochloro Isomer A/ Monochloro Isomer B
Carbon disulfide	2.10
Benzene	1.17
Carbon tetrachloride	0.63

Thus, the effect of certain solvents in the photochlorination of adamantane apparently is to decrease the activity of the chlorinating species as evidenced by the selectivity of attack and the decrease in polychlorination. These results are in agreement with those reported earlier.[8-10]

A derivative which contained a sulfonic acid group was isolated from the reaction of adamantane with sulfur dioxide and oxygen according to the "Hostapon" process.[11] Elemental analysis indicated that this compound was the monohydrate of adamantane sulfonic acid. Infrared analysis clearly showed the presence of a hydrated sulfonic acid group. It was not determined whether the sulfonic acid was the secondary or tertiary derivative.

The free radical addition of adamantane to formaldehyde yielded a product from which hydroxymethyladamantane was isolated.[12] Although the position of the hydroxymethyl group on the adamantane nucleus was not determined, the melting point of our derivative coincides with that reported recently for 1-hydroxymethyladamantane.[6]

It was reported that adamantane is not attacked by concentrated nitric acid even under the most severe conditions.[2] Also in our studies, no nitration occurred when adamantane reacted with 20% nitric acid at 130° and 500 psi nitrogen pressure. The absence of a mutual solvent for the reagents probably is the main reason for the failure to react.

In an attempt to carry the reaction out under more ideal conditions, a mutual solvent was employed. Nitration did occur in carbon tetrachloride when adamantane and nitrogen dioxide were subjected to 140–160° and 300 p.s.i.ga. nitrogen pressure.[13] The use of carbon tetrachloride in the reaction, however, was not satisfactory, because attack on the solvent by reaction intermediates led to the formation of chloroadamantane derivatives in addition to the nitration products.[14] The formation of chloro compounds by such an attack on carbon tetrachloride has been reported in other reactions.[15,16]

Glacial acetic acid was a more amenable solvent for the nitration reaction. The reaction of adamantane and concentrated nitric acid in this medium led to nitro compounds as the major products plus minor amounts of oxidation products (carbonyl and hydroxy derivatives). As in the bromination reaction, nitration of adamantane gave a highly selective attack in the tertiary positions. If the reaction was carried out at 140° and 500 psi nitrogen pressure, the major product was 1-nitroadamantane. Further nitration of this product at 170° and 600 p.s.i.ga. nitrogen pressure yielded 1,3-dinitroadamantane (20% yield from adamantane) as the principal product. Reaction temperatures above 170° afforded a greater proportion of oxidation products, whereas at 100° little or no reaction occurred. A trinitroadamantane derivative also was isolated from the reaction mixture.[17]

Catalytic hydrogenation of 1,3-dinitroadamantane to 1,3-diaminoadamantane was essentially quantitative. A few derivatives of this diamine (a known compound prepared by an independent route[18]) which included the picrate, the dihydro-

(11) T. B. Brooks, *The Chemistry of the Nonbenzenoid Hydrocarbons*, Reinhold, New York, 1950, p. 190.

(12) A procedure similar to that employed by Fuller and Rust with other hydrocarbons was used (G. Fuller and F. R. Rust, *J. Am. Chem. Soc.*, 80, 6148 (1958)).

(13) Reaction also occurred with nitrogen dioxide in the absence of a solvent, but under the conditions employed (batch reaction), the reaction was difficult to control.

(14) The presence of chloro and chloronitro derivatives of adamantane was indicated by qualitative and quantitative analyses as well as infrared analysis (a band at 9.70 μ is characteristic of chloroadamantane).

(15) P. Wilder, Jr., and A. Winston, *J. Am. Chem. Soc.*, 75, 5370 (1953).

(16) W. G. Dauben and H. Tilles, *J. Am. Chem. Soc.*, 72, 3183 (1950).

(17) The alkali-insolubility of this trinitro derivative and the high selectivity for attack at the tertiary positions observed in the nitration reaction suggest that this compound is the 1,3,5- isomer.

(18) V. Prelog and R. Seiwerth, *Ber.*, 74, 1771 (1941).

chloride, a carbonate, and the dibenzamide were prepared. An agreement of the melting points of our derivatives with those of known compounds showed that our compound was the 1,3- isomer. A rather stable dinitrous acid salt of the diamine also was prepared.

Air oxidation of adamantane afforded both adamantanone and 1-hydroxyadamantane, as well as at least one unidentified polysubstituted derivative. The reaction was carried out in a mixture of benzene and glacial acetic acid (50/50 vol.%) in the presence of cobalt acetate and an organic peroxide at 140–145° and 800 p.s.i.ga. air pressure. At 100° very little oxidation occurred, while at 170° the oxidation apparently proceeded too far as evidenced by a smaller yield of total oxidate.

A comparison of the air oxidates from two runs, identical except for the peroxide used, is given in Table II. These results show that larger amounts of oxidation products were isolated when di-*t*-butyl peroxide was used as the catalyst. Also, this peroxide apparently caused a greater selectivity for attack at the tertiary positions as evidenced by the increase in the concentration of 1-hydroxyadamantane relative to the concentration of adamantanone.

TABLE II

ADAMANTANE AIR OXIDATE

	% Yield[a]	
	Run A[b]	Run B[c]
1-Hydroxyadamantane	8	21.5
Adamantanone	10	12.0
Unknown[d]	6	4.8
Total Oxidate	24	38.3

[a] Calculated from vapor chromatography results. [b] Benzoyl peroxide used as catalyst. [c] Di-*t*-butyl peroxide used as catalyst. [d] For calculation, the unknown was assumed to be a hydroxyadamantanone.

The ketone derivative was catalytically hydrogenated in the presence of ammonia to yield 2-aminoadamantane. A mixed melting point of the monohydroxyadamantane derivative isolated from the air oxidate with 1-hydroxyadamantane prepared by the hydrolysis of 1-bromoadamantane gave no depression.

In general, the reactions of adamantane indicated that attack occurs preferentially at the tertiary positions. In the case of a more reactive agent, such as a chlorine radical, the attack becomes more random. However, when the reactivity of the attacking group is moderated in some manner, a greater selectivity is realized.

EXPERIMENTAL[19]

Preparation of adamantane. The general procedure as outlined by Schleyer was employed in the preparation of adamantane.[3] Final purification of adamantane was accomplished by recrystallization from petroleum ether (b.p. 60–90°). The pure hydrocarbon melted at 268.5–269.5°.

Analysis of compounds. The infrared analyses were made on a Perkin-Elmer Model 21 spectrophotometer using sodium chloride optics. The vapor-phase chromatography was performed on an F & M Scientific Corporation high temperature vapor fractometer (Model 17A). The column consisted of 5 feet of silicone-on-Celite and temperatures are mentioned in the description of the individual experiments.

1-Bromoadamantane. Bromination of adamantane was carried out in a manner similar to the procedure employed by Landa and co-workers.[4] A mixture of 6.8 g. (0.05 mole) of adamantane and 32.0 g. (0.20 mole) of bromine was placed in a glass-lined shaker bomb and heated at 100° for 4.0 hr. at 400 p.s.i.ga. nitrogen pressure. The reaction mixture was dissolved in carbon tetrachloride, washed successively by 10% sodium sulfite solution and 5% sodium bicarbonate solution, and dried over anhydrous calcium chloride. Concentration of the dried solution and sublimation of the residue at 15–20 mm. pressure and 80–100° afforded 8.3 g. (76% yield) of white solid, m.p. 115–117°. Vapor chromatography (temperature 244°) showed that only one component was present, discounting trace quantities (<1%) of another compound (higher retention time). Recrystallization of the product from methanol and subsequent sublimation yielded the pure compound, m.p. 117.0–117.5° (lit.,[6] m.p., 118°).

Anal. Calcd. for $C_{10}H_{15}Br$: C, 55.82; H, 7.03; Br, 37.1. Found: C, 55.32; H, 7.08; Br, 36.8.

Chlorination of adamantane. The photochlorination of adamantane was carried out at 25–30° by metering 0.037 mole of chlorine into a solution of 10.0 g. (0.074 mole) of adamantane in 100 ml. of solvent in the presence of illumination by a 150-watt G.E. flood lamp. The solvents employed were carbon tetrachloride, benzene, and carbon disulfide. After a short induction period (approximately 2 min.) the reaction was initiated as evidenced by the fading of the chlorine color and the evolution of hydrogen chloride. The reaction mixture was washed by 5% sodium carbonate solution, water, and dried over anhydrous sodium sulfate. The product obtained by concentration of the dried solution was shown by vapor chromatography (temperature—200°) to consist mainly of adamantane and the two monochloroadamantane isomers.

Recrystallization from methanol and sublimation of one chlorination product led to the isolation of the monochloroadamantane isomer with the shortest retention time as indicated by vapor chromatography. This waxy compound melted at 168.5–169.5° (lit.,[6] m.p. for 1-chloroadamantane, 165°).

Anal. Calcd. for $C_{10}H_{15}Cl$: C, 70.36; H, 8.86. Found: C, 70.45; H, 8.93.

Vapor chromatography of this product, however, showed that small amounts of the other monochloro isomer and adamantane were still present as minor contaminants.

Adamantane sulfonic acid hydrate. Sulfur dioxide (0.0736 mole) and oxygen (0.0736 mole) were metered simultaneously into a mixture of 5.0 g. (0.0368 mole) of adamantane, 75 ml. of acetic anhydride, and 2.0 ml. of 30% hydrogen peroxide at 70° for 1.0 hr. During the reaction period the mixture was illuminated by a 150-watt G.E. flood lamp. At the end of the reaction time, the reaction mixture was cooled and poured over 200 g. of ice. Sulfur dioxide was then passed into the ice mixture for a few minutes to decompose the intermediate peranhydride. The acid solution was filtered to remove 2.9 g. of unchanged adamantane. Concentration of the filtrate at reduced pressure yielded a pale yellow viscous residue (mixture of liquid and solid) which, after drying for several days in a vacuum desiccator, weighed 8.1 g. Ethyl acetate (10 ml.) was mixed with this residue, and the resulting insoluble white solid was filtered to give 1.25 g. of

(19) All melting point determinations were made in sealed capillaries and are uncorrected.

material which melted with decomposition at approximately 170–175°. Recrystallization from ethyl acetate yielded colorless crystals, m.p. 174.4–175.9° (some decomposition) which, when dissolved in water, produced a strongly acidic solution.

Anal. Calcd. for $C_{10}H_{18}O_4S$: C, 51.26; H, 7.74. Found: C, 50.99; H, 7.78.

The elemental analysis indicated that the compound was the monohydrate of adamantane sulfonic acid. Infrared analysis supported the elemental analysis of showing evidence for the presence of a hydrated sulfonic acid group in the pure compound.

The ethyl acetate from which the sulfonic acid derivative was filtered was concentrated, and on standing the residue slowly crystallized (presumably additional sulfonic acid compound).

Hydroxymethyladamantane. A mixture of 20.4 g. (0.15 mole) of adamantane, 9.3 g. (0.114 mole of formaldehyde) of formalin, 2.20 g. of di-*t*-butyl peroxide and 120 ml. of benzene (thiophene-free) was heated in a stainless steel autoclave at 145° and approximately 500 p.s.i.ga. nitrogen pressure for 12 hr. The reaction mixture then was dissolved in additional benzene and ethyl ether and dried over anhydrous magnesium sulfate. Concentration of the dried solution yielded 19.5 g. of a pale yellow solid, which infrared analysis indicated was mainly unchanged adamantane with a minor amount of a hydroxy compound and a trace of a carbonyl derivative. Vapor chromatography (temperature 245°) showed that adamantane comprised 87% of the crude product while a second compound of higher retention time comprised the balance (approximately 12%) of the product. Recrystallization of the crude material from absolute ethanol effected a separation of a large amount of the less soluble adamantane. Concentration of the filtrate from this recrystallization, sublimation (100° and 15–20 mm. pressure) of the residue, and recrystallization of a portion of the sublimate from petroleum ether (b.p., 60–90°) afforded colorless crystals, m.p. 113.2–114.5° (lit.,[6] m.p. of 1-hydroxymethyladamantane, 115°).

Anal. Calcd. for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.50; H, 11.04.

Nitration of adamantane. 1-Nitroadamantane. A mixture of 68.0 g. (0.50 mole) of adamantane and 500 ml. of glacial acetic acid was charged to a stirred stainless steel 1-l. autoclave which was pressurized with nitrogen to a total pressure of 500 p.s.i.ga. After the mixture was heated to 140°, 90.0 g. (1.0 mole) of concd. nitric acid was introduced into the reaction zone by means of a feed pump at a rate of 5–6 ml. per min. When the acid feed was completed, the reaction temperature was maintained at 140° for 15 min., after which time the reaction mixture was cooled to room temperature and diluted with an excess of water to precipitate the products. The filtered solids were slurried with a mixture of 100 ml. of methanol, 150 ml. of water, and 17 g. of potassium hydroxide for 18.0 hr. at room temperature. After dilution with 150 ml. water, the alkali-insoluble material was extracted by petroleum ether (b.p., 60–90°). The petroleum ether extracts were washed by water and dried over anhydrous magnesium sulfate. Concentration of this solution afforded a white solid, m.p. 125–144°, which weighed 38.0 g. The aqueous alkali solution from which the alkali-insoluble material had been extracted was cooled to 0–3° and neutralized by the dropwise addition of an aqueous acetic acid-urea mixture according to the procedure of Kornblum and Graham.[20] The alkali-soluble nitro derivative regenerated by this procedure weighed 1.5 g. and melted over the range 136–160°. Vapor chromatography (temperature 261°) showed that the alkali-insoluble sample was largely mononitroadamantane (72%) with a smaller amount of dinitroadamantane as well as a few unidentified components in minor quantities. The separation of analytically pure mononitroadamantane from the other components of the alkali-insoluble product was difficult. However, by recrystallization from methanol and repeated sublimation (80–90° at 15–20 mm.) a pure sample of 1-nitroadamantane, a white, waxy compound, m.p. 158.5–159.0°, was obtained.[21]

Anal. Calcd. for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.22; H, 8.34; N, 7.50.

The infrared spectrum of this compound showed that the symmetrical and asymmetrical stretching bands of the NO_2 group are located at 7.32 μ and 6.52 μ, respectively.

1,3-Dinitroadamantane. This dinitro derivative, which was formed in small amounts under the above conditions, was obtained as the major product either by further nitrating the above alkali-insoluble product at 170° and 600 psi nitrogen pressure or by a more facile procedure of nitrating adamantane in two steps without isolation of the intermediate mononitro derivative. The latter procedure is described in the following. A mixture of 90 g. (0.66 mole) of adamantane and 500 g. of glacial acetic acid was charged to a stirred stainless steel 1-l. autoclave and pressurized to 500 p.s.i.ga. with nitrogen. After heating the contents of the autoclave to 140°, 85 ml. of conc. nitric acid (1.32 moles nitric acid) was introduced into the reaction zone by means of a feed pump at a rate of 8 ml. per min. At the completion of the acid feed and an additional 10-min. period, the pressure was increased to 600 p.s.i.ga. with nitrogen and the temperature was increased to 170°. At this point, 43 ml. of concd. nitric acid (0.66 mole nitric acid) was fed into the reaction zone as before. After completion of this second acid feed, the reaction mixture was maintained at 170° for 10 min. and then cooled to room temperature. The alkali-insoluble and alkali-soluble products were separated as described earlier. The white alkali-insoluble product, m.p. 160–166°, weighed 46 g., and the alkali-soluble product regenerated from its *aci*-salt weighed 7.8 g. Vapor chromatography (at 283°) of the alkali-insoluble product indicated the following composition.

Identity of Component[a]	% of Product
Adamantane	2–3
Mononitroadamantane	16
Unknown	7
Unknown	8
Dinitroadamantane	61[b]
Unknown	2
Trinitroadamantane	4

[a] In order of increasing retention times. [b] Corresponds to a 20% yield from adamantane.

Recrystallization of this alkali-insoluble product from methanol afforded a separation of the less soluble dinitro derivative. Sublimation (100° and 15–20 mm.) of pure 1,3-dinitroadamantane, m.p. 213.5–214.0°, yielded long, silky, colorless needles.

Anal. Calcd. for $C_{10}H_{14}N_2O_4$: C, 53.09; H, 6.24; N, 12.38. Found: C, 53.25; H, 6.28; N, 12.38.

The infrared spectrum of this compound placed the nitro group absorption bands at 6.48 μ and 7.32 μ.

Trinitroadamantane. One alkali-insoluble nitration product was recrystallized from an excess of methanol in order to obtain only the least soluble product. This product was extracted by boiling ethyl ether, and the insoluble white solid was recrystallized from a mixture of ethanol, petroleum ether (b.p., 90–120°), and chloroform to yield white crystals, m.p. 291.0–291.8°.

Anal. Calcd. for $C_{10}H_{13}N_3O_6$: C, 44.28; H, 4.83; N, 15.49. Found: C, 44.50; H, 5.11; N, 15.55.

The positions of the symmetrical and asymmetrical stretching nitro bands in the infrared spectrum are 7.31 μ and 6.47 μ, respectively.

(20) N. Kornblum and G. E. Graham, *J. Am. Chem. Soc.*, **73**, 4041 (1951).

(21) Melting point reported for this compound is 173° [H. Stetter, J. Mayer *et al.*, *Ber.*, **93**, 226 (1960)].

1,3-Diaminoadamantane. A mixture of 16.2 g. of 1,3-dinitroadamantane (m.p. 213.5–214.0°), 175 ml. of absolute ethanol, and approximately 20 g. of Raney nickel was hydrogenated in a Parr apparatus at 50–60° and an initial hydrogen pressure of 50 p.s.i.ga. After 100 min. the theoretical amount of hydrogen had been absorbed. Concentration of the colorless solution (after filtration to remove catalyst) at reduced pressure (15–20 mm.) gave a semisolid residue. After drying in a vacuum desiccator for several days, the white solid weighed 11.0 g. (92.4% yield). Due to the hygroscopic nature of the diamine, a melting point was not obtained. Vapor chromatography (at 208°) of the product showed that only a single component was present.

When exposed to the atmosphere a sample of the diamine, at first, appeared wet as it rapidly absorbed water and carbon dioxide, but on standing became a dry solid. Elemental analysis indicated that one mole of carbon dioxide and two moles of water were absorbed by the diamine.

Anal. Calcd. for $C_{10}H_{18}N_2 \cdot CO_2 \cdot 2\ H_2O$: C, 53.64; H, 9.00. Found: C, 53.61; H, 8.95.

1,3-Diaminoadamantane dihydrochloride. The dihydrochloride was obtained by bubbling dry hydrogen chloride into an ether solution of the diamine. The dihydrochloride was purified by dissolving in a small amount of water and reprecipitating by adding an excess of acetone. On heating this compound did not melt, but gradually decomposed above 300°, apparently decomposing completely at approximately 430°.[22]

Anal. Calcd. for $C_{10}H_{20}N_2Cl_2$: C, 50.25; H, 8.43; N, 11.71. Found: C, 49.58; H, 8.59; N, 11.84.

The picrate of this diamine was prepared according to the procedure of Shriner and Fuson.[23] The picrate melted and decomposed at approximately 300°. This result agrees fairly well with the value (290–295°) reported in the literature.[18]

Dibenzamide of 1,3-diaminoadamantane. This derivative was prepared by adding benzoyl chloride to a 10% aqueous solution of the diamine. After addition of dilute sodium hydroxide solution, the mixture was stirred for 1.0 hr. The insoluble spongy mass was separated from the aqueous solution and stirred in petroleum ether (b.p. 60–90°) to yield a white crystalline material. Recrystallization of this product from absolute ethanol gave colorless crystals, m.p. 246.5–248.0 (lit.[18] m.p., 248°).

Anal. Calcd. for $C_{24}H_{26}N_2O_2$: C, 76.97: H, 7.00; N, 7.48. Found: C, 76.94; H, 6.98; N, 7.27.

1,3-Adamantyl diammonium nitrite. A mixture of 4.4 g. (0.0265 mole) of 1,3-diaminoadamantane, 0.06 g. of cupric chloride, 20 ml. of methanol, and 5 ml. of water was placed in a small stainless steel shaker bomb, pressurized by nitric oxide to 200–300 p.s.i.ga. and heated at 70° for 3.0 hr. The reaction mixture was concentrated to a solid dark residue at reduced pressure (15–20 mm.) and last traces of water were removed azeotropically with ethanol. Treatment of this residue with a mixture of ethanol and ethyl ether yielded a white solid which was filtered and washed with a small amount of ethanol. After drying, the white solid melted at 158.5–159.5° with some decomposition and weighed 1.2 g. (17.4%). Purification was carried out by dissolving the compound in a minimum of boiling methanol and then diluting with an equal volume of boiling acetone to precipitate the product. The pure compound melted sharply with decomposition at 165.5°.

Anal. Calcd. for $C_{10}H_{20}N_4O_4$: C, 46.14; H, 7.75; N, 21.53. Found: C, 46.36; H, 7.82; N, 21.28.

The infrared spectrum of this compound confirmed the presence of the $-NH^+_3$ group as well as the $—ONO^-$ group. The presence of ionic nitrite also was indicated by a positive Griess test.

The above ammonium nitrite derivative also was obtained in 74% yield by the reaction of the diamine dihydrochloride and freshly precipitated silver nitrite according to the procedure of Monserrat and Prosper.[24]

Air oxidation of adamantane. To a 1-l. stirred stainless steel autoclave was added 60.0 g. (0.441 mole) of adamantane, 0.7 g. of cobalt acetate tetrahydrate, 0.5 g. of di-*t*-butyl peroxide, 150 ml. of glacial acetic acid, and 150 ml. of benzene. The system was pressurized with 800 p.s.i.ga. air pressure and heated to 140–145° for 4.0 hr. After cooling to room temperature the reaction mixture was diluted with 1250 ml. of water, and the insoluble material was extracted by benzene. The benzene extract was washed with water and 5% sodium bicarbonate solution, and dried over anhydrous magnesium sulfate. Concentration of the dried benzene solution yielded 46.5 g. of a yellow solid. Infrared analysis of this product indicated that carbonyl and hydroxy compounds as well as unreacted adamantane were present. Vapor chromatography (at 201°) of the oxidate identified three of the four components from their retention times. The following concentrations were estimated from the vapor chromatogram.

Component[a]	% of Oxidate
Adamantane	44
Hydroxyadamantane	31
Adamantanone	17
Unknown	7.5

[a] Listed in order of increasing retention time.

Sublimation (80–100° and 15–20 mm.) of the air oxidate afforded only a partial separation of the products.

2,4-Dinitrophenylhydrazone of adamantanone. This derivative was prepared from a mixture of hydroxyadamantane and adamantanone according to a standard procedure.[23] The compound was purified by recrystallization from a mixture of 95% ethyl alcohol and ethyl acetate to yield golden yellow silky needles, m.p. 213.5–214.5°.

Anal. Calcd. for $C_{16}H_{18}N_4O_4$: C, 58.17; H, 5.49; N, 16.96. Found: C, 58.95; H, 5.47; N, 16.19.

Oxime of adamantanone. The oxime derivative was prepared from a mixture of hydroxyadamantane and adamantanone according to Procedure B outlined by Shriner and Fuson.[25] Recrystallization of the crude oxime from aqueous ethyl alcohol gave colorless needles, m.p. 162.8–163.6.

Anal. Calcd. for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.74; H, 9.11; N, 9.13.

Adamantanone. A sample of the purified oxime (see above) was hydrolyzed by heating with 10% hydrochloric acid at 100° for 2.0 hr. The ketone which separated from solution was extracted by ethyl ether and the ether extract was washed by water and 5% sodium bicarbonate solution, and finally was dried over anhydrous magnesium sulfate. Sublimation (75–80° at 15–20 mm.) of the residue obtained by concentration of the ether solution yielded a white solid, m.p. 224.0–225.0°.

Anal. Calcd. for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 80.00; H, 8.99.

1-Hydroxyadamantane. A solution of 6.1 g. of a portion of the sublimed air oxidate in 100 ml. of 95% ethyl alcohol saturated with ammonia was hydrogenated in the presence of 2.0 g. of 5% palladium-on-alumina in a Parr apparatus at 50–55° and an initial hydrogen pressure of 45 p.s.i.ga.

(22) Prelog reported that this compound did not melt below 360°.[18]

(23) R. L. Shriner and R. C. Fuson, *The Systematic Identification of Organic Compounds*, John Wiley & Sons, Inc., New York, 1948, p. 171.

(24) M. P. Monserrat and F. E. Prosper, *Rev. cienc. apl. (Madrid)*, **12**, 293 (1958).

(25) R. L. Shriner and R. C. Fuson, *The Systematic Identification of Organic Compounds*, John Wiley & Sons, Inc., New York, 1948, p. 202.

After the hydrogen absorption ceased, the reaction mixture was cooled to room temperature and filtered to remove the catalyst. The solid residue obtained by concentration of the alcohol solution at reduced pressure was treated with dilute hydrochloric acid to separate the amine as its water-soluble hydrochloride, and the water-insoluble hydroxy derivative was extracted by ethyl ether. After washing the ether extract with equal volumes of water and 5% sodium bicarbonate solution and drying over anhydrous magnesium sulfate, the solution was concentrated to yield 3.6 g. of white solid. Recrystallization of this product from methanol afforded a white solid, m.p. 277.0–278.0° (lit.,[6] m.p. 282°). Sublimation of this material gave colorless needles with no change in melting point.

Anal. Calcd. for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.82; H, 10.54.

The hydrolysis of 1-bromoadamantane by refluxing with dilute aqueous silver nitrate solution afforded a hydroxyadamantane with the same melting point as that obtained from the air oxidate derivative. A mixed melting point of these two compounds gave no depression.

2-Aminoadamantane hydrochloride. The aqueous hydrochloride acid solution from which hydroxyadamantane was separated (see above) was neutralized in 10% sodium hydroxide solution. The free amine which separated was extracted by ethyl ether and the solution was dried over anhydrous magnesium sulfate. Concentration of the solution yielded 0.6 g. of the amine, which on sublimation (75° and 15–20 mm.) afforded pure 2-aminoadamantane, m.p. 230.5–236°. (Due to the rapid absorption of water and carbon dioxide from the atmosphere, an analytically pure sample of the free amine was not obtained.)

The sublimed 2-aminoadamantane was dissolved in ethyl ether plus a small amount of ethyl alcohol, and the hydrochloride derivative was precipitated by passing dry hydrogen chloride into the solution. Recrystallization of the amine hydrochloride from isopropyl alcohol yielded colorless needles of 2-aminoadamantane hydrochloride which, on heating in a capillary, gradually decomposed over the range 300–325°.

Anal. Calcd. for $C_{10}H_{18}NCl$: C, 63.99: H, 9.67; N, 7.46. Found: C, 64.35; H, 9.59; N, 7.43.

Acknowledgment. The authors wish to express their appreciation to Mr. L. J. Lohr for the interpretation of the infrared spectra and the vapor-phase chromatographic work.

GIBBSTOWN, N. J.

[CONTRIBUTION FROM THE EVANS CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

Condensed Cyclobutane Aromatic Compounds. XIV. Naphtho[*b*]cyclobutene: Reactions of the Aromatic Nucleus

M. P. CAVA AND R. L. SHIRLEY

Received December 21, 1960

Peracetic acid oxidation of naphtho[*b*]cyclobutene (I) gave the quinone 1,2-dihydrocyclobuta[*b*]naphthalene-3,8-dione (II). The butadiene adduct (III) of this quinone was reduced to diol IV, which was dehydrated with rearrangement to 9,10-ethanoanthracene. The 3-nitro and 3-amino derivatives of naphtho[*b*]cyclobutene are described, and the effect of the cyclobutene ring upon the chromophores of these compounds is discussed.

The synthesis of the hydrocarbon naphtho[*b*]-cyclobutene (I) was described in a previous paper of this series.[1] Some transformations of I are now described which involve attack upon the naphthalene nucleus of this molecule.

The direct oxidation of naphtho[b]cyclobutene with peracetic acid occurred readily to give, in 22% yield, a single bright yellow neutral compound $C_{12}H_8O_2$. This substance was assigned the structure 1,2-dihydrocyclobuta[b]naphthalene-3,8-dione (II) on the basis of the analogous oxidation of 2,3-dimethylnaphthalene to 2,3-dimethyl-1,4-naphthoquinone.[2] This assignment was verified by an interesting series of transformations leading to 9,10-ethanoanthracene.

I II

The new quinone II reacted with butadiene at 90–100° to give, after ninety minutes, a colorless adduct (III), m.p. 92–93°, in 93% yield. In contrast to this behavior, 2,3-dimethyl-1,4-naphthoquinone was recovered unchanged after five days under the same conditions. The greatly enhanced reactivity of quinone II as a dienophile must be attributed to the decrease in strain which results by conversion of the cyclobutene ring of II to the cyclobutane system of the adduct.

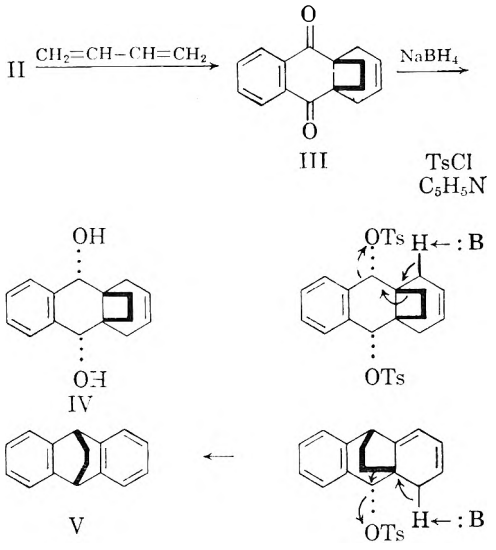
The diketone III was reduced smoothly by sodium borohydride to a single diol IV, m.p. 205.5–206°, in 79% yield. The configuration assigned to the diol, on mechanistic grounds, is that in which the hydroxyl groups are *cis* to each other as well as to the cyclohexene ring. This stereochemistry would result from attack of borohydride ion on the carbonyls of III from the less hindered cyclobutane side of the molecule.

Diol IV reacted with two equivalents of *p*-toluenesulfonyl chloride in pyridine to give directly, in 60% yield, 9,10-ethanoanthracene (V).[3] This

(1) M. P. Cava and R. L. Shirley, *J. Am. Chem. Soc.*, 82, 654 (1960).

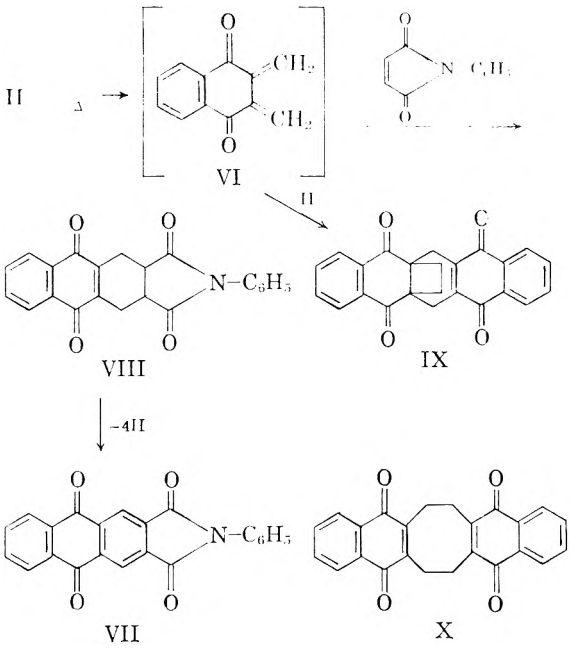
(2) R. T. Arnold and R. Larson, *J. Org. Chem.*, 5, 250 (1940).

rearrangement reaction can be explained most simply as proceeding via the ditosylate of diol IV, by a series of two solvolytic carbonium ion shifts, probably concerted in nature as shown below. Both the relief of strain resulting from expansion of the cyclobutane ring and the aromatization of the cyclohexene system provide driving forces for the process.



Although quinone II reacts normally as a dienophile in the Diels-Alder reaction, it may also react as a diene at elevated temperatures, probably by thermal rupture of the cyclobutene ring to generate a transient true diene intermediate VI. Thus II reacted with *N*-phenylmaleimide at 200–220° to give *N*-phenyl-9,10-anthraquinone-2,3-dicarboximide (VII) in 14% yield. This anthraquinone derivative was identical with a sample prepared by the chromic acid oxidation of *N*-phenylanthracene-2,3-dicarboximide.[1] The expected initial adduct (VIII) was not found: probably it was dehydrogenated directly to VII by quinone II, a hypothesis consistent with the low yield of VII obtained in the reaction.

Careful observation of the melting point behavior of quinone II revealed that, upon rapid heating, it melted at about 185–190° but immediately resolidified to a sparingly soluble yellow dimer (IX), melting at 255–260° with decomposition. A compound of structure IX would be formed by the thermal cleavage of II to diene VI, followed by a rapid Diels-Alder addition of VI to unchanged quinone II. In support of structure IX, the ultraviolet spectrum of the dimer was essentially identical to that of an equimolar solution of the butadiene adduct III and 2,3-dimethyl-1,4-naphthoquinone. The spectral evidence eliminated from serious consideration the alternate dimer formulation X, which should show ultraviolet



absorption quite similar to that of 2,3-dimethyl-1,4-naphthoquinone alone.

Nitration of naphtho[*b*]cyclobutene with 70% nitric acid gave 3-nitronaphtho[b]cyclobutene (XI). The ultraviolet spectrum of XI exhibited a chromophore very different from that of 2,3-dimethyl-1-nitronaphthalene. Comparison of these spectra with the ultraviolet spectrum of 1-nitronaphthalene[4] showed the 2,3-dimethylnaphthalene derivative to be the anomalous member of this series. Its spectrum shows a simple naphthalene type chromophore, whereas the other two nitro compounds possess characteristic spectra similar to each other. This apparent anomaly may be explained by steric considerations. In 1-nitronaphthalene the nitro group can rotate freely and thus can resonate with the aromatic naphthalene system. The same is true for 3-nitronaphtho[*b*]cyclobutene, the methylene groups being tied back sufficiently so as not to interfere with the free rotation of the nitro group. In 2,3-dimethyl-1-nitronaphthalene, however, the adjacent methyl group prevents the nitro group from becoming coplanar with the naphthalene ring system and resonance is effectively inhibited. Thus, 2,3-dimethyl-1-nitronaphthalene exhibits a naphthalene type chromophore rather than a nitronaphthalene type chromophore.

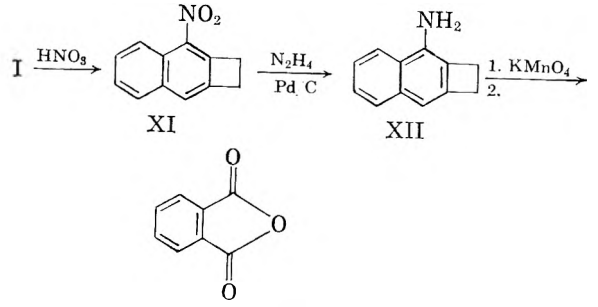
3-Nitronaphtho[*b*]cyclobutene was reduced catalytically with palladium on carbon and hydrazine[5] to 3-aminonaphtho[b]cyclobutene (XII). The ultraviolet spectrum of XII is similar to that of 1-amino-2,3-dimethylnaphthalene except for small differences in the position of the maxima beyond 300 mμ. These minor changes are attributed to the

(3) An authentic comparison sample of this hydrocarbon was prepared by hydrogenation of 9,10-ethenoanthracene, kindly provided by Prof. C. A. Grob.

(4) H. Mohler, *Helv. Chem. Acta*, **26**, 121 (1943); ultraviolet data were approximated from a spectrum given therein.

(5) S. Pietro, *Ann. Chim.* (*Rome*), **45**, 850 (1955).

strain provided by the cyclobutene ring in XII rather than to any steric rotation effects in the two compounds.



Permanganate oxidation of amine XII gave phthalic acid which was isolated as the anhydride. This result confirmed the assumption that naphtho[*b*]cyclobutene was nitrated in the *alpha* position adjacent to the four-membered ring.

EXPERIMENTAL[6]

1,2-Dihydrocyclobuta[b]naphthalene-3,8-dione (II). To a solution of naphtho-[*b*] cyclobutene (2.0 g.) in glacial acetic acid (30 ml.) at 50°, was added 30% hydrogen peroxide (6 ml.). The temperature was raised to 80–85° for 5 hr., then one half the acetic acid was evaporated *in vacuo*, water added, and the mixture cooled to give orange crystals which were filtered, washed well with water and aqueous sodium bicarbonate (10%), then again with water, and dried. Trituration with petroleum ether (b.p. 30–60°) afforded starting material (0.29 g.) upon evaporation of the petroleum ether. The orange needles, crystallized from acetic acid, gave 0.45 g. (22%) of the quinone, m.p. 200–210° dec. (see discussion). A benzene solution of the quinone was passed through a column of Woelm alumina (neutral, activity I) and the solvent evaporated to give the analytical sample as bright yellow needles, m.p. 185–190° (rapid heating). Upon very slow heating, a thermal transformation product was obtained at the melting point. This product melted at 255–260° with decomposition.

Anal. Calcd. for $C_{12}H_8O_2$: C, 78.25; H, 4.38; mol. wt., 184. Found: C, 78.38, 78.47; H, 4.56, 4.33; mol. wt. (isothermal distillation in methylene chloride), 191.

Ultraviolet spectrum (ethanol): λ_{max} 232 (log ϵ 4.16), 240 (4.12), 245, 250 (4.14), 265 (4.08), 338 (3.26), shoulder at 312 mμ.

The *ultraviolet spectrum of 2,3-dimethyl-1,4-naphthoquinone* (in ethanol) was grossly similar to that of II but showed less fine structure: λ_{max} 244 (log ϵ 4.26), 249 (4.27), 264 (4.21), 270 (4.25), 330 (3.44).

Thermal treatment of quinone II. A solution of quinone II (0.02 g.) in 1,2-bis(2-methoxy)ethane (1 ml.) was heated to 185–190° in an oil bath overnight (*ca.* 10 hr.) Upon cooling the solution, yellow needles (0.02 g., 100%), m.p. 255–260° dec. precipitated. The material was insoluble in benzene, but could be crystallized from chloroform. It was unreactive toward bromine and *N*-phenylmaleimide.

Anal. Calcd. for $C_{24}H_{16}O_4$: C, 78.25; H, 4.38; mol. wt., 368. Found: H, 4.75, 4.60; C, 78.59, 78.37; 4.75, 4.60; mol. wt. (Rast in camphor), 440.

The high value found for the molecular weight probably resulted from the limited solubility of the dimer in camphor.

(6) Analyses were performed by Galbraith Laboratories, Knoxville, Tenn., and Schwarzkopf Microanalytical Laboratories, Woodside, N. Y. Melting points are uncorrected unless stated otherwise.

Ultraviolet spectrum (ethanol): λ_{max} 226 (log ϵ 4.54), 246 (4.42), 308 (3.44), 333 (3.44).

1,4-Dihydro-4a,9a-ethanoanthracene-9,10-dione (III). Quinone II (0.10 g.), benzene (2 ml.), and excess butadiene (*ca.* 1.5 ml.) were sealed in a Pyrex tube (*ca.* 10 ml.) and heated on a steam bath for 1.5 hr. Within 1 hr., the solution had become almost colorless. The excess butadiene was evaporated, and the remaining solution was passed through a column of alumina, which was eluted with benzene. The eluate was evaporated to dryness to give slightly yellow crystals of dione III (0.12 g., 93%), m.p. 92–93°. Sublimation at 110° (1 mm.) gave the analytical sample as white needles, m.p. 93.0–93.5° (corr.).

Anal. Calcd. for $C_{16}H_{14}O_2$: C, 80.64; H, 5.92. Found: C, 80.47; H, 6.11.

Ultraviolet spectrum (ethanol): λ_{max} 226 (log ϵ 4.53), 251 (3.94), 299 (3.14).

1,4,9,10-Tetrahydro-4a,9a-ethanoanthracene-9,10-diol (IV). To a solution of sodium borohydride (0.08 g.) in water (1 ml.) and methanol (1 ml.) was added slowly, at room temperature, a solution of dione III (0.20 g.) in methanol (2 ml.). Small white plates precipitated out almost immediately. The mixture was heated on the steam bath for 10 min., then water was added until the solution became cloudy, and the mixture was cooled to give diol IV (0.16 g., 79%) as white plates, m.p. 205.5–206.0°.

Anal. Calcd. for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.18; H, 7.52.

9-10-Ethanoanthracene (V). *A. Rearrangement of diol IV.* Diol IV (0.10 g.), *p*-toluenesulfonyl chloride (0.30 g.), and pyridine (0.7 ml.) were stirred at 5° for 2 hr. Stirring was continued for a total of 5.5 hr. while the temperature was slowly increased to 50°. The mixture was diluted with hydrochloric acid (sp. gr. 1.19) and poured over ice. The precipitated gum was extracted with benzene and chromatographed on alumina (neutral Woelm, activity I). A fluorescent band containing the product was easily followed by means of an ultraviolet lamp. The eluate was evaporated to dryness to give a slightly yellow residue, m.p. 100–140°. Three crystallizations from ethanol gave large white needles (0.05 g., 60%), m.p. 142–143°, giving no depression upon admixture with authentic ethanoanthracene (see B below). The infrared spectrum of the rearranged product was identical to that of the authentic sample.

B. Catalytic hydrogenation of 9,10-ethenoanthracene. 9,10-Ethenoanthracene[3] (0.10 g.) absorbed the theoretical amount of hydrogen in 1.5 min. using 10% palladium on carbon as catalyst and ethanol as solvent. The mixture was filtered and the filtrate concentrated and cooled to give large white needles (0.09 g., 94%), m.p. 142–143° (reported:[7] 142–143°).

N-Phenyl-9,10-anthraquinone-2,3-dicarboximide (VII). *Method A.* A mixture of quinone II (0.18 g.), *N*-phenylmaleimide (0.20 g.), and 1,2-bis(2-methoxy-ethoxy)ethane (3 ml.) was heated to 200–220° for 1 hr. and then cooled. The small orange needles were filtered and washed with water and dried. Crystallization from acetic acid gave the anthraquinone derivative VII (0.05 g., 14%,) m.p. 347–350°, identical in melting point, infrared, and ultraviolet spectra to that prepared in *B* below.

Anal. Calcd. for $C_{22}H_{11}O_4N$: C, 74.78; H, 3.14; N, 3.96. Found: C, 74.90; H, 3.23; N, 4.02.

Ultraviolet spectrum (ethanol): λ_{max} 230 (log ϵ 4.57) 258 (4.66), 332 (3.62).

Method B. To a refluxing solution of *N*-phenyl-2,3-anthracenedicarboximide[1] (0.07 g.) in acetic acid (*ca.* 90 ml.) was added 1 drop of a solution of chromic anhydride (0.18 g.) in a few drops of water. Almost instantaneously the reaction solution turned from orange-red to green. The remaining chromic acid solution was added and the refluxing was continued for 20 min. Some acetic acid (*ca.* 30 ml.) was removed by distillation; then the solution was cooled in the refrigera-

(7) C. L. Thomas (Universal Oil Products Co.), U. S. Patent 2,406,645, August 27, 1946.

tor and yellow amorphous material precipitated which was filtered and recrystallized from acetic acid to give anthraquinone VII (0.065 g., 85%) m.p. 347–350°, identical in all respects to that prepared in *A* above.

3-Nitronaphtho[b]cyclobutene (XI). Naphtho[*b*]cyclobutene (1.54 g.) was added slowly with stirring to 70% nitric acid (1.53 g.) ccoled by an ice bath to 0°. The reaction mixture became dark and viscous, but became lighter as the yellow crystalline nitro derivative appeared. After 1 hr., the ice bath was removed and the reaction allowed to run its course at room temperature for an additional 3 hr. As the reaction progressed, stirring became very difficult and more nitric acid (*ca.* 2 ml.) was added. The mixture was nearly a solid mass at the end of the reaction. Water was added and the crystalline material filtered, washed with 5% aqueous sodium bicarbonate, then water, and dried. Three crystallizations from ethanol gave yellow-orange needles (0.80 g., 40%), m.p. 129.0–130.5°. A fourth recrystallization gave the analytical sample, m.p. 131.0–131.5° (corr.).

Anal. Calcd. for $C_{12}H_9O_2N$: C, 72.35; H, 4.55; N, 7.03. Found: C, 72.24; H, 4.71; N, 6.94.

Ultraviolet spectrum (ethanol): λ_{max} 244 (log ϵ 3.85) 342 (3.77).

3-Aminonaphtho[b]cyclobutene (XII). A mixture of 3-nitronaphtho[b]cyclobutene (0.20 g.), 10%, palladium on carbon (0.01 g.), excess hydrazine hydrate[5] (0.5 ml.), and 95% ethanol (20 ml.) was refluxed for 1 hr. and filtered hot. Water (*ca.* 20 ml.) was added to the filtrate until it became cloudy, and the mixture cooled in the refrigerator. The small white needles (0.12 g.) m.p. 91.0–91.5°, were filtered and dried. Concentration of the filtrate yielded an additional 0.02 g. of amine XII (total yield: 82%), which was recrystallized from petroleum ether (b.p. 30–60°).

Anal. Calcd. for $C_{12}H_{11}N$: C, 85.17; H, 6.55; N, 8.28. Found: C, 85.32; H, 6.68; N, 8.30.

Ultraviolet spectrum (ethanol): λ_{max} 241 (log ϵ 4.42) 311 (3.66).

Permanganate oxidation of 3-aminonaphtho[b] cyclobutene. Two per cent aqueous potassium permanganate solution was added drop by drop to a suspension of amine XIII (32 mg.) in water (5 ml.) until the reaction solution remained pink. The excess permanganate was decomposed by formaldehyde and the manganese dioxide removed by filtration. The slightly yellow solution was passed through a column of hydrochloric acid–washed Amberlite IR 120 (washed with distilled water until chloride ion test was negative). The acid fraction (eluate was tested with Alkacid paper) was collected and the water evaporated *in vacuo* to give a light brown paste which was sublimed at atmospheric pressure to give white needles (10 mg.), identified as phthalic anhydride by infrared analysis. The infrared spectrum showed no trace of pyromellitic or succinic anhydrides.

2,3-Dimethyl-1-nitronaphthalene was prepared by the procedure of Willstaedt.[8] After several crystallizations from ethanol it melted at 111° (reported[8] m.p. 111°).

Ultraviolet spectrum (ethanol): λ_{max} 269 (log ϵ 358), 307 (3.02), 321 (3.02).

2,3-Dimethyl-1-aminonaphthalene. To a solution of 2,3-dimethyl-1-nitronaphthalene (2.0 g.) in 95% ethanol (35 ml.) was added hydrazine hydrate (8 ml.) and 10% palladium on carbon (0.15 g.). The mixture was refluxed for 2 hr., filtered, and diluted with water until cloudy. Slow evaporation of the alcohol at room temperature resulted in the precipitation of pink leaflets (1.62 g., 95%), m.p. 48–50° (reported,[8] m.p. 42°). Neither sublimation, distillation (177° at 14 min.) nor crystallization from petroleum ether changed the melting point. Because of the discrepancy with the reported melting point, elemental analyses were carried out.

Anal. Calcd. for $C_{12}H_{13}N$: C, 84.17; H, 7.65; N, 8.18. Found: C, 84.33; H, 7.80; N, 8.38.

Ultraviolet spectrum (ethanol): λ_{max} 244 (log ϵ 4.47) 320 (3.63), shoulder at 328 mμ.

Acknowledgment. This work was supported in part by a grant from the National Science Foundation and by a Fellowship from the Nitrogen Division, Allied Chemical Corp. This aid is gratefully acknowledged.

COLUMBUS 10, OHIO

(8) H. Willstaedt, *Svensk. Kem. Tid.*, **54**, 223 (1942).

[CONTRIBUTION FROM THE CHEMISCHES INSTITUT]

Synthesis of Some Methyl-Substituted Anthracenes

ENNO WOLTHUIS[1,2]

Received October 17, 1960

A new route to the synthesis of a variety of methyl-substituted anthracenes is described. *o*-Dibromobenzene, or its homolog, is metallated with butyllithium to give benzyne, or its homolog, which is treated with furan or methyl-substituted furans to give 1,4-epoxy-1,4-dihydronaphthalenes. The latter, as dienophiles, are condensed with methyl-substituted butadienes, and the products dehydrated, and then dehydrogenated to produce the methylated anthracenes. These products have been used to study the bathochromic effect of the methyl group on the ultraviolet spectrum maxima of anthracene.

When fluorobenzene is treated with phenyllithium the fluorine atom becomes unusually active and is easily replaced by a phenyl group to give, after hydrolysis, biphenyl. Wittig[3] first suggested that this reaction probably proceeds *via* the intermediate, benzyne, or dehydrobenzene. Since that time many other reactions involving metallation of halogenated benzenes have been explained in terms of such an intermediate.[4–6]

One of the best indications that benzyne is actually formed, though short-lived, is the fact, discovered by Wittig,[7] that the product is a dieno-

(1) Present address: Calvin College. Grand Rapids, Mich.

(2) This work was done at the University of Heidelberg under a National Science Foundation Faculty Fellowship, 1959–60.

(3) G. Wittig, *Naturwissenschaften*, **30**, 696 (1942).

(4) G. Wittig, *Angew. Chem.*, **69**, 245 (1957).

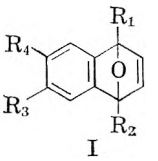
(5) R. Huisgen and J. Sauer, *Angew. Chem.*, **72**, 91 (1960).

(6) J. D. Roberts, *Chem. Soc. Symposia*, Bristol, 1958, Special Publication No. 12, p. 115.

(7) G. Wittig and L. Pohmer, *Ber.*, **89**, 1334 (1956).

TABLE I

METHYL-SUBSTITUTED 1,4-EPOXY-1,4-DIHYDRONAPHTHALENES



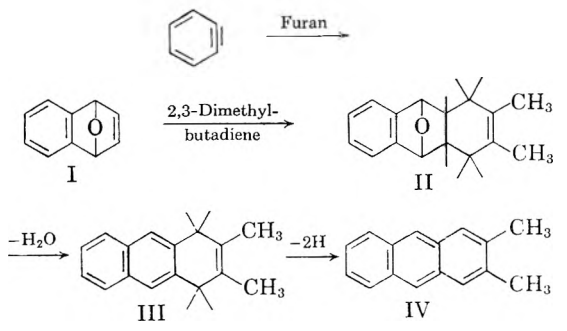
I

No.	R_1	R_2	R_3	R_4	Yield, %	M.P.[a]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
1	H	H	H	H	70	56[b]	$C_{10}H_8O$				
2[c]	CH_3	H	H	H	56	Liq.[d]	$C_{11}H_{10}O$	83.51	83.55	6.37	6.18
3[e]	CH_3	CH_3	H	H	45	35–35.5	$C_{12}H_{12}O$[f]	83.68	83.75	7.02	6.82
4[g]	H	H	CH_3	H	54	Liq.[h]	$C_{11}H_{10}O$	83.51	83.09	6.37	6.63
5[i]	H	H	CH_3	CH_3	55	72.5–73	$C_{12}H_{12}O$	83.68	83.93	7.02	6.89
6	CH_3	CH_3	CH_3	CH_3	25	52–52.5	$C_{14}H_{16}O$	83.96	84.01	8.05	8.31

[a] All melting points in this paper are corrected. [b] Ref. (7). [c] The 2-methylfuran used was distilled over sodium, b.p. 64°/750 mm., n_D^{20} 1.4322. [d] B.p. 57–59°/0.2 mm., n_D^{20} 1.5510. [e] The 2,5-dimethylfuran, ref. (9), was distilled over sodium, b.p. 92–93°/750 mm., n_D^{20} 1.4413. [f] This compound was isomerized with boiling methanolic hydrochloric acid to give 80% 4-methyl-1-naphthol, m.p. 82–83°. [g] The 3,4-dibromotoluene was prepared from *p*-toluidine by bromination followed by the Sandmeyer reaction giving b.p. 58–60°/0.4 mm., n_D^{20} 1.5970. Dauben and Tilles[10] report n_D^{30} 1.5822. [h] B.p. 57–59°/0.2 mm., n_D^{20} 1.5510. [i] The 4,5-dibromo-1,2-dimethylbenzene was prepared by the method of Mills and Nixon,[11] m.p. 88°.

phile and reacts as such with furan and other dienes. Such reactions have interesting applications for they make possible the synthesis of a variety of fused ring systems. Furthermore, the product of the reaction with furan, 1,4-epoxy-1,4-dihydronaphthalene, is also a dienophile and reacts in turn with other dienes to extend the polycyclic system.

The present investigation was concerned with the synthesis of methyl-substituted anthracenes. Benzyne was condensed with furan or methyl-substituted furans to give methyl-substituted 1,4-epoxy-1,4-dihydronaphthalenes, of type I. The latter were then treated with methyl-substituted butadienes and the products, like II, successively dehydrated to III and dehydrogenated to give the desired methyl-substituted anthracenes, IV. A typical series of reactions is as follows:



The preparation of benzyne and its reaction with furans was carried out essentially as described previously,[8] except that *o*-dibromobenzene was added to the butyllithium-furan mixture. The furans used were: furan, 2-methylfuran, 2,5-dimethylfuran. The following *o*-dibromobenzenes were used: *o*-dibromobenzene, 3,4-dibromotoluene, and 4,5-dibromo-1,2-dimethylbenzene. The products, type I are listed in Table I, all of which are new except compound 1.[7]

Compounds of type I were condensed with methyl-substituted butadienes in two different ways. At first the reaction was accomplished without a solvent and under pressure at 150°, since the preliminary trials in xylene as solvent were not successful. Later, however, the reaction was found to proceed equally well in a very small amount of xylene at reflux temperature. In either case a small amount of hydroquinone was usually added to minimize polymerization of the diene. The butadienes used were: isoprene, 1,3-dimethylbutadiene, and 2,3-dimethylbutadiene. The products of this reaction, type II, are listed in Table II. None of these compounds has been reported previously.

Dehydration of the type II compounds was accomplished most efficiently by adding a little concentrated hydrochloric acid to the boiling methanolic solution of the compound. The reaction is an exothermic one, decidedly so in those instances where the epoxy compound contains methyl substituents in the 9 and/or 10 positions. It is likely that the initial step in this reaction is the protonation of the epoxy oxygen atom, which is facilitated by the increased electron charge on this atom contributed by the methyl groups on the adjacent carbon atoms. The products, type III, are listed

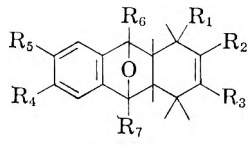
(8) H. Gilman and R. D. Gorsich, *J. Am. Chem. Soc.*, **79**, 2625 (1957).

(9) E. Campaigne and W. Foye, *J. Org. Chem.*, **17**, 1405 (1952).

(10) W. Dauben and H. Tilles, *J. Am. Chem. Soc.*, **72**, 3185 (1950).

(11) W. Mills and I. Nixon, *J. Chem. Soc.*, 2510 (1930).

TABLE II. METHYL-SUBSTITUTED 9,10-EPOXY-1,4,4a,9,9a,10-HEXAHYDROANTHRACENES

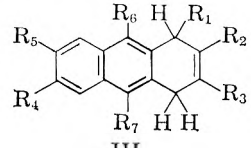


II

No.	Method	R_1	R_2	R_3	R_4	R_5	R_6	R_7	Yield, %	Solvent of Crystn.	M.P.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
1[a]	A	H	CH_3	H	H	H	H	H	30	Pet. ether	58–58.5	$C_{15}H_{16}O$	84.87	84.97	7.60	7.48
2[b]	A	H	CH_3	CH_3	H	H	H	H	86	Methanol	108.8–109	$C_{16}H_{18}O$	84.91	85.11	8.02	8.21
3[c]	A	CH_3	H	CH_3	H	H	H	H	92[d]		Liq.[d]	$C_{16}H_{18}O$				
4	B	H	CH_3	CH_3	H	H	CH_3	H	82	Methanol	96.5–97	$C_{17}H_{20}O$	84.96	84.83	8.39	8.23
5	B	H	CH_3	CH_3	H	H	CH_3	CH_3	80	Methanol	100–100.5	$C_{18}H_{22}O$	84.99	84.92	8.72	8.90
6	A	H	CH_3	CH_3	CH_3	H	H	H	77	Pet. ether	107–107.5	$C_{17}H_{20}O$	84.96	84.99	8.39	8.23
7	B	H	CH_3	CH_3	CH_3	CH_3	H	H	85	Pet. ether	155.2–155.4	$C_{18}H_{22}O$	84.99	85.31	8.72	8.83
8	B	H	CH_3	CH_3	CH_3	CH_3	CH_3	CH_3	77	Pet. ether	141.5–142	$C_{20}H_{26}O$	85.05	85.08	9.28	9.36

[a] The isoprene used was freshly distilled, b.p. 34°/745 mm., n_D^{20} 1.4216. [b] The 2,3-dimethylbutadiene was freshly distilled, b.p. 69–70°/750 mm., n_D^{20} 1.4370. [c] The 1,3-dimethylbutadiene was freshly distilled, b.p. 75–76°/750 mm. [d] Yield is that of the crude oil. It decomposed on attempted distillation, and was used in the next step without purification.

TABLE III. METHYL-SUBSTITUTED 1,4-DIHYDROANTHRACENES



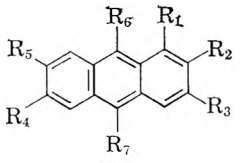
III

No.	R_1	R_2	R_3	R_4	R_5	R_6	R_7	Solvent of Crystn.	Yield, %	M.P.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
1	H	CH_3	H	H	H	H	H	Methanol	73	98.5–99	$C_{15}H_{14}$	92.74	92.63	7.26	7.23
2	H	CH_3	CH_3	H	H	H	H	Ethanol	63	189–190[a]					
3	CH_3	H	CH_3	H	H	H	H	Pet. ether	49[b]	54–54.5	$C_{16}H_{16}$	92.21	92.16	7.74	7.55
4	H	CH_3	CH_3	H	H	CH_3	H	Ethanol	90	112–112.5	$C_{17}H_{18}$	91.84	91.80	8.16	8.17
5	H	CH_3	CH_3	H	H	CH_3	CH_3	Ethanol-benzene, 3:1	94.5	178.5–179[c]	$C_{18}H_{20}$				
6	H	CH_3	CH_3	CH_3	H	H	H	Methanol	48.5	195–196 d.[d]	$C_{17}H_{18}$	91.84	91.91	8.16	8.14
7	H	CH_3	CH_3	CH_3	CH_3	H	H	Ligroin	47	250.5–251 d.[e]	$C_{18}H_{20}$	91.47	91.64	8.53	8.48
8	H	CH_3	CH_3	CH_3	CH_3	CH_3	CH_3	Ligroin	96.5	211–212	$C_{20}H_{24}$	90.85	91.03	9.15	8.97

[a] Jadot and Roussel[12] report m.p. 185°. [b] Yield based on unpurified II. [c] Jadot and Roussel[12] report m.p. 177.5°; Fieser and Webber[13] report m.p. 175.3–176.3°. [d] Immersed in melting point bath at 190°. [e] Immersed at 240°.

TABLE IV

METHYL-SUBSTITUTED ANTHRACENES



IV

No.	Method	R_1	R_2	R_3	R_4	R_5	R_6	R_7	Solvent of Crystn.	Yield	M.P.	Formula
1	A	H	CH_3	H	H	H	H	H	Pet. ether	35	206–206.5[a]	$C_{15}H_{12}$
2	A	H	CH_3	CH_3	H	H	H	H	Pet. ether	51	250.5–251[b,c]	$C_{16}H_{14}$
3	A	CH_3	H	CH_3	H	H	H	H	Methanol	68	79–79.5[d,e]	$C_{16}H_{14}$
4	B	H	CH_3	CH_3	H	H	CH_3	H	Ethyl acetate	99	124–124.5[f]	$C_{17}H_{16}$
5	B	H	CH_3	CH_3	H	H	CH_3	CH_3	Pet. ether	97	138.3–138.8[g]	$C_{18}H_{18}$
6	A	H	CH_3	CH_3	CH_3	H	H	H	Pet. ether	30	249–249.5[h,i]	$C_{17}H_{16}$
7	B	H	CH_3	CH_3	CH_3	CH_3	H	H	Ethyl acetate	97	299–300[j]	$C_{18}H_{18}$
8	B	H	CH_3	CH_3	CH_3	CH_3	CH_3	CH_3	Ethyl acetate	98	223–224[k]	

[a] Melting points reported generally vary from 200 to 209°. [b] Fairbourne[16] reports m.p. 246°. [c] Barnett and Marrison[17] report m.p. 252°. [d] Fieser and Heymann[18] report m.p. 78.2–79.6°. [e] Clemo and Ghatge[19] report m.p. 78°. [f] Barnett and Marrison[17] report m.p. 125°. [g] Fieser and Webber[13] report m.p. 139.4–140.2°. [h] Morgan and Coulson[20] report m.p. 255°. [i] Carruthers[21] reports m.p. 244–245°. [j] Carruthers[21] reports m.p. 292–293°. [k] *Anal.* Calcd.: C, 91.55; H, 8.45. Found: C, 91.26; H, 8.65.

in Table III. Two of these compounds, numbers 2[12] and 5,[13] have been reported previously.

Dehydrogenation of the 1,4-dihydroanthracenes, III, was done in some cases with selenium but the yields were generally low. Nearly quantitative yields were easily obtained by using chloranil as oxidizing agent in xylene as solvent at reflux temperature. In order to avoid difficulties in removing excess chloranil from the product, care should be taken to use no more than the theoretical amount of this reagent. Table IV lists the methyl-substituted anthracenes, IV, one of which is new, namely, 2,3,6,7,9,10-hexamethylanthracene.

One interesting fact deserves mention. As a rule the melting points of the compounds in the foregoing synthesis increase with each step. However, there is one exception to this rule, namely, the change from 2,3,9,10-tetramethyl-1,4-dihydroanthracene to 2,3,9,10-tetramethylanthracene, in which case the melting point drops about 40°. These data confirm those published for these two compounds.[13]

Effect of methyl substitution on the ultraviolet spectrum of anthracene. One of the objectives of this study was to obtain a variety of substituted anthracenes in order to examine the effect of methyl-substitution on the positions of the ultraviolet spectrum maxima.

The ultraviolet absorption spectrum of anthracene has two rather distinct parts, one with maxima in the 240–260 mμ range (41,670 cm.$^{-1}$ to 38,460 cm.$^{-1}$), the other between 290 and 380 mμ (34,480 and 26,310 cm.$^{-1}$). It has been suggested[14,15] that these parts are related to different types of electronic excitations. On this theory the 240–260 mμ maxima are associated primarily with electronic shifts, and therefore polarization, along the horizontal axis, while the 290–380 mμ maxima are related to polarization along the vertical axis of the anthracene molecule. The spectra of anthracenes containing unsaturated, or conjugatable, substituents strongly suggests the plausibility of this theory. But even methyl groups, though they have a smaller effect, also are reported to show the same trend. Jones[14,15] has examined the bathochromic shifts due to methyl and other substituents in various positions using the data available for four such compounds. We have now obtained the spectra of the compounds prepared in this study, and present herewith additional data on the bathochromic effect of methyl substituents in anthracene.

Table V presents the spectral data for the compounds synthesized by the method outlined in

(12) J. Jadot and J. Roussel, *Bull. soc. roy. sci. Liège*, **23**, 69 (1954).

(13) L. Fieser and T. Webber, *J. Am. Chem. Soc.*, **62**, 1360 (1940).

(14) R. Jones, *J. Am. Chem. Soc.*, **67**, 2127 (1945).

(15) R. Jones, *Chem. Revs.*, **41**, 353 (1947).

(16) A. Fairbourne, *J. Chem. Soc.*, 1573 (1921).

(17) E. Barnett and F. Marrison, *Ber.*, **64**, 535 (1931).

(18) L. Fieser and H. Heymann, *J. Am. Chem. Soc.*, **64**, 376 (1942).

(19) G. Clemo and N. Ghatge, *J. Chem. Soc.*, 1068 1(956).

(20) G. Morgan and E. Coulson, *J. Chem. Soc.*, 2551 (1929).

(21) W Carruthers, *J. Chem. Soc.*, 603 (1956).

TABLE V

ABSORPTION SPECTRA DATA ON METHYL-SUBSTITUTED ANTHRACENE[a]

Compound	Principal Maxima									
	mμ	log ε	mμ	log ε	mμ	log ε	mμ	log ε	mμ	log ε
Anthracene (A)	253	5.48	324	3.54	339	3.83	356	4.02	375	4.01
2-Methyl A	255	5.48	[b]		340	3.65	358	3.80	377	3.75
2,3-Dimethyl A	257	5.60	326	3.57	341	3.83	358	3.97	378	3.91
2,3,6-Trimethyl A	259	5.50	[b]		342	3.70	360	3.82	379	3.72
2,3,6,7-Tetramethyl A	261	5.64	328	3.53	343	3.73	359	3.85	379	3.73
2,3,9-Trimethyl A	261	5.57	333	3.59	350	3.87	368	4.04	388	3.99
2,3,9,10-Tetramethyl A	265	5.34	342	3.40	359	3.71	379	3.90	400	3.81
2,3,6,7,9,10-Hexamethyl A	269	5.16	343	3.11	360	3.38	380	3.54	402	3.45
1,3-Dimethyl A	257	5.38	[b]		344	3.72	360	3.87	381	3.83

[a] Solvent: cyclohexane. [b] These maxima were not distinct enough to permit accurate measurement.

TABLE VI

BATHOCHROMIC SHIFTS IN THE ANTHRACENE SPECTRUM DUE TO METHYL SUBSTITUTION

Position of Methyl Groups	Anthracene Spectrum Maxima				
	257 mμ 39,520 cm.$^{-1}$	324 30,910	339 29,500	356 28,090	375 26,670
	Bathochromic Shift in cm.$^{-1}$				
2	300		90	160	140
2,3	600	230	180	160	230
2,3,6	910		260	310	280
2,3,6,7	1200	420	350	230	280
2,3,9	1200	880	930	910	890
2,3,9,10	1780	1670	1640	1700	1670
2,3,6,7,9,10	2350	1760	1720	1780	1790
1,3	610		430	310	420

this paper. Only the principal maxima are given for comparison with each other. Of the compounds listed, only the spectra of 1,3-di-[18] and 2,3,9,10-tetramethylanthracene[13] have been reported.

Table VI shows the bathochromic shifts of the principal maxima. The values for the shifts are given in wave numbers to facilitate comparison with other literature data on such shifts. Examination of these data reveals a number of interesting facts which we now discuss briefly.

Methyl substitution has the largest bathochromic effect on the shortest intense maximum, 39,520 cm.$^{-1}$ The shift per methyl group is very nearly 300 cm.$^{-1}$ (2 mμ) and is additive to a remarkable degree. On the other hand, a *beta* methyl group has a smaller effect upon the other maxima of longer wave length, and, except for the 29,500 cm.$^{-1}$ band, there is no semblance of additivity in the shifts. Our data on 2-methylanthracene confirm the prediction of Peters[22] that a *beta*-methyl group should cause a bathochromic shift of 2 mμ in the p-band (26,670 cm.$^{-1}$) of anthracene. His calculations are based upon the assumption that the shift is due to conjugation of the methyl group with the parent hydrocarbon resulting in a perturbation of the molecular orbitals of anthracene.

Methyl substitution in the *meso* position has a very pronounced effect on all the spectral maxima of anthracene. In the case of the shortest wave-length band (39,520 cm.$^{-1}$) the frequency shift per methyl group is about 600 cm.$^{-1}$, a value twice as great as that due to a *beta*-methyl substituent. These results agree fairly well with those reported for 9-methyl- and 9,10-dimethylanthracene.[23] It should also be noted that, as in the case of *beta* substitution, *meso* substitution also causes a shift of the shortest wave-length maximum which is additive.

With respect to the effect of *meso*-methyl substitution on the longer wave-length maxima, it is clear that the bathochromic shifts are much larger

(22) D. Peters, *J. Chem. Soc.*, 646 (1957).

(23) L. Fieser and J. Hartwell, *J. Am. Chem. Soc.*, 60, 2555 (1938).

and are more consistently so than those caused by *beta*-substitution, and are fairly additive. The shift per methyl group of the 375 mμ band (*p*-band) agrees well with the theoretical prediction of Peters,[22] and the uniformly large effect of *meso*-methyl substitution confirms the observations on the spectra of 9-methyl- and 9,10-dimethylanthracene.[15]

An adequate theoretical explanation of the observed shifts is not readily at hand. Most theoretical treatments of the bathochromic effect of alkyl substituents assume the conjugative effect to predominate, the methyl group being regarded as a modified vinyl group. On this assumption the effect of conjugation would be to reduce the energy of the excited state, the degree of such reduction varying with the number and positions of the methyl substituents, and the effect upon the different spectral maxima depending upon the positions of the substituents, that is, upon the direction of polarization.

There is no doubt a qualitative correspondence between the bathochromic shifts due to methyl and clearly conjugatable substituents which points to such conjugation and polarization along mutually perpendicular axes of the molecule. However, as Jones[15] has observed, alkyl groups in the 9 and/or 10 positions have a uniformly large effect upon *all* the spectral maxima while unsaturated groups in these positions have a far more selective effect. Our data on the *beta*-substituted anthracenes also show that, although there is a selective bathochromic effect favoring the shortest wave-length maximum, the effect upon the longer wavelength maxima cannot be ignored.

In summary, then, our additional data confirm the theory that the conjugative effect of methyl groups is important, and that, therefore, the positions of these groups account for their selective bathochromic effects upon the various spectral maxima of anthracene. However, there must be other factors also affecting these shifts. The theory of Jones[15] that the ground state energy is also modified by alkyl substituents seems to provide at least a qualitative explanation for the general bathochromic shifts of all the maxima of the anthracene spectrum.

EXPERIMENTAL

General method for making methyl-substituted 1,4-epoxy-1,4-dihydronaphthalenes. n-Butyllithium in ether, 50 ml. of 1.10*N* solution (0.055 mole) was added to a flask previously evacuated and then filled with pure nitrogen, and cooled to −70°. Furan, or a methyl-substituted furan, 30 ml., freshly distilled, was added below 55° during about 15 min., after which there was added, during 30 min. at −70° to −55°, a solution of 11.8 g. (0.050 mole) *o*-dibromobenzene, or an equivalent amount of its homolog, distilled over phosphorus pentoxide, in 20 ml. of dry ether. During this addition, and for 40 min. more at −70° to −55°, the mixture was stirred vigorously. After allowing it to warm to 0°, 100 ml. of water was added, the layers separated, the aqueous layer washed twice with ether, the washings added to the ether layer and washed with water to remove any alkali. After drying over potassium carbonate, most of the ether and unused furan were recovered by fractionation. The residue was either fractionated further, in case the product was a liquid, or crystallized from petroleum ether (b.p. 60-80°) in those cases where the product was a solid.

Condensation of 1,4-epoxy-1,4-dihydronaphthalenes with dienes. Method A. The epoxy compound, 0.02 mole, the diene, 0.022 mole, and a few small crystals of hydroquinone were sealed in a pressure tube (15-ml. cap.) after flushing out the air with dry nitrogen. It was heated over night at 140–150°, cooled, and the volatile materials removed *in vacuo*. The crude product was boiled with methanol, and the polymerized diene removed by filtration. The product was recovered from the filtrate by crystallization, or by distillation in case it was a liquid.

Method B. The epoxy compound, 0.02 mole, the diene, 0.022 mole, and a few small crystals of hydroquinone were dissolved in 4 ml. of xylene and heated at reflux temperature over night. The volatile materials were removed *in vacuo* and the crude product was extracted with methanol and worked up as in method *A*.

Dehydration of epoxy compounds to form methyl-substituted 1,4-dihydroanthracenes. Methyl-substituted 9,10-epoxy-1,4,-4a,9,9a,10-hexahydroanthracene, 0.01 mole, was dissolved in 60 ml. of methanol. At reflux temperature 6 ml. of concd. hydrochloric acid was carefully added through the condenser. The mixture was refluxed overnight in most cases, although 2 hr. were found to be enough for the 9- and/or 10-methyl–substituted compounds. In all cases the crystalline product precipitated soon after the acid addition. After cooling several hours in the refrigerator the product was filtered, washed with cold methanol, and dried *in vacuo* at room temperature. In some cases it was pure without further crystallization.

Dehydrogenation of methyl-substituted 1,4-dihydroanthracenes. Method A. Methyl-substituted 1,4-dihydroanthracene, 0.01 mole, was mixed with 0.01 mole of selenium powder and heated in an oil bath for 4 to 8 hr. at 270–300°, or until no more hydrogen selenide was evolved. After cooling, the product was extracted with petroleum ether or benzene, clarified with carbon, evaporated to dryness and recrystallized.

Method B. Methyl-substituted 1,4-dihydroanthracene, 0.01 mole and 0.01 mole of chloranil were dissolved in 40 ml. of dry xylene and heated at reflux temperature for 1 hr. After cooling in the refrigerator for 4 to 5 hr., large crystals of tetrachloroquinone formed and were removed by filtration. The filtrate was purified chromatographically on neutral alumina, the product running through the column very readily as was evident by observation under ultraviolet light. Evaporation of the eluate gave the product in fairly pure form. In a few cases recrystallization improved the purity a little.

Acknowledgment. The author expresses his gratitude to Professor G. Wittig of the Chemisches Institut, Heidelberg, in whose private laboratory this work was done, and who inspired and supported the research with his interest and many valuable suggestions. The author is thankful to the National Science Foundation for the grant which supported this work.

HEIDELBERG, GERMANY

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, BERKELEY]

Synthetic Routes for Isotopically Labeled 1,5-Hexadiene

FRED L. GREENWOOD[1]

Received July 29, 1960

Synthetic routes were devised which would make possible the preparation of 1,5-hexadiene isotopically labeled in the terminal positions or in the central positions. The reaction sequence which would make possible the synthesis of 1,6-labeled diene was: adipyl chloride → *N,N,N′,N′*-tetramethylamide → 1,6-bisdimethylaminohexane → amine oxide → 1,5-diene. For diene labeled in the central positions this sequence would be preceded by: ethylene dibromide → diethyl adipate → adipyl chloride.

The literature method[2] for the preparation of 1,5-hexadiene of treating allyl chloride with a metal does not lend itself to the synthesis of 1,5-hexadiene isotopically labeled in specific positions. For the synthesis of 1,6-deuterium-labeled diene an adipic acid derivative could be reduced with lithium aluminum deuteride, and the unsaturation introduced by subsequent transformations. A conceivable reaction sequence could be: diethyl adipate → 1,6-hexanediol → 1,6-dibromohexane → 1,6-diquaternary nitrogen base → 1,5-diene. The troublesome step of this sequence would be expected to be the last. No example of pyrolysis of an open-chain, diquaternary nitrogen base which could lead to an isolated diene could be found in the literature. Blomquist and co-workers[3] have prepared successfully bismethylene cyclic compounds by the pyrolysis of bifunctional quaternary nitrogen bases. These pyrolyses led to the desired conjugated diene, and the formation of an isolated diene was impossible. There are examples[4] of the pyrolysis of unsaturated quaternary nitrogen bases where the expected product would be an isolated diene. In some instances it was possible to obtain a rather poor yield of the isolated diene, but the principal product was usually a conjugated diene which was formed by isomerization of the isolated diene.

The above-mentioned reaction sequence was successful in all steps except the last, and this failed miserably. The 1,6-diquaternary nitrogen base did not undergo elimination satisfactorily, and careful fractional distillation of the pyrolysate gave but a 43% yield of hydrocarbon. Of this material only 4% was acceptable as 1,5-hexadiene on the basis of boiling point and refractive index. From physical constants the bulk of the hydrocarbon appeared to be conjugated hexadienes.

Cope and Bumgardner[5] have been able to convert unsaturated tertiary amines to isolated dienes by pyrolysis of the corresponding amine oxides, and there was no isomerization of the double bonds to a conjugated system. The application of this reaction for the preparation of 1,6-deuterium-labeled-1,5-hexadiene would require the sequence: adipyl chloride → *N,N,N′,N′*-tetramethyl amide → 1,6-bisdimethylaminohexane → amine oxide → 1,5-hexadiene. This sequence proved fairly successful. The amide was reduced to the amine with lithium aluminum hydride in 72% yield and the amine was converted through the amine oxide to a 55% yield of 1,5-hexadiene. This diene exhibited no absorption in the 215–300 mμ region, and this indicated the absence of conjugated diene.

To obtain 1,5-hexadiene isotopically labeled in internal positions one could start with 1,2-dibromoethane which was labeled, and convert this to adipic acid. Such a conversion would involve the reaction of the dibromide with malonic ester to obtain 1,1,4,4-tetracarbethoxybutane, which could be taken to adipic acid. The tetraester has been reported in the literature,[6] and the yield has always been given by the remark that it was low. Cason and Allen[7] have reported that by controlling the relative amounts of sodium, malonic ester, and 1,3-dibromopropane, the reaction could be carried out to give mainly the tetracarbethoxy compound or mainly the 1,1-dicarbethoxycyclobutane. Application of their findings to the reaction with 1,2-dibromoethane produced no significant amount of tetracarbethoxy compound. By taking advantage of Perkin's discovery[8] that 1,1-dicarbethoxycyclopropane would undergo the Michael reaction, it was possible to convert 1,2-dibromoethane to diethyl adipate in a reasonable yield. One mole of dibromoethane in an excess of malonic ester was refluxed with two moles of sodium ethoxide. A third mole of sodium ethoxide was added and the reaction mixture again refluxed. The high-boiling residue from the reaction mixture was hydrolyzed, decarboxyl-

(1) On leave from Tufts University, Medford, Mass National Science Foundation Science Faculty Fellow, 1959–1960.

(2) A Turk and H. Chanan, *Org. Syntheses*, Coll. Vol. III, 121 (1955).

(3) A. T. Blomquist *et al.*, *J. Am. Chem. Soc.*, **77**, 1806 (1955); *J. Am. Chem. Soc.*, **78**, 6057 (1956); *J. Am. Chem. Soc.*, **79**, 3916 (1957).

(4) J. Weinstock, *J. Org. Chem.*, **21**, 540 (1956) and references cited therein.

(5) A. C. Cope and C. L. Bumgardner, *J. Am. Chem. Soc.*, **79**, 960 (1957).

(6) J. H. Brewster, *J. Am. Chem. Soc.*, **73**, 366 (1951) and references cited therein.

(7) J. Cason and C. F. Allen, *J. Org. Chem.*, **14**, 1036 (1949).

(8) W. H. Perkin, *J. Chem. Soc.*, **65**, 572 (1894).

ated, and esterified to give a 48% yield of diethyl adipate.

It was not possible to convert satisfactorily diethyl adipate to *N,N,N′,N′*-tetramethyladipamide by treatment of the ester with dimethylamine. Also, it was not feasible to convert the crude adipic acid which was obtained by decarboxylation of the butanetetracarboxylic acid to the acid chloride. To convert 1,2-dibromoethane to 1,5-hexadiene the diethyl adipate obtained from the dibromide would have to be hydrolyzed and the acid taken to the acid chloride. The acid chloride could then be carried through the amide and amine oxide to the diene.

EXPERIMENTAL

1,6-Dibromohexane to diene. A mixture of 132.2 g. (2.24 moles) of anhydrous trimethylamine, 45 ml. of absolute methanol and 60.3 g. (0.247 mole) of 1,6-dibromohexane (b.p. 111–112°/8.5 mm.; n_D^{26} 1.5044) was carried through the usual Hofmann elimination procedure. Distillation of the pyrolysate from hydroquinone in a nitrogen atmosphere through a spinning-band column gave the following materials: 0.91 g., b.p. 40.4–58.0°, n_D^{25} 1.3765–1.3967; 0.36 g., b.p. 58.0–58.3°, n_D^{25} 1.4003; 7.36 g., b.p. 58.3–81.6°, n_D^{25} 1.4010–1.4539. Total weight of distillate, 8.63 g., 43% yield of diene. The 1,5-hexadiene reported below had b.p. 58.4°, n_D^{25} 1.4005. The literature[9] values for the hexadienes are: 1,3-diene, b.p. 73°, n_D^{25} 1.435; 2,4-diene, b.p. 80°, n_D^{25} 1.447; 1,5-diene, b.p. 59.5°, n_D^{25} 1.4010. From the physical constants it was clear that this method of preparation gave a mixture of hexadienes, and that little 1,5-diene of good purity could be isolated.

N,N,N′,N′-Tetramethyladipamide. In a 2 l., three-necked flask fitted with a stirrer, ice-cooled reflux condenser and inlet tube was placed 70.9 g. (0.387 mole) of adipyl chloride (b.p. 103°/4 mm.) and 1 l. of dry ether. The reaction flask was cooled in an ice water bath. In a second flask was placed 76.8 g. (1.70 moles) of anhydrous dimethylamine, and this flask was connected by means of rubber tubing to the inlet tube of the three necked flask. The dimethylamine was allowed to evaporate into the reaction flask during a period of 1.5 hr., and the reaction mixture allowed to stand at room temperature for a day.

The reaction mixture was transferred with 200 ml. of water rinsings to a beaker, and the mixture stirred until the solid dissolved in the water. To this mixture was added with stirring 23 ml. of concd. hydrochloric acid. The ether layer was separated and extracted with two 100-ml. portions of water. The combined aqueous solutions were placed in a continuous chloroform extractor. After a 12-hr. extraction the bulk of the chloroform was removed from the extract on the steam bath. Residual chloroform could be removed from the residue only by evacuating the flask to 4 mm. and immersing it in a bath at 95°. The residual amide was powdered and placed in a vacuum desiccator over phosphorus pentoxide. The product, 77.1 g., 99.5% yield, had m.p. 82.8–84.0°. For the amide Prelog[10] has reported m.p. 85°.

Diethyl adipate was treated with anhydrous dimethylamine under various conditions, and to obtain reaction it was necessary to heat the reactants in a pressure vessel at 150°. The amide obtained in this case was inferior in purity and yield to that obtained from adipyl chloride.

1,6-Bisdimethylaminohexane. The procedure was based on the suggestions of Mićović and Mihailović.[11] In a 2 l., three necked flask fitted with a stirrer, reflux condenser, and dropping funnel was placed 18.1 g. (0.477 mole) of lithium aluminum hydride and 500 ml. of dry ether. This mixture was refluxed for 2 hr. A solution of 73.5 g. (0.376 mole) of *N,N-N′,N′*-tetramethyladipamide in 600 ml. of 1,2-dimethoxyethane (distilled from lithium aluminum hydride) was added to the reaction mixture at such a rate that refluxing was maintained. The reaction mixture was refluxed for 1.5 hr. after the completion of the addition of the diamide. The reaction flask was cooled in an ice water bath, and the excess hydride decomposed by the dropwise addition of 280 ml. of saturated sodium sulfate. The precipitate was collected in a Büchner funnel and washed with ether. The combined filtrate and washings was shaken in a separatory funnel with a solution of 1200 ml. of water and 80 ml. of concd. hydrochloric acid. The aqueous layer was separated and made strongly alkaline with sodium hydroxide. The diamine was water soluble but it could be extracted with one 250-ml. and five 150-ml. portions of ether. The ether extract was dried with sodium hydroxide pellets.

The ether was removed from the solution through a helix-packed column, and the residue distilled through a helix-packed column (packed portion, 20 mm. o.d. × 110 mm.). The diamine, collected in several fractions, weighed 45.5 g. (72% yield) and had b.p. 104°/16 mm., n_D^{25} 1.4333–1.4337.

1,5-Hexadiene. (*Cf.* Cope and Bumgardner.[5]) In a flask fitted with a stirrer was placed 42.6 g. (0.247 mole) of 1,6-bisdimethylaminohexane. The flask was cooled in an ice water bath, and 158 ml. (containing 1.482 moles of hydrogen peroxide) of 30% hydrogen peroxide was added dropwise to the diamine. The reaction mixture was homogeneous, and was allowed to stand at room temperature for 2 days. At this point the reaction mixture did not color phenolphthalein. The excess peroxide was destroyed by stirring the reaction mixture with platinum black,[12] first for 10 hr. with cooling and then for 36 hr. at room temperature. The platinum was removed by filtration, and the filtrate concentrated with a rotary evaporator at a pressure of 12 mm. During the evaporation the flask containing the reaction mixture was in a bath which was kept at 35°.

For pyrolysis the flask containing the light yellow-colored sirup was fitted with a helix-packed column and a capillary tube which carried nitrogen. For condensation there was a Dry Ice–cooled trap followed by a liquid nitrogen-cooled trap. The pyrolysis system was evacuated to 56 mm., and the temperature of the oil bath surrounding the pyrolysis flask gradually increased. The material in the flask eventually solidified, and did not pyrolyze at a reasonable rate until the oil bath reached a temperature of 190°. After 2 hr. at 190° the pyrolysis flask was virtually empty. The condensate was warmed, mixed with water, and neutralized with sulfuric acid. The organic layer was separated, washed once with water, and placed over freshly heated sodium sulfate.

The organic layer was distilled from hydroquinone in a nitrogen atmosphere through a spinning-band column. After a small low-boiling fraction there were collected several fractions of combined weight 11.16 g. (55% yield), b.p. 58.2–58.4°/755 mm., n_D^{25} 1.4004–1.4007. The literature[9] values for 1,5-hexadiene are b.p. 59.5°/760 mm., n_D^{25} 1.4010. The absence of conjugated diene in this product was shown by the absence of absorption at 215–300 mμ.

1,2-Dibromoethane to diethyl adipate. In a 1 l., three necked flask fitted with a stirrer, reflux condenser, and dropping funnel were placed 150 ml. of absolute alcohol[13] and 7.4 g. (0.32 g.-atom) of sodium. After dissolution of the sodium, 153.8 g. (0.96 mole) of diethyl malonate (b.p. 97.4°/16 mm.) was added to the flask. The reaction mixture was refluxed,

(9) F. D. Rossini *et al.*, *Selected Values of Physical and Thermodynamic Properties of Hydrocarbons and Related Compounds*, Carnegie Press, Pittsburgh, Pa., 1953, p. 63.

(10) V. Prelog, *Collection Czechoslov. Chem. Comm.*, 2, 712 (1930); *Chem. Abstr.*, 25, 1218 (1931).

(11) V. M. Mićović and M. L. Mihailović, *J. Org. Chem.*, 18, 1190 (1953).

(12) R. Feulgen, *Ber.*, 54, 360 (1921).

(13) R. H. Manske, *J. Am. Chem. Soc.*, 53, 1101 (1931).

and 30.1 g. (0.16 mole) of 1,2-dibromoethane (b.p. 130°/762 mm.) was added dropwise during 0.76 hr. The reaction mixture was refluxed for an additional hour, and then a solution of 3.7 g. (0.16 g.-atom) of sodium in 100 ml. of absolute alcohol was added. After refluxing the reaction mixture for 4 hr., 185 ml. of alcohol was distilled during 1 hr. from the mixture by warming the reaction flask on the steam bath. The residue was cooled and poured into 600 ml. of ice-cold water. This mixture was extracted with one 300-ml. and four 100-ml. portions of ether. The ether extract was dried over freshly heated sodium sulfate.

After removal of the drying agent, the ether was removed through a helix-packed column. The residue was distilled through an 18 mm. o.d. × 165 mm. helix-packed column. When the oil bath used to heat the distilling flask reached 190°, the distillation was interrupted. Distillate weighing 95.0 g., b.p. 84–86°/9 mm., n_D^{25} 1.4117–1.4185, was collected, and 36.9 g. of residue remained in the flask. Pertinent refractive indexes are: diethyl malonate, n_D^{25} 1.4118; 1,1-dicarbethoxyeyclopropane, n_D^{20} 1.4331; 1,1,4,4-tetracarbethoxybutane, n_D^{25} 1.4470.

The residue was stirred and refluxed with 50 ml. of concd. hydrochloric acid and 100 ml. of water for 4 hr. The mixture was filtered, and the filtrate evaporated to dryness *in vacuo* in a rotary evaporator. Water was added to the residue, and the solution again evaporated to dryness. The flask containing the solid residue was immersed in an oil bath at 180–185° until evolution of gas ceased. The residue was refluxed for 24 hr. with 170 ml. of absolute alcohol and 1 ml. of concd. sulfuric acid. This solution was poured into 700 ml. of water, and this mixture placed in a continuous benzene extractor. The benzene extract was dried over sodium sulfate, the benzene removed through a helix-packed column, and the residue distilled through a 12 mm. o.d. ×90 mm. helix-packed column to give several fractions (15.6 g., 48% yield) of diethyl adipate, b.p. 125–126°/9 mm., n_D^{25} 1.4260–1.4268. Authentic diethyl adipate had n_D^{25} 1.4254.

A second experiment was carried out with the same quantities of materials. After the first reflux and before addition of the second quantity of sodium ethoxide the reaction mixture was poured into water, the mixture extracted with ether, and the ether solution distilled. After removal of the ether there was obtained 140.8 g., b.p. 86–96°/9 mm., of distillate and 9.5 g. of high-boiling residue. This 9.5 g. of residue provided that not much tetracarbethoxy compound was formed during the first reflux with sodium ethoxide, and that the reaction proceeded primarily to give cyclic product. The 140.8 g. of distillate was refluxed with a second portion of sodium ethoxide, and the reaction mixture worked up as described above to obtain the high-boiling residue. The combined high-boiling residue was hydrolyzed, decarboxylated, and esterified to give a 49% yield of diethyl adipate, b.p. 126°/9 mm., n_D^{25} 1.4259.

1,2-Dibromoethane to adipyl chloride. The reaction was carried out as described above to obtain diethyl adipate. After the high-boiling residue was hydrolyzed and decarboxylated, the residue was refluxed with thionyl chloride. Much solid was formed and only a 25% yield (based on dibromide) of adipyl chloride was obtainable. It was clear that the preferred way to get the adipic acid from the reaction mixture was by esterification.

BERKELEY 4, CALIF.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF NORTH CAROLINA]

The Preparation and Reaction of Some Substituted Benzotrifluorides

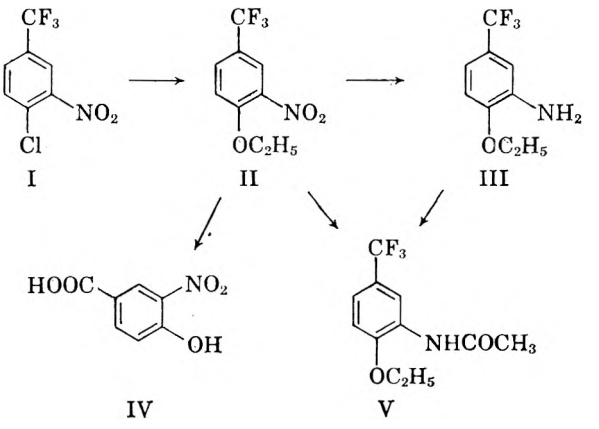
T. C. FRAZIER,[1] C. ROBERT WALTER, JR.,[1] AND R. L. McKEE[2]

Received August 22, 1960

The preparation of several substituted benzotrifluorides is described, and a few reactions of these benzotrifluorides are noted.

In connection with some other work in these laboratories it became of interest to study the properties and synthesis of several amino and acetamido derivatives of benzotrifluoride having an ether function. Accordingly the synthesis of the isomers 3-amino-4-ethoxybenzotrifluoride (III) and 5-amino-4-ethoxybenzotrifluoride and their corresponding acetyl derivatives was undertaken.

4-Chloro-3-nitrobenzotrifluoride (I) was treated with ethanolic potassium hydroxide to give 4-ethoxy-3-nitrobenzotrifluoride (II), which was converted to III by reduction. The corresponding acetyl derivative V was formed directly from III and by reductive acetylation from II. A similar sequence starting from 2-chloro-5-nitrobenzotrifluoride yielded 5-amino-3-ethoxybenzotrifluoride and its acetyl derivative, 5-acetamido-2-ethoxybenzotrifluoride. The structure of the intermediate nitro compounds II and 2-ethoxy-5-nitrobenzotrifluoride was demonstrated by hydrolysis to the

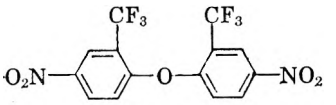


(1) Present address: Allied Chemical Corp., Nitrogen Division, Hopewell, Va.

(2) Present address: Chemistry Department of the University of North Carolina, Chapel Hill, N. C.

corresponding hydroxy acids IV and 2-hydroxy-5-nitrobenzoic acid using 100% sulfuric acid.[3]

In another procedure 5-acetamido-2-nitrobenzotrifluoride[4] was reduced to 5-acetamido-2-aminobenzotrifluoride, but attempted replacement of the 2-amino group with the ethoxide group by diazotization followed either by heating or treatment with ethanol and copper, resulted only in elimination of the amino group to give 3-acetamidobenzotrifluoride. The previously unknown intermediate, 5-acetamido-2-aminobenzotrifluoride, was hydrolyzed to the known 2,5-diaminobenzotrifluoride.[5]



VI

In connection with the conversion of 2-chloro-5-nitrobenzotrifluoride to 2-ethoxy-5-nitrobenzotrifluoride, the use of sodium ethoxide in ether gave a different compound the elemental analysis of which corresponded to 4,4′-dinitro-2,2′-bis(trifluoromethyl)diphenyl ether (VI). The use of potassium hydroxide in isopropyl alcohol also gave VI. Although rigorous structural proof was not carried out, the infrared absorption spectrum is consistent with this structure.

EXPERIMENTAL

Materials. 4-Chloro-3-nitrobenzotrifluoride and 2-chloro-5-nitrobenzotrifluoride were supplied by the Hooker Chemical Corp.

4-Ethoxy-5-nitrobenzotrifluoride (II). A solution of 22.5 g. (0.10 mole) of 4-chloro-3-nitrobenzotrifluoride (I) in absolute ethanol (60 cc. total volume) was added during 1 hr. to a solution of 300 cc. of absolute ethanol containing 5.6 g. of potassium hydroxide. After refluxing 72 hr. the ethanol was removed at reduced pressure, and inorganic salts were removed by slurrying the residue with ethyl ether and filtering. An oily-crystalline slurry was obtained upon evaporation of the ether. Purification was effected by dissolving the residue in petroleum ether (b.p. 60–90°) and treating with decolorizing charcoal to give 19.9 g. (84.6%) of light yellow crystals II, m.p. 31–32°. An analytical sample of II was prepared by recrystallizing from petroleum ether (b.p. 60–90°) and distilling under reduced pressure, 110–112°/4 mm. giving white crystals, m.p. 30–31°.

Anal. Calcd. for $C_9H_8F_3NO_3$: C, 45.95; H, 3.43; N, 5.96. Found: C, 45.81; H, 3.45; N, 5.94.

3-Amino-4-ethoxybenzotrifluoride (III). *Method A.* To a solution of 7.05 g. (0.03 mole) 4-ethoxy-3-nitrobenzotrifluoride (II) dissolved in a solution of 10 cc. of ethanol and 30 cc. of concd. hydrochloric acid was added 15.0 g. of mossy tin at a rate to give a brisk reaction. The reaction mixture was refluxed for 1 hr., then made basic to litmus with sodium hydroxide. Steam distillation of the mixture gave 5.5 g. (89%) III, m.p. 50.0–52.5°.

Method B. To a mixture of 20.0 g. of iron powder, 3.0 g. of ammonium chloride and 300 cc. of water was added during 30 min. a solution of 20 g. (0.085 mole) of 4-ethoxy-3-nitrobenzotrifluoride (II) dissolved in 150 cc. of methanol. After refluxing the mixture for 4 hr. a white crystalline product was collected by steam distillation. After cooling the distillate, filtering and drying, 11.7 g. (67%) III was obtained.

An analytical sample was obtained by recrystallizing crude III from petroleum ether (b.p. 60–90°) giving white crystals, m.p. 51.4–52.5°.

Anal. Calcd. for $C_9H_{10}F_3NO$: C, 52.68; H, 4.91; N, 6.83. Found: C, 52.52; H, 4.76; N, 6.87.

4-Hydroxy-3-nitrobenzoic Acid (IV). A mixture of 2.35 g. (0.01 mole) of 4-ethoxy-3-nitrobenzotrifluoride (II) and 1.0 g. of 100% sulfuric acid was heated in an oil bath until evolution of gas ceased. The reaction mixture was poured on ice and the product collected by filtration. Recrystallization of the product from water and treating with decolorizing charcoal gave 1.2 g. of IV, m.p. 183–185° (lit.,[6] m.p. 184°).

The ethyl ester was prepared by reacting IV with ethanol in the presence of concentrated sulfuric acid. Upon recrystallization from ethanol-water a yellow solid was obtained, m.p. 69–70° (lit.,[7] m.p. 69°).

3-Acetamido-4-ethoxybenzotrifluoride (V). *Method A.* To a solution of 7.05 g. (0.03 mole) of 4-ethoxy-3-nitrobenzotrifluoride (II) in 30 cc. of acetic anhydride was added *ca.* 25 mg. of platinum oxide and reduction effected in a Parr low pressure hydrogenation apparatus at 59 p.s.i.g. The catalyst was removed by filtration and the filtrate heated for 30 min. on a steam cone. Four volumes of ice water were added and 3 g. (40%) of V as white crystals was obtained upon filtration and drying, m.p. 110–113°.

Method B. To a suspension of 4.98 g. (0.025 mole) of 3-amino-4-ethoxybenzotrifluoride (III) and 2.1 cc. of concd. hydrochloric acid in 100 cc. of water, heated at 50°, was added 2.91 g. (0.03 mole) of acetic anhydride. Immediately thereafter a solution of 3 g. sodium acetate in 20 cc. of water was added. On cooling to 0° the product separated and was collected by filtration. Recrystallization from ethanol-water gave 4.0 g. (54%) of V; further recrystallization from ethanol water gave white crystals, m.p. 113.5–114.7°.

Anal. Calcd. for $C_{11}H_{12}F_3NO_2$: C, 53.44; H, 4.89; N, 5.65. Found: C, 53.23; H, 4.59; N, 5.73.

2-Ethoxy-5-nitrobenzotrifluoride. A solution of 45.10 g. (0.20 mole) of 2-chloro-5-nitrobenzotrifluoride in 225 cc. of absolute ethanol was added during 1 hr. to a solution of 11.2 g. of potassium hydroxide in 250 cc. of absolute ethanol. After stirring at room temperature 24 hr. the mixture was heated at 50° for 12 hr. followed by 24 hr. of refluxing. Inorganic salts were removed by filtration and the filtrate concentrated under reduced pressure to *ca.* 60 cc. Upon cooling the solution the crude product separated and was collected by filtration. Recrystallization from ethanol-water gave 19.5 g. (41.5%) of 2-ethoxy-5-nitrobenzotrifluoride, m.p. 47.5–49.5°, b.p. 106–108°/3 mm.

Anal. Calcd. for $C_9H_8F_3NO_3$: C, 45.95; H, 3.43; N, 5.96. Found: C, 45.65; H, 3.59; N, 5.86.

5-Amino-3-ethoxybenzotrifluoride. Method A. Same as Method A used for III. The crude product weighed 5.3 g. (86%). Recrystallization from 95% ethanol gave 5-amino-3-ethoxybenzotrifluoride as a white crystalline solid, m.p. 55–56°.

Method B. Same as Method B used for III. Quantities of reagents used were, 9.0 g. (0.039 mole) of 2-ethoxy-5-nitrobenzotrifluoride, 100 cc. of methanol, 20 g. of iron powder, 3 g. of ammonium chloride, and 100 cc. of water. The crude product 5-amino-3-ethoxybenzotrifluoride weighed 5.1 g. (67.8%). Recrystallization from 95% ethanol (decolorizing charcoal) gave white crystals, m.p. 55.5–56.4°.

Anal. Calcd. for $C_9H_{10}F_3NO$: C, 52.68; H, 4.91; N, 6.83. Found: C, 52.49; H, 4.84; N, 6.84.

(3) LeFave, G. M., *J. Am. Chem. Soc.*, **71**, 4148 (1949).

(4) Jones, R., *J. Am. Chem. Soc.*, **69**, 2346 (1947).

(5) Rouche, H., *Bull. aci. acad. roy. Belg.*, **13**, 346 (1927); *Chem. Abstr.*, **22**, 2149 (1928).

(6) Cavill, G. W. K., *J. Soc. Chem. Ind.*, **64**, 212 (1945).

(7) Thieme, P., *J. fur. Prakt. Chem.* (2), **43**, 453 (1891).

2-Hydroxy-5-nitrobenzoic acid. Same as procedure used for IV. There was obtained 1.8 g. of the crude acid. The acid was purified by recrystallizing from water (decolorizing charcoal) m.p. 225–229° (lit.,[8] m.p. 227°, 229–230°). The ethyl ester prepared as before, was recrystallized from ethanol-water, m.p. 96–97° (lit.,[9] m.p. 102°).

5-Acetamido-2-ethoxybenzotrifluoride. Method A. Same as Method A, used for V. Recrystallization of the product from ethanol-water gave 4.2 g. (57%) of 5-acetamido-2-ethoxybenzotrifluoride as white crystals, m.p. 137.5–139.0°.

Method B. Same as Method B, used for V. Recrystallization of the product from ethanol-water (decolorizing charcoal) gave 4.8 g. (65%) of 5-acetamido-2-ethoxybenzotrifluoride as white crystals, m.p. 138.0–139.0°.

Anal. Calcd. for $C_{11}H_{12}F_3NO_2$: C, 53.44; H, 4.89; N, 5.65. Found: C, 53.48; H, 4.93; N, 5.67.

5-Acetamido-2-aminobenzotrifluoride. Method A. A solution of 30.0 g. (0.12 mole) of 5-acetamido-2-nitrobenzotrifluoride in 200 cc. of ethanol was added dropwise during 1 hr. to a boiling mixture of 25.0 g. of iron powder, 3.0 g. of ammonium chloride, and 250 cc. of water. After refluxing the reaction mixture for 4 hr. the hot mixture was filtered. The product was removed from the cooled filtrate by several ether extractions. After drying the ether extract over anhydrous magnesium sulfate the ether was removed by evaporation giving 15.0 g. (57%) of crude product. Several recrystallizations from benzene gave 5-acetamido-2-aminobenzotrifluoride as white crystals, m.p. 118–119°.

Method B. To a solution of 6.2 g. (0.025 mole) of 5-acetamido-2-nitrobenzotrifluoride in 50 cc. of methanol *ca.* 25 mg. of platinum oxide was added. Reduction was effected in a Parr low pressure catalytic hydrogenation apparatus at 60 p.s.i.g. After removal of the catalyst by filtration, the filtrate was evaporated to near dryness. The product was purified by recrystallization from benzene giving 4.0 g. (76%) of 5-acetamido2-aminobenzotrifluoride as tan crystals m.p. 116–118°.

Anal. Calcd. for $C_9H_9F_3N_2O$: C, 49.54; H, 4.16; N, 12.85. Found: C, 49.29; H, 4.00; N, 13.04.

(8) Causse, M. H., *Bull. Soc., Chem. Fr.*, 11, 1188 (1894).
(9) Thieme, P., *op. cit.*, p. 469.

5-Acetamido-2-aminobenzotrifluoride was hydrolyzed in the presence of hydrochloric acid. Neutralization of the acid solution gave 2,5-diaminobenzotrifluoride, m.p. 55–57°, (lit.,[10] m.p. 58°).

Diazotization of 5-acetamido-2-aminobenzotrifluoride, sulfuric acid and sodium nitrite, followed by reduction with copper in the presence of ethanol or by heating, gave 3-acetamidobenzotrifluoride, m.p. 103–104° (lit., [11] m.p. 105°).

4,4'-Dinitro-2,2'-bis(trifluoromethyl)diphenyl ether (VI) *Method A.* A solution of 22.55 g. (0.1 mole) of 2-chloro-5-nitrobenzotrifluoride in 50 cc. of absolute ethyl ether was added to an etheral suspension of 8.15 g. of sodium ethylate. After refluxing the heterogeneous reaction mixture 34 hr. 8 g. of starting material was recovered by steam distillation. The residual mixture from the steam distillation was filtered and the solid product recrystallized several times from absolute ethanol (decolorizing charcoal) gave 5.5 g. (14%) of VI light cream-colored needles, m.p. 140–141°.

Method B. A solution of 22.55 g. (0.1 mole) of 2-chloro-5-nitrobenzotrifluoride in 150 cc. of absolute isopropyl alcohol was added to a solution of 14.0 g. of potassium hydroxide dissolved in 200 cc. of absolute isopropyl alcohol. After agitating the solution 4 hr. at room temperature, the mixture was refluxed 1 hr. Isopropyl alcohol was removed by distillation leaving *ca.* 100 cc. of the reaction mixture. After removing the inorganic salts by filtration an equal volume of ice and water was added to the filtrate. The solid product was collected by filtration. Product was purified by recrystallization from 95% ethanol giving 4.5 g. (11%) VI. The product had the same melting point as that prepared by Method A and there was no depression when the two were mixed.

Anal. Calcd. for $C_{14}H_6F_6N_2O_5$: C, 42.44; H, 1.53; N, 7.07. Found: C, 42.35; H, 1.56; N, 7.09.

HOPEWELL, VA.

(10) Rouche, *op. cit.*
(11) Brown, J. H., Suckling, C. W., and Whalley, W. B., *J. Chem. Soc.*, 1949 (Suppl. Issue No. 1), S95–99 (1949).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MISSOURI]

Substituted Styrenes. VI. Syntheses of the Isomeric Formylstyrenes and *o*- and *m*-Vinylbenzoic Acid

WESLEY J. DALE, LEON STARR, AND CHARLES W. STROBEL

Received September 30, 1960

Laboratory methods have been devised for the preparation of *o*-, *m*-, and *p*-formylstyrene and for *o*- and *m*-vinylbenzoic acid.

In a continuation of studies[1] concerning the preparation, absorption spectra and reactions of substituted styrenes, syntheses were devised for the isomeric formylstyrenes and for *o*- and *m*-vinylbenzoic acid.

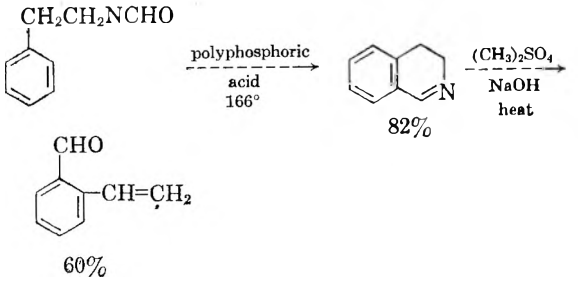
Wiley and Hobson[2] have reported the preparation of *p*-formylstyrene by the decarboxylation of *p*-formylcinnamic acid. Impure *m*-formylstyrene was obtained by the same method but attempts to prepare the *ortho* isomer by the decarboxylation of *o*-formylcinnamic acid afforded only 1-indanone. Morris and co-workers[3] have observed that a

(1) W. J. Dale and C. W. Strobel, *J. Am. Chem. Soc.*, **76**, 6172 (1954); W. J. Dale and G. Buell, *J. Org. Chem.*, **21**, 45 (1956); W. J. Dale and H. E. Hennis, *J. Am. Chem. Soc.*, **80**, 3645 (1958); W. J. Dale and H. E. Hennis, *J. Am. Chem. Soc.*, **81**, 2143 (1959); W. J. Dale and P. E. Swartzentruber, *J. Org. Chem.*, **24**, 955 (1959).

(2) R. H. Wiley and P. H. Hobson, *J. Am. Chem. Soc.*, **71**, 2429 (1949).
(3) L. R. Morris, R. A. Mock, C. A. Marshall, and J. H. Howe, *J. Am. Chem. Soc.*, 81, 377 (1959).

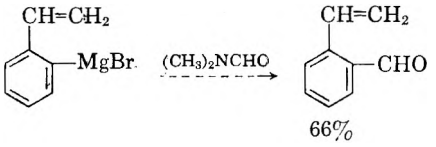
Sommelet reaction performed on a mixture of *o*- and *p*-vinylbenzyl chlorides resulted in a mixture of *o*- and *p*-formylstyrenes.

In the present study, *o*-formylstyrene was prepared from 2,3-dihydroisoquinoline by reaction with dimethyl sulfate in sodium hydroxide solution,[4] a general method of cleavage employed by Gensler[5] for a variety of *o*-acylstyrenes.



The preparation of 3,4-dihydroisoquinoline in low yield by a similar reaction has been reported previously.[6] However, by using a slight modification of the method of Snyder and Werber (heating at 166° for three hours rather than at 145° for an hour and a half), this compound was obtained in 82% yield from *N*-β-phenylethylformamide. The extent of formation of *o*-vinylbenzoic acid from the aldehyde during the reaction in strongly basic solution was negligible when the reaction temperature was maintained below 85°.

o-Formylstyrene was also prepared in this study in 66% yield by reaction of the Grignard reagent from *o*-bromostyrene with dimethylformamide in tetrahydrofuran solution, a modification of the Bouveault reaction for aromatic aldehydes, as described by Smith and Bayliss.[7]



The *para* isomer was obtained in a similar way in 55% yield from the reaction of *p*-vinylphenylmagnesium chloride[8] with dimethylformamide. The reactions of *p*-vinylphenylmagnesium chloride with *N*-methylformanilide and with ethyl orthoformate were also investigated as possible routes to *p*-formylstyrene. However, the *N*-methylformanilide was difficult to remove from the impure styrene and the product from the reaction with ethyl orthoformate, after hydrolysis in acid solution, consisted mostly of polymer.

m-Formylstyrene was prepared in 71% yield from *m*-vinylphenylmagnesium bromide in a manner similar to the above preparations for the *ortho para* isomers. It is noteworthy that the attempted preparation of *m*-vinylphenylmagnesium chloride from *m*-chlorostyrene gave only polymer, whereas the Grignard reagent formed satisfactorily from *p*-chlorostyrene. The preparation of the Grignard reagent from *m*-bromostyrene using either dry ether or tetrahydrofuran as solvent was successful. However, with ether as solvent, the yield of *m*-formylstyrene was lower (52%) than with tetrahydrofuran as solvent (71%) and there was difficulty in initiating the Grignard reaction.

The *o*- and *m*-vinylbenzoic acid were obtained in 94 and 83% yields, respectively, by carbonation of the Grignard reagents derived from *o*- and *m*-bromostyrene.

EXPERIMENTAL[9]

3,4-Dihydroisoquinoline. This compound was prepared by a modification of the method of Snyder and Werber.[6] Into a 1-l. round bottomed flask, equipped with a Hershberg stirrer, were placed 500 ml. of polyphosphoric acid and 250 g. (1.68 moles) of *N*-β-phenylethylformamide.[10] The mixture was warmed to 120° and stirring was begun. The temperature was raised slowly to 166° and maintained at this level, with vigorous stirring, for 3 hr. The mixture was then poured onto 2 l. of cracked ice and water and stirred until all the polyphosphoric acid had dissolved. Sodium hydroxide and ice were added alternately to the cold solution until it was strongly basic. The mixture was then extracted with four 250-ml. portions of ether and the combined extracts were dried over sodium sulfate. The solvent was removed under reduced pressure and the residue was distilled. There was obtained 181 g. (82%) of 3,4-dihydroisoquinoline, b.p. 69–72° (2 mm.), n_D^{20} 1.5910; m.p. of picrate, 179–181°; lit.,[6] m.p. 176–177°.

o-Formylstyrene from 3,4-dihydroisoquinoline. Into a 2-l. round bottomed flask, equipped with a stirrer and condenser, were placed 300 g. of sodium hydroxide and 1200 ml. of water. Stirring was begun and the temperature was raised to 70°. Fifty grams (0.382 mole) of 3,4-dihydroisoquinoline was added, after which 150 ml. of dimethyl sulfate was added slowly, with stirring. The mixture was stirred for 2 hr. at a temperature of 82–85°. It was then cooled, extracted with three 150-ml. portions of ether, washed five times with dilute hydrochloric acid, twice with water, twice with saturated sodium carbonate solution, and dried over magnesium sulfate. The ether was removed by distillation and distillation of the residue yielded 30 g. (60%) of *o*-formylstyrene, b.p. 113–115° (18 mm.); n_D^{20} 1.5829.

Anal. Calcd. for C_9H_8O: C, 81.79; H, 6.10. Found: C, 81.46; H, 6.04. Semicarbazone, white needles from ethanol; m.p. 190–191°.

Anal. Calcd. for $C_{10}H_{11}N_3O$: C, 63.47; H, 5.86. Found: C, 63.13; H, 5.79. 2,4-Dinitrophenylhydrazone, orange needles from ethanol; m.p. 197–198°.

Anal. Calcd. for $C_{15}H_{12}N_4O_4$: C, 57.69; H, 3.87. Found: C, 57.82; H, 4.00.

(4) The preparation of o-formylstyrene is taken from a portion of a thesis submitted by C. W. Strobel in partial fulfillment of the requirements for the Ph.D. degree, University of Missouri, 1956.

(5) W. J. Gensler, E. M. Healy, I. Onshuus, and A. J. Bluhm, *J. Am. Chem. Soc.*, **78**, 1713 (1956).

(6) H. R. Snyder and F. X. Werber, *J. Am. Chem. Soc.*, **72**, 2962 (1950).

(7) L. I. Smith and M. Bayliss, *J. Org. Chem.*, **6**, 437 (1941).

(8) J. R. Leebrick and H. E. Ramsden, *J. Org. Chem.*, **23**, 935 (1958).

(9) All melting points are uncorrected. The carbon and hydrogen analyses were performed by Drs. Weiler and Strauss of Oxford, England.

(10) H. Decker, *Ann.*, **395**, 286 (1913).

o-Formylstyrene from o-bromostyrene. *o*-Bromostyrene was prepared from *o*-bromophenylmethylcarbinol[11] by the method of Emerson and Lucas,[12] b.p. 60–61° (3 mm.), n_D^{25} 1.5985; lit.,[13] b.p. 65° (4 mm.), n_D^{25} 1.5983. The Grignard reagent prepared from 18.6 g. (0.1 mole) of *o*-bromostyrene and 2.4 g. (0.1 g.-atom) of magnesium turnings in 150 ml. of tetrahydrofuran was cooled to 20°; a solution of 6.8 g. (0.1 mole) of dimethylformamide in 50 ml. of tetrahydrofuran was then added dropwise over a 0.5-hr. period. The reaction mixture was stirred for 2 hr. after the addition was complete and then was allowed to remain overnight under a nitrogen atmosphere. The mixture was hydrolyzed with saturated ammonium chloride solution, the layers were separated and the aqueous layer was extracted twice with 50-ml. portions of ether. The extracts were combined and dried over magnesium sulfate. After removal of the solvent under reduced pressure, the residue was distilled; yield, 8.8 g. (66%) of *o*-formylstyrene, b.p. 70–75° (1 mm.), n_D^{20} 1.5827.

Preparation of p-Formylstyrene. A solution of 14.6 g. (0.2 mole) of dimethylformamide in 100 ml. of dry tetrahydrofuran was added dropwise over a 1 hr. period to a solution of *p*-vinylphenylmagnesium chloride[8] (0.2 mole, from 27.6 g. *p*-chlorostyrene and 4.9 g. of magnesium) in 150 ml. of tetrahydrofuran. The temperature was maintained at 20° during the addition; higher temperatures resulted in polymer formation and lower yields. The reaction mixture was stirred for 2 hr. and then allowed to remain overnight under a nitrogen atmosphere. The product was hydrolyzed with saturated ammonium chloride solution and the layers were separated. The aqueous layer was extracted three times with 50-ml. portions of ether; the extracts were combined and dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue was distilled. The fraction distilling at 75–80° (1 mm.) was collected; yield, 14.4 g. (55%), n_D^{23} 1.5892; lit.,[2] b.p. 92–93° (14 mm.), n_D^{25} 1.5872.

The 2,4-dinitrophenylhydrazone of *p*-formylstyrene was prepared in the usual manner, m.p. 235–236°.

Anal. Calcd. for $C_{15}H_{12}N_4O_4$: C, 57.69; H, 3.87. Found: C, 57.33; H, 3.93.

Attempts were made to prepare *p*-formylstyrene from the reaction of *p*-vinylphenylmagnesium chloride with *N*-methylformanilide in dry tetrahydrofuran solution. The infrared spectrum of the impure product showed the presence of *p*-formylstyrene and unchanged *N*-methylformanilide. The mixture could not be separated satisfactorily by distillation and the procedure was abandoned.

In another experiment, *p*-vinylphenylmagnesium chloride and ethyl orthoformate in tetrahydrofuran were refluxed for 1 hr. Hydrolysis of the product with dilute sulfuric acid apparently caused polymerization of any *p*-formylstyrene so formed.

Preparation of m-formylstyrene. *m*-Bromostyrene was prepared from *m*-bromophenylmethylcarbinol[11] using the dehydration method of Emerson and Lucas.[12] Magnesium (5.5 g., 0.23 g.-atom) was placed in a three necked flask equipped with stirrer, reflux condenser, and dropping funnel. *m*-Bromostyrene (36.6 g., 0.2 mole) in 150 ml. dry tetrahydrofuran was then added dropwise, over a period of 1.5 hr., while nitrogen gas was bubbled through the solution; the temperature throughout the addition was 65° and this temperature was maintained for one-half hour after addition was complete. The mixture was stirred for an additional hour without heating and then cooled to 20°. While this temperature was maintained, a solution of 14.6 g. (0.2 mole) of dimethylformamide in 100 ml. of tetrahydrofuran was added dropwise to the Grignard reagent. The reaction mixture was stirred for 2 hr. after the addition was complete and then was allowed to remain overnight under nitrogen. The solution was poured onto cracked ice and hydrolyzed with saturated ammonium chloride solution. The layers were separated and the aqueous layer was extracted twice with 50-ml. portions of ether; the extracts were combined and dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue was distilled. The fraction distilling at 74–78° (1 mm.) was collected; yield, 18.6 g. (71%), n_D^{25} 1.5760.

Anal. Calcd. for C_9H_8O: C, 81.79; H, 6.10. Found: C, 81.41; H, 6.16. A 2,4-dinitrophenylhydrazone was prepared in the usual manner, m.p. 229–230°.

Anal. Calcd. for $C_{15}H_{12}N_4O_4$: C, 57.69; H, 3.87. Found: C, 57.45; H, 3.57.

m-Vinylbenzoic acid. The Grignard reagent prepared from 18.4 g. (0.1 mole) of *m*-bromostyrene and 2.4 g. (0.1 g.-atom) of magnesium in 100 ml. of tetrahydrofuran was cooled and poured onto crushed dry ice. The product was hydrolyzed with dilute hydrochloric acid, the layers were separated and the aqueous layer was extracted twice with 50-ml. portions of ether. The ether extracts were added to the original organic layer which was then stirred into a 20% sodium hydroxide solution. The ether layer was discarded, the aqueous layer was filtered to remove polymer and then was acidified with dilute hydrochloric acid. The crude acid which separated was collected on a filter and recrystallized from a 20% ethanol-water solution; yield, 12 g. (83%) m.p. 95–96° (lit., [14] m.p. 95–96°).

Anal. Calcd. for $C_9H_8O_2$: C, 72.96; H, 5.44. Found: C, 73.30; H, 5.63.

o-Vinylbenzoic acid. This compound was prepared from *o*-bromostyrene in a manner very similar to the above preparation for the *meta* isomer; yield (94%), m.p. 94–95°.

Anal. Calcd. for $C_9H_8O_2$: C, 72.96; H, 5.44. Found: C, 72.94; H, 5.19.

COLUMBIA, MO.

(11) C. G. Overberger, J. H. Saunders, R. E. Allen, and R. Gander, *Org. Syntheses*, Coll. Vol. III, 200 (1955).

(12) W. S. Emerson and V. E. Lucas, *J. Am. Chem. Soc.*, **70**, 1180 (1948).

(13) C. S. Marvel and N. S. Moon, *J. Am. Chem. Soc.*, **62**, 47 (1940).

(14) R. H. Wiley and P. H. Hobson, *J. Polymer Sci.*, **5**, 483 (1950).

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE VIRGINIA POLYTECHNIC INSTITUTE]

Some New Alkyl 1,2,3,4-Dibenzopyrenes

FRANK A. VINGIELLO AND WALTER W. ZAJAC[1,2,3]

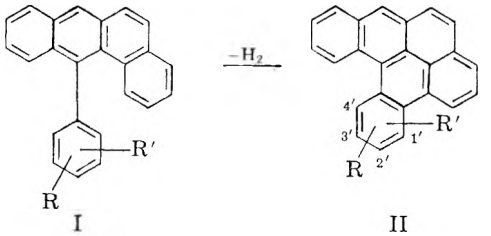
Received October 3, 1960

Using a previously described method, 9-mono- and dimethylphenyl-1,2-benzanthracenes were prepared and catalytically cyclodehydrogenated to give a series of new alkyl-substituted 1,2,3,4-dibenzopyrenes.

Recent studies on the environmental and health aspects of air pollution have unveiled the fact that the organic fraction of air pollutants contains polycyclic aromatic hydrocarbons,[4] some of them known carcinogens, others unknown compounds.[5] This discovery has led some workers to associate the presence of polycyclic aromatic compounds in air with the increase in the incidence of lung cancer. Shore and Katz[5] have pointed out the difficulty of identifying small quantities of alkyl substituted polynuclear aromatic hydrocarbons of unknown structure suspected of being present in polluted air. We sought to alleviate this problem by preparing some methyl[6] derivatives of 1,2,3,4-dibenzopyrene, a potent carcinogen discovered over twenty years ago[7] and a likely air pollutant. Only the 7-methyl-[8] and 5-phenyl[7]-1,2,3,4-dibenzopyrenes have been prepared previously.

An observation of Vingiello and Borkovec[9] made during a study of the aromatic cyclodehydration of ketones to 9-aryl-1,2-benzanthracenes (I) suggested the possibility of cyclodehydrogenating these compounds to 1,2,3,4-dibenzopyrenes (II).

The 9-mono- and dimethylphenyl-1,2-benzanthracenes (I) required for this study were synthesized



I II

I. (a) R = R′ = H
(b) R = 2-CH_3, R′ = H
(c) R = 3-CH_3, R′ = H
(d) R = 4-CH_3, R′ = H
(e) R = 2-CH_3, R′ = 3-CH_3
(f) R = 2-CH_3, R′ = 4-CH_3
(g) R = 2-CH_3, R′ = 5-CH_3
(h) R = 3-CH_3, R′ = 4-CH_3
(i) R = 3-CH_3, R′ = 5-CH_3

II. (a) R = R′ = H
(b) R = 4′-CH_3, R′ = H
(c) R = 3′- or 1′-CH_3, R′ = H
(d) R = 2′-CH_3, R′ = H
(e) R = 4′-CH_3, R′ = 3′-CH_3
(f) R = 4′-CH_3, R′ = 2′-CH_3
(g) R = 4′-CH_3, R′ = 1′-CH_3
(h) R = 3′- or 1′-CH_3, R′ = 2′-CH_3
(i) R = 3′-CH_3, R′ = 1′-CH_3

according to the procedure of Vingiello and Borkovec.[9,10] Of all the benzanthracenes (Ia–Ii) in only two cases, namely, Ic and Ih, are the *ortho*-positions in the phenyl ring different, leading to the possibility of two isomeric products being formed by the loss of hydrogen. In Chart I the structures given for IIc and IIh list as the first possibility that structure resulting from loss of a hydrogen atom in the phenyl ring *para* to a methyl group in preference to loss of a hydrogen *ortho* to a methyl group.

The dehydrogenating activity of aluminum chloride has often been used in the preparation of highly condensed aromatic hydrocarbons. Unfortunately, the reaction suffers because the yields are often low and isolation of the desired product is difficult. However, since Clar and Stewart[11] were able to effect cyclodehydrogenation of 9-phenyl-1,2-benzanthracene (Ia) to 1,2,3,4-dibenzopyrene (IIa) with aluminum chloride in boiling benzene, although in unspecified yield, the use of this reagent appeared to be an attractive approach to the cyclodehydrogenation of the hydrocarbons Ib–Ii. Of the many different reagents

(1) Presented before the Division of Organic Chemistry at the Southeastern Regional Meeting of the American Chemical Society, Birmingham, Ala., November 1960.

(2) This paper has been abstracted from the Doctorate thesis presented to the Virginia Polytechnic Institute by Walter W. Zajac in 1959.

(3) This investigation was supported in part by a research grant (S-73) from the Bureau of State Services (Division of Sanitary Engineering Services and Division of Special Health Services) of the National Institutes of Health, Public Health Service.

(4) J. Thomas, B. Tebbens, M. Mukai, and E. Sanborn, *Anal. Chem.*, 29, 1835 (1957).

(5) V. Shore and M. Katz, *Anal. Chem.*, 28, 1399 (1956).

(6) It is known that methyl groups may greatly enhance the carcinogenic activity of aromatic polynuclear hydrocarbons.

(7) E. Clar, *Ber.*, 63, 112 (1930).

(8) J. Cook and E. Kennaway, *Am. J. Cancer*, 33, 50 (1938).

(9) F. A. Vingiello and A. Borkovec, *J. Am. Chem. Soc.*, 77, 4823 (1955). During the purification of the 9-aryl-1,2-benzanthracenes *via* column chromatography on alumina the following was reported. "The occurrence of a yellow band on the chromatography column, when the cyclization product was chromatographed, suggests that a small amount of the dibenzopyrene is formed. Presumably the initial cyclodehydration reaction is followed by a small amount of cyclodehydrogenation."

(10) F. A. Vingiello and A. Borkovec, *J. Am. Chem. Soc.*, 78, 1240 (1956).

(11) E. Clar and D. Stewart, *J. Chem. Soc.*, 687 (1951).

studied we found aluminum chloride to be the most successful; therefore, its use is described in some detail in the experimental section of this paper.

With the exception of 9-(3,4-dimethylphenyl)-1,2-benzanthracene (Ih), all the 9-(monomethyl- and dimethylphenyl)-1,2-benzanthracenes (Ib–Ii) can be cyclodehydrogenated to the corresponding monomethyl- and dimethyl-1,2,3,4-dibenzopyrenes (IIb–IIi) with aluminum chloride in boiling benzene. The yields are low, ranging from 23% to 2% (see Table I), but typical of those obtained from cyclodehydrogenation reactions.

TABLE I

9-(Phenyl)-1,2-benzanthracenes (I)	Yield of the 1,2,3,4-Dibenzopyrenes (II)
Ib. R = 2-CH_3, R′ = H	19% IIb (R = 4′-CH_3, R′ = H)
Ic. R = 3-CH_3, R′ = H	13% IIc (R = 3′-CH_3, or 1′-CH_3, R′ = H)
Id. R = 4-CH_3, R′ = H	17% IId (R = 2′-CH_3, R′ = H)
Ie. R = 2-CH_3, R′ = 3-CH_3	23% IIe (R = 4′-CH_3, R′ = 3′-CH_3)
If. R = 2-CH_3, R′ = 4-CH_3	2% IIf (R = 4′-CH_3, R′ = 2′-CH_3)
Ig. R = 2-CH_3, R′ = 5-CH_3	3% IIg (R = 4′-CH_3, R′ = 1′-CH_3)
Ih. R = 3-CH_3, R′ = 4-CH_3	No dibenzopyrene could be isolated
Ii. R = 3-CH_3, R′ = 5-CH_3	2% IIi (R = 3′-CH_3, R′ = 1′-CH_3)

A rather large variety of reagents and reaction conditions were tried in an attempt to improve the yields, but to no avail. The following known reagents and reaction conditions were tried: aluminum chloride in boiling carbon disulfide,[12] aluminum chloride in boiling *p*-cymene,[13] aluminum chloride-sodium chloride melt,[14] anhydrous ferric chloride in boiling benzene, anhydrous stannic chloride in boiling benzene, anhydrous aluminum chloride-anhydrous stannic chloride in boiling benzene,[15] phosphorus oxychloride in boiling benzene, palladium-charcoal at 350°, palladium-charcoal in boiling *p*-cymene, and sulfur at 325° (5 mm.).

(12) L. Ruzicka and H. Hosli, *Helv. Chem. Acta*, **17**, 470 (1934); L. Ruzicka and K. Hoffman, *Helv. Chem. Acta*, **20**, 1155 (1937); L. Ruzicka and E. Morgeli, *Helv. Chem. Acta*, **19**, 377 (1936); L. Ruzicka and K. Hoffman, *Helv Chem. Acta*, **22**, 126 (1939); L. Ruzicka and R. Markus, *Helv. Chem. Acta*, **23**, 385 (1940); J. Cook, C. Hewett, W. Mayeord, and E. Roe, *J. Chem. Soc.*, 1727 (1934); J. Cook and C. Hewett, *J. Chem. Soc.*, 365 (1934); J. Cook and C. Hewett, *J. Chem. Soc.*, 1098 (1933); Ng. Buu-Hoi, Ng. Hoan, and P. Jacquignon, *J. Chem. Soc.*, 1381 (1951).

(13) R. Linstead and K. Michaelis, *J. Chem. Soc.*, 1134 (1940).

(14) R. Weitzenbock and C. Seer, *Ber.*, **46**, 1994 (1913); H. Reimlinger and A. van Overstraeten, *Chem. Ber.*, **91**, 2151 (1958).

(15) E. Clar and M. Zander, *Chem. Ber.*, 1861 (1958).

All the mono- and dimethyl-1,2,3,4-dibenzopyrenes (IIb–IIi) prepared in this investigation crystallize as tiny yellow needles with melting points around 200°. They all can be readily sublimed at low pressures (0.10 mm.). The 1,2,3,4-dibenzopyrenes are slightly soluble in ethanol and in acetic acid, readily soluble in benzene, in toluene, and in xylene, and very soluble in nitrobenzene. In solution the dibenzopyrenes possess a brilliant yellow-green fluorescence. The dibenzopyrenes dissolve in concentrated sulfuric acid imparting a claret color to the solution which changes to an olive green color within a minute. Picrates of IIa–IId were prepared and melted as follows: IIa, 231–232°; IIb, 226–227°; IIc, 220–221°; IId, 217–218°.

The ultraviolet absorption spectra and the visible absorption spectra of the dibenzopyrenes were obtained using a Perkin-Elmer model 3000 Spectracord (1-cm., quartz cell) at a concentration of 5 mg. per liter for the ultraviolet spectra and 10 mg. per liter as the concentration for the visible spectra. The solvent was 95% ethanol. It is well established that a bathochromic shift is observed most characteristically in the spectra of alkyl derivatives of polynuclear aromatic hydrocarbons.[16] The wave-length maxima of the dibenzopyrenes (II) are recorded in Table II. It can be seen from these data that the expected bathochromic shift was observed.

TABLE II

ABSORPTION MAXIMA OF THE 1,2,3,4-DIBENZOPYRENES (II)

Wave Length in mμ							
IIa	IIb	IIc	IId	IIe	IIf	IIg	IIi
240	243	244	244	244	243	243	244
253	254	253	256	256	255	254	253
261	263	263	263	264	263	263	264
271	272	273	272	273	271	271	272
289	288	289	288	288	287	289	287
301	298	298	297	300	298	301	299
315	315	314	315	318	312	314	317
330	330	329	329	333	328	329	332
359	360	361	362	358	358	356	356
379	378	378	379	380	379	375	378
401	399	400	399	401	400	399	399

Although incomplete at this time, the carcinogenic activity tests being conducted by Dr. W. F. Dunning, Prof. Exper. Pathology, Cancer Research Laboratory, University of Miami, on 2′-methyl-1,2,3,4-dibenzopyrene (IId) reveal that this compound is a potent carcinogen.

EXPERIMENTAL[17,18,19]

Cyclodehydrogenation of 9-(4-methylphenyl)-1,2-benzanthracene (Id). A. *Aluminum chloride and benzene.* Six grams of

(16) R. Jones, *J. Am. Chem. Soc.*, **67**, 2127 (1945).

(17) All melting points are corrected.

(18) All analyses were carried out by Geller Microanalytical Laboratories, Bardonia, N. Y.

anhydrous aluminum chloride was added to a solution of 1.0 g. of 9-(4-methylphenyl)-1,2-benzanthracene (Id) in 60 ml. of anhydrous benzene. The mixture was heated on a steam bath for 2 hr. The mixture was allowed to cool to room temperature and then decomposed with 100 ml. of a 10% hydrochloric acid solution. The orange organic layer which possessed a brilliant yellow-green fluorescence was separated. The aqueous layer was extracted with five 25-ml. portions of fresh benzene and the combined benzene extracts were washed twice with water and dried over anhyd. magnesium sulfate. The solvent was removed until only an oil remained. This oil was dissolved in 5 ml. of benzene and chromatographed on a column packed with Fisher's Alumina (80–200 mesh). The first fraction was eluted with petroleum ether (b.p. 30–60°) and possessed a blue fluorescence under ultraviolet radiation (3660 Å). Unfortunately the time required to remove this band was about 1 week. After this fraction was removed, the yellow band which remained on the column was eluted with benzene (500 ml. of benzene was required to remove this band). Concentration of the benzene solution yielded a red oil which was triturated with *ca.* 20 drops of ethyl acetate. The expected 2′-methyl-1,2,3,4-dibenzopyrene (IId) crystallized as a yellow solid, m.p. 208–209°; yield, 0.17 g. (17%). The hydrocarbon was recrystallized from a benzene-ethanol mixture as tiny yellow needles, m.p. 210–211°.

An analytical sample was prepared by sublimation (0.1 mm.) followed by recrystallization of the sublimate from a mixture of benzene and ethanol. The melting point remained unchanged.

Anal. Calcd. for $C_{25}H_{16}$: C, 94.90; H, 5.09. Found: C, 95.21; H, 5.02.

The other cyclodehydrogenations using aluminum chloride were carried out in a similar fashion. The new dibenzopyrenes are listed in Table III together with their respective melting points and analytical data.

TABLE III

NEW DIBENZOPYRENES

Hydrocarbon	M.P.	Carbon, %		Hydrogen, %	
		Calcd.	Found	Calcd.	Found
IIb	206–207	94.90	94.90	5.09	4.86
IIc	213–214	94.90	94.84	5.09	4.90
IId	210–211	94.90	95.21	5.09	5.02
IIe	201–202	94.50	94.40	5.49	5.77
IIf	198–199	94.50	94.78	5.49	4.88
IIg	207–209	94.50	94.75	5.49	4.82
IIi	215–216	94.50	94.85	5.49	4.79

Of the great number of experiments using various reagents and reaction conditions which were tried in unsuccessful attempts to cyclodehydrogenate the benzanthracenes (I) only the following appear worthy of mention.

B. *Stannic chloride and benzene.* Ten grams of anhydrous fuming stannic chloride was added to a solution of 1.5 g. of 9-(4-methylphenyl)-1,2-benzanthracene (Id) in 150 ml. of anhydrous benzene. The mixture was heated on a steam bath for 2 hr. and then worked-up in the usual manner. There was obtained 1.47 g. of the original hydrocarbon, m.p. 115–117°, (lit.,[9] m.p. 116.5–117.5°).

C. *Aluminum chloride–stannic chloride and benzene.* A mixture of 1.0 g. of 9-(4-methylphenyl)-1,2-benzanthracene (Id), 1.0 g. of anhydrous powdered aluminum chloride, 1.0 g. of anhydrous fuming stannic chloride, and 10 ml. of anhydrous benzene was heated for 1 hr. The mixture was allowed to cool to room temperature and then decomposed with 100 ml. of a 10% hydrochloric acid solution and worked-up in usual manner. The only material which could be isolated from the chromatographic separation was an unpurifiable red solid, m.p. 129–240°. This red solid could not be purified by sublimation under reduced pressure (0.1 mm.). Its ultraviolet absorption spectrum indicated an untractable mixture of compounds.

D. *Palladium-charcoal and p-cymene.* In a three-neck flask equipped with a stirrer and a water cooled condenser, a mixture of 1.0 g. of 9-(4-methylphenyl)-1,2-benzanthracene (Id), 3.0 g. of 10% palladium on charcoal, and 50 ml. of *p*-cymene was heated for 39 hr. The mixture was cooled to room temperature and then worked-up in the usual manner. There were obtained white plates, yield 0.95 g., m.p. 114–116° of the starting hydrocarbon.

E. *Aluminum chloride and carbon disulfide.* Five grams of anhydrous powdered aluminum chloride was added to a solution of 0.75 g. of 9-(4-methylphenyl)-1,2-benzanthracene (Id) in 75 ml. of carbon disulfide. The mixture was heated on a steam bath for 3 hr. The mixture was cooled to room temperature and then decomposed with 100 ml. of a 10% hydrochloric acid solution and worked-up in the usual manner. Only 0.15 g. of 9-(4-methylphenyl)-1,2-benzanthracene (Id) could be isolated and identified.

F. *Palladium-charcoal at 350°.* In a 100-ml. round bottom flask, 2.0 g. of 9-(4-methylphenyl)-1,2-benzanthracene (Id) and 3.0 g. of 10% palladium on charcoal were intimately mixed. The mixture was then heated in a nitrogen atmosphere for 6 hr. at 350° (±10°). The mixture was then allowed to cool to room temperature and the mixture was extracted with 100 ml. of hot benzene and worked-up in the usual manner. There was obtained 9-(4-methylphenyl)-1,2-benzanthracene (Id) 1.19 g. (60%). No other material could be isolated and no yellow band corresponding to a 1,2,3,4-dibenzopyrene was observed on the chromatographic column.

G. *Sodium chloride and aluminum chloride.* An intimate mixture of 15.0 g. of powdered anhydrous aluminum chloride, 3.0 g. of sodium chloride, and 1.2 g. of 9-(4-methylphenyl)-1,2-benzanthracene (Id) was placed in a 100-ml. round-bottom flask and placed in an oil bath preheated to 100°. The temperature of the bath was raised to 145° and the mixture was heated at that temperature for 2 hr. The melt was poured onto ice water and the resulting gummy mass was extracted with 200 ml. of benzene and worked-up in the usual manner. There was obtained 0.11 g. (10%) of the expected cyclodehydrogenation product, 2′-methyl-1,2,3,4-dibenzopyrene (IId), m.p. 205–206°.

BLACKSBURG, VA.

(19) The chromatographic separations were all done on a column 18 mm. × 370 mm. wet packed (30–60° petroleum ether) with Fisher's adsorption alumina, 80 200 mesh.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

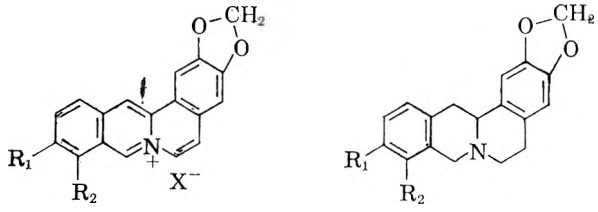
Aromatic Cyclodehydration. XLVI.[1] Synthesis of Tetrahydropalmatine and Its Analogs[2]

C. K. BRADSHER AND N. L. DUTTA

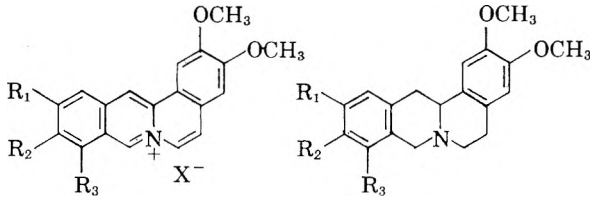
Received September 6, 1960

Tetrahydropalmatine (X) and a number of protoberberine alkaloids (XI–XIV) have been synthesized from 6,7-dimethoxyisoquinoline-1-carboxaldehyde (XVI) and its oxime (XVII) by following the general procedure described earlier. Tetrahydrocoptisine or stylopine (IV) has also been synthesized from 6,7-methylenedioxyisoquinoline-1-carboxaldehyde.

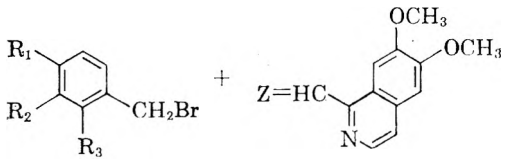
It has been shown[3] that tetrahydroberberine (III) could be synthesized from 6,7-methylenedioxyisoquinoline-1-carboxaldehyde or its oxime, using the methods of quaternization and cyclodehydration developer earlier.[4] The present communication describes the synthesis of 6,7-dimethoxyisoquinoline-1-aldehyde (XVI) and its use in the synthesis of tetrahydropalmatine (X), and some related compounds.



I. $R_1 = R_2 = OCH_3$ III
II. $R_1 - R_2 = OCH_2O$ IV



V. $R_1 = H, R_2 = R = OCH_3$ X
VI. $R_1 = H, R_2 - R_3 = OCH_2O$ XI
VII. $R_1 - R_2 = OCH_2O, R_3 = H$ XII
VIII. $R_1 = R_2 = OCH_3, R_3 = H$ XIII
IX. $R_1 = R_3 = H, R_2 = OCH_3$ XIV



XV

XVI. Z = O
XVII. Z = NOH

By following the same procedure, tetrahydrocoptisine (or stylopine IV) has been prepared from 6,7-methylenedioxyisoquinoline-1-carboxaldehyde.[3]

It was found that 1-methyl-6,7-dimethoxyisoquinoline, conveniently prepared by the Bischler-Napieralski cyclization of homoveratrylacetamide, followed by dehydrogenation,[5] could be oxidized to the corresponding aldehyde in 35% yield by the action of selenium dioxide. When this new aldehyde was quaternized in the usual way with 2,3-dimethoxybenzyl bromide (XV. $R_1 = H$, $R_2 = R_3 = OCH_3$) in the presence of acetonitrile[3] and the crude salt with cyclized by heating it with concentrated hydrochloric acid, the over-all yield of the new dehydropalmatine bromide (V. X = Br), was only 30%. The yield was raised to 80% when the oxime (XVII) of the 6,7-dimethoxyisoquinoline-1-carboxaldehyde (XVI) was used, and the quaternization effected in presence of dimethylformamide. It has also been found that the oxime method is superior in the case of synthesis of other analogs. The ultraviolet and visible spectra of the dehydropalmatine bromide (V. X = Br) thus prepared, resembled those of benz-[a]acridizinium salts previously prepared.[4] Reduction of the new salt (V. X = Br) in presence of Adams' catalyst produced (±)-tetrahydropalmatine as the hydrobromide, and the free base (X) was found to be identical with an authentic sample.[6,7,8] Other analogs tetrahydropalmatine were obtained by starting with the appropriate alkoxybenzyl halides. The oxime (XVII) was quaternized with 2,3-methylenedioxybenzyl bromide[4] (XV. $R_1 = H$, $R_2 - R_3 = OCH_2O$) and the crude salt was cyclized with hydrochloric acid, affording the expected dehydroepiberberinium chloride (VI. X = Cl; 65% yield). Catalytic hydrogenation of the new salt (VI. X = Cl) afforded the tetrahydroepiberberine[9,10] (XI.

(1) For the preceding communication of this series, see C. K. Bradsher and T. W. G. Solomons, *J. Org. Chem.*, **25**, 191 (1960).

(2) This research was supported by a research grant (H-2170) from the National Heart Institute of the National Institutes of Health, and was presented before the International Symposium on the Chemistry of Natural Products, Melbourne, Australia, August 15–25, 1960. A preliminary communication appeared in *Nature*, **184**, 1943 (1959).

(3) C. K. Bradsher and N. L. Dutta, *J. Am. Chem. Soc.*, **82**, 1145 (1960).

(4) C. K. Bradsher and J. H. Jones, *J. Org. Chem.*, **23**, 430 (1958).

(5) E. Späth and N. Polgar, *Monatsh.*, **51**, 190 (1929).

(6) E. Späth and H. Quietensky, *Ber.*, **58**, 2267 (1925); E. Späth and E. Mosettig, *Ber.*, **59**, 1496 (1926); E. Späth and E. Kruba, *Monatsh.*, **50**, 341 (1928).

(7) R. D. Haworth, J. B. Koepfli, and W. H. Perkin, Jr., *J. Chem. Soc.*, 548 (1927).

(8) T. R. Govindachari, S. Radjurai, M. Subramanian, and N. Viswanthan, *J. Chem. Soc.*, 2943 (1957).

sinactine) in 50% yield. Buck and Perkin, Jr.,[11] following a procedure described by Pictet and Gams,[12] synthesized a new compound, which they named tetrahydropseudoepiberberine. This alkaloid can be prepared conveniently by cyclization of the quaternary salt obtained from the oxime (XVII) and 3,4-methylenedioxybenzyl bromide,[1,13] followed by catalytic reduction of the resulting dehydropseudoepiberberinium chloride (VII. X = Cl).

In the same way, when veratryl bromide was quaternized with the oxime (XVII), and cyclized as above, the dehydronorcoralydine chloride (VIII. X = Cl) was obtained in 75% yield. On catalytic reduction of the salt (VIII. X = Cl), the expected (±)-norcoralydine (XIII) hydrochloride[14] was obtained in 60% yield.

With *m*-methoxybenzyl bromide and the oxime (XVII), the 2,3,10-trimethoxybenz[a]acridizinium chloride (IX. X = Cl) was prepared as above in good yield. The catalytic reduction of the salt (IX. X = Cl) yielded the expected new alkaloid, 2,3,10-trimethoxydibenzo[a,g]quinolizidine (XIV).

When the oxime of 6,7-methylenedioxyisoquinoline-1-carboxaldehyde[3] was quaternized with 2,3-methylenedioxybenzyl bromide,[4] the crude salt was found to cyclize easily, producing the expected dehydrocoptisine chloride (II. X = Cl) in 85% yield. The catalytic reduction of the salt afforded tetrahydrocoptisine ((±)-stylopine,[9,15,16] IV).

EXPERIMENTAL[17]

1-Methyl-6,7-dimethoxyisoquinoline. The homoveratrylamine, required for this purpose, was best prepared from 3,4-dimethoxynitrostyrene[18] by reduction with lithium-aluminum hydride in tetrahydrofuran, an improvement over the Soxhlet extraction method using ether.[19,20] The method is essentially that described earlier[21,22] and the yield of the amine obtained was up to 85%. For most of our experiments we used homoveratrylamine generously donated by the Lilly Research Laboratories (Eli Lilly & Co., Indianapolis, Ind.).

1-Methyl-3,4-dihydro-6,7-dimethoxyisoquinoline, prepared by cyclization of the crude homoveratrylacetamide, was dehydrogenated by heating 20.5 g. for 2 hr. with 6 g. of 10% palladium-on-charcoal catalyst at 175°, and crystallizing the product from benzene-petroleum ether (b.p. 30–60°) as colorless needles, m.p. 112° (lit.,[5] m.p. 111–112°); yield 15 g. (74%). Purification was effected by passing it through a column of alumina, eluting it with benzene.

6,7-Dimethoxyisoquinoline-1-carboxaldehyde.[23] To a clear hot and stirred solution of selenium dioxide (3.5 g.) in dioxane (50 ml.) and water (3 ml.), was added dropwise a solution of 1-methyl-6,7-dimethoxyisoquinoline (5 g.) in purified dioxane (50 ml.) in the course of 30 min. Within a short time, a red precipitate started forming and the whole mixture was heated on the steam bath with continuous agitation for 2 hr., after which the solution was filtered hot from the precipitated selenium. The bulk of the dioxane was removed by distilling the filtrate, under diminished pressure. The residual material was diluted with water, made alkaline with sodium hydroxide solution, and exhaustively extracted with ether. The dark colored ethereal solution was dried (sodium sulfate) and decolorized with Norit. The almost colorless solution was filtered and freed from ether and dioxane. The residue was crystallized from ethanol. The aldehyde was obtained as colorless plates, m.p. 176°; yield 1.8 g. (35%).

Anal. Calcd. for $C_{12}H_{11}NO_3$: C, 66.40; H, 5.07; N, 6.45. Found: C, 66.18; H, 5.28; N, 6.85.

The oxime (XVII) of the aldehyde (XVI), prepared in the usual way, crystallized from ethanol as colorless plates, m.p. 247–248°.

Anal.[24] Calcd. for $C_{12}H_{12}N_2O_3$: N, 12.06. Found: N, 12.02.

2,3,9,10-Tetramethoxybenz[a]acridizinium bromide (dehydropalmatine bromide, V, X = Br).[23] (a) *By the aldehyde method.* One gram of aldehyde (XVI) was refluxed for 2 hr. with 1.2 g. of 2,3-dimethoxybenzyl bromide[25] in 15 ml. of acetonitrile, under a nitrogen atmosphere. The solvent was removed under vacuum and the red semisolid residue was washed several times with ether. Concentrated hydrochloric acid (20 ml.) was then added to the solid which slowly went into solution. The solution was heated on the steam bath for about 1 hr. The solvent was removed under diminished pressure, and the residue was crystallized from ethanol, producing orange needles, m.p. 250° dec. (in sealed tube); yield 0.61 g. (30%). The yield was not improved by changing the solvent or the refluxing time.

(b) *By the oxime method.* The oxime (XVII, 1 g.) was dissolved in 20 ml. of dimethylformamide by heating on a steam bath and 1 g. of 2,3-dimethoxybenzylbromide was added to the hot solution. The whole mixture was kept at 50° for about 1 hr. and then left at the room temperature for 3 days. The quaternary salt was precipitated by adding ethyl acetate and dry ether, and the yellow precipitate was collected, washed several times with anhydrous ether, and dried under vacuum. The crude salt (1.8 g.) was dissolved in 30 ml. of concd. hydrochloric acid and heated on the

(9) R. D. Haworth and W. H. Perkin, Jr., *J. Chem. Soc.*, 1769 (1926).

(10) K. Goto and Z. Kitasato, *J. Chem. Soc.*, 1234 (1930).

(11) J. S. Buck and W. H. Perkin, Jr., *J. Chem. Soc.*, 125, 1675 (1924).

(12) A. Pictet and A. Gams, *Ber.*, **44**, 2480 (1911).

(13) G. M. Robinson and R. Robinson, *J. Chem. Soc.*, 105, 1456 (1914).

(14) L. E. Craig and D. S. Tarbell, *J. Am. Chem. Soc.*, **70**, 2783 (1948).

(15) E. Späth and P. L. Julian, *Ber.*, 64B, 1131 (1931).

(16) Z. Kitasato, *Proc. Imp. Acad. Tokyo*, **2**, 124 (1926). *Brit. Chem. Abstr.*, 1160 (1926).

(17) Except as noted all melting points were determined on the Fisher-Johns block and are uncorrected. Infrared absorption spectra were determined by the potassium bromide plate method using the Perkin-Elmer model Infracord Spectrophotometer. All ultraviolet spectra were measured in 95% ethanol solution using a Warren Spectracord spectrophotometer and 1-cm. silica cells. Except as noted all analyses were by Drs. Weiler and Strauss, Oxford, England.

(18) E. Knoevenagel and L. Walker, *Ber.*, **37**, 4506 (1904).

(19) F. A. Ramirez and A. Burger, *J. Am. Chem. Soc.*, **72**, 2797 (1950).

(20) R. I. T. Cromartie and J. Harley-Mason, *J. Am. Chem. Soc.*, **74**, 2525 (1952).

(21) M. Erne and F. Ramirez, *Helv. Chim. Acta*, **33**, 912 (1950).

(22) W. J. Gensler and C. M. Samour, *J. Am. Chem. Soc.*, **73**, 5556 (1951).

(23) A small quantity of this compound was prepared earlier by Dr. Dieter Pawellek, working in this laboratory.

(24) Analysis by Galbraith Laboratories, Knoxville, Tenn.

(25) C. K. Bradsher and J. H. Jones, *J. Am. Chem. Soc.*, **79**, 6033 (1957).

steam bath for 1 hr.[26] The acid was distilled and the red residue was carefully dried on a porous plate and then crystallized from methanol. The product was obtained as orange needles, m.p. 250° dec. (in sealed tube); yield, 1.6 g. (80%). The analytical sample melted at the same temperature; λ_{max} 246, 285, 328, 355, and 464 mμ; min., 268, 306, 344, and 404 mμ.

Anal. Calcd. for $C_{21}H_{20}O_4NBr$: C, 58.60; H, 4.65; N, 3.25. Found: C, 58.83; H, 4.74; N, 3.26.

The *perchlorate* formed red needles from methanol, m.p. 310–312° dec. (sealed tube).

Anal. Calcd. for $C_{21}H_{20}ClNO_8$: C, 56.20; H, 4.45; N, 3.12. Found: C, 55.80; H, 4.60; N, 2.92.

2,3,9,10-Tetramethoxydibenzo[a,g]quinolizidine (tetrahydropalmatine, X). A solution containing 0.35 g. of the above dehydropalmatine bromide in 150 ml. of methanol, was hydrogenated at atmospheric pressure in presence of 50 mg. of platinum oxide. The solution was filtered from the catalyst and the filtrate was concentrated under vacuum, affording an almost colorless solid. This was dissolved in water, and ammonia was added to precipitate the base, which was extracted with ether. The ethereal solution was dried (magnesium sulfate) and the ether removed. The residue was crystallized twice from dilute methanol (Norit), when the (±)-tetrahydropalmatine (X) was obtained as colorless prisms, m.p. 147° (lit.,[7] m.p. 147°): yield, 152 mg. (53%). The base gave no depression of melting point when mixed with an authentic sample[27] and infrared spectra of the two were identical.

Anal. Calcd. for $C_{21}H_{25}O_4N$: C, 70.99; H, 7.04; N, 3.94. Found: C, 71.08; H, 7.04; N, 4.24.

The *hydrochloride*, prepared by passing hydrogen chloride into a dry ethereal solution of the base, was crystallized from methanol as colorless needles, m.p. 215–216° (lit.,[28] m.p. 215°).

2,3-Dimethoxy-9,10-methylenedioxybenz[a]acridizinium chloride (dehydroepiberberinium chloride) (VI. X = Cl). The oxime (XVII, 1 g.) was quaternized in the usual way with 2,3-methylenedioxybenzyl bromide[25] and the crude salt cyclized in concentrated hydrochloric acid. The product crystallized from a mixture of methanol and ethanol as orange needles, m.p. 275–277° dec. (sealed tube); yield 1.4 g. (80%); λ_{max} 248, 275, 327, 358, and 492; min. 262, 304, 340, and 417 mμ.

Anal. Calcd. for $C_{20}H_{16}ClNO_4 \cdot 2H_2O$: C, 59.18; H, 4.93; N, 3.45. Found: C, 58.91; H, 4.63; N, 3.66.

The *perchlorate* was obtained in the usual way and crystallized from dimethylformamide and ethanol as scarlet red needles, m.p. 315–316° dec. (sealed tube).

Anal. Calcd. for $C_{20}H_{16}ClNO_8$: C, 55.36; H, 3.69; N, 3.23. Found: C, 55.11; H, 3.90; N, 3.16.

2,3-Dimethoxy-9,10-methylenedioxydibenzo[a,g]quinolizidine(tetrahydroepiberberine, XI). A suspension of 2,3-dimethoxy - 9,10 - methylenedioxybenz[a]acridizinium chloride (VI. X = Cl, 500 mg.) in methanol (200 ml.) was hydrogenated in presence of platinum oxide catalyst (80 mg.) for 24 hr. The crude free base (250 mg., 55%) was crystallized twice from ethanol and was obtained as colorless prisms, m.p. 167–168° (lit.,[9,10] m.p. 169–170°, 168°). A minute crystal was dissolved in glacial acetic acid to which a drop of concentrated sulphuric acid was added, giving a colorless solution which slowly turned violet. Tetrahydroepiberberine shows the same reaction.[9,10]

Anal. Calcd. for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.55; H, 6.16; N, 4.22.

The *hydrochloride* crystallized from water as colorless needles which decomposed at 246°. The melting point could not be raised by further crystallization (lit.[10,29] dec, about 286°; dec. 285–290°).

Anal.[24] Calcd. for $C_{20}H_{21}O_4N \cdot HCl$: C, 63.91; H, 5.85. Found: C, 63.95; H, 5.81.

2,3-Dimethoxy-10,11-methylenedioxybenz[a]acridizinium chloride (dehydropseudoepiberberinium chloride, VII. X = Cl). The quaternary salt, obtained from the oxime (XVII, 500 mg.) and 3,4-methylenedioxybenzyl bromide[3,13] in dimethylformamide, was cyclized in the usual way. The yellow product crystallized from excess methanol as greenish yellow microneedles, m.p. 278–280 dec. (sealed tube); yield 800 mg. (quantitative); λ_{max} 276, 309, 322, and 413; min. 250, 285, 317, and 367 mμ.

Anal. Calcd. for $C_{20}H_{16}ClNO_4 \cdot H_2O$: C, 61.93; H, 4.64; N, 3.61. Found: C, 61.57; H, 4.54; N, 3.82.

2,3-Dimethoxy-10,11-methylenedioxydibenzo[a,g]quinolizidine (tetrahydropseudoepiberberine, XII). A suspension of the above salt in methanol was hydrogenated and the base obtained in the usual way was crystallized from dilute methanol as colorless needles, m.p. 160° (lit.,[11] m.p. 160–161°): yield, 225 mg. (55%).

Anal. Calcd. for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.85; H, 6.37; N, 4.20.

The *picrate* was prepared the usual way, m.p. 150° dec. (lit.,[11] m.p. 149–150°).

2,3,10,11-Tetramethoxybenz[a]acridizinium chloride (dehydronorcoralydine, VIII. X = Cl). The oxime (XVII, 1 g.) quaternized easily with veratryl bromide (1 g.) in the presence of dimethylformamide (10 ml.) producing stout yellow prisms which, on cyclization for 10 min. with concentrated hydrochloric acid, afforded yellow crystals. These crystallized from methanol as fine yellow needles, m.p. 240–242° dec. (sealed tube); yield, 1.4 g. (75%); λ_{max} 278, 309, 322, 417; min. 250, 286, 318, and 370 mμ.

Anal. Calcd. for $C_{21}H_{20}ClNO_4 \cdot H_2O$: C, 59.78; H, 5.69; N, 3.32. Found: C, 59.61; H, 5.60; N, 3.20.

The *perchlorate* was prepared in aqueous methanolic solution and was obtained as yellow needles from dimethylformamide, m.p. 367–368° dec. (sealed tube).

Anal. Calcd. for $C_{21}H_{20}ClNO_8$: C, 56.06; H, 4.44; N, 3.11. Found: C, 56.25; H, 4.69; N, 3.12.

2,3,10,11-Tetramethoxydibenzo[a,g]quinolizidine(norcoralydine, XIII). The above salt (VIII) was hydrogenated in the usual way and the colorless norcoralydine hydrochloride thus obtained was crystallized several times from dilute methanol as colorless prisms, m.p. 232° dec. (lit.,[14,30] m.p. 234–237° dec., 236–237°); yield 60%. The product gave no depression when mixed with an authentic sample[31] of hydrochloride.

Anal. Calcd. for $C_{21}H_{25}NO_4 \cdot HCl$: C, 63.39; H, 6.64; N, 3.83. Found: C, 63.33, 63.11; H, 6.57; 6.73; N, 3.63.

2,3,10-Trimethoxybenz[a]acridizinium chloride (IX. X = Cl). *m*-Methoxybenzylbromide (1.5 g.) was quaternized with the oxime (XVII. 1 g.) in presence of dimethylformamide and the quaternary salt was cyclized with concentrated hydrochloric acid. The yellow precipitate was crystallized from a mixture of ethanol and methanol. The product was obtained as yellow needles, m.p. 242 dec. (sealed tube); yield 1.2 g. (72%); λ_{max} 277, 312, 332, 435; min. 250, 300, 322, and 380 mμ.

Anal. Calcd. for $C_{20}H_{18}ClNO_3 \cdot CH_3OH \cdot \frac{1}{2}H_2O$: C, 62.06; H, 5.66; N, 3.44. Found: C, 62.03; H, 5.94; N, 3.42.

The *perchlorate* was obtained as greenish yellow needles from methanol and ethanol, m.p. 310–311° dec. (sealed tube).

Anal. Calcd. for $C_{20}H_{15}ClNO_7$: C, 57.27; H, 4.30; N, 3.34. Found: C, 56.95; H, 4.41; N, 3.42.

2,3,10-Trimethoxydibenzo[a,g]quinolizidine (XIV). The above acridizinium chloride (IX) was hydrogenated with platinum oxide catalyst in methanol. The almost color-

(26) In subsequent experiments it was found that the cyclization time could be shortened to 10–20 min.

(27) We are indebted to Prof. Alfred Burger for the gift of this sample.

(28) K. Feist, *Arch. Pharm.*, 245, 586 (1906).

(29) W. H. Perkin, Jr., *J. Chem. Soc.*, 113, 492 (1918).

(30) R. H. F. Manske, *Can. J. Research*, 16B, 81 (1938).

(31) We are indebted to Professor D. S. Tarbell for the gift of a sample of the free base.

less product thus obtained was crystallized several times from dilute methanol (Norit) as colorless prisms, m.p. 214–215°; yield 50%.

Anal. Calcd. for $C_{20}H_{23}NO_3 \cdot HCl \cdot H_2O$: C, 63.24; H, 6.85; N, 3.68. Found: C, 63.21; H, 6.95; N, 3.65.

2,3,9,10-Bismethylenedioxybenz[a]acridizinium chloride (dehydrocoptisine chloride, II, X = Cl). A mixture of the oxime of 6,7-methylenedioxyisoquinoline 1-carboxaldehyde[3] (0.9 g.) 2,3-methylenedioxybenzylbromide[4] (1 g.) and dimethylformamide (15 ml.) was allowed to react in the usual way and the quaternary salt was cyclized with concentrated hydrochloric acid. The red precipitate was collected and crystallized from a mixture of ethanol and methanol as red needles, decomposing above 300° (sealed tube); yield 1.5 g. (85%); λ_{max} 248, 317, 356, 490; min. 264, 294, 337, and 418 mμ.

The analytical sample was recrystallized from excess methanol, without change in melting point.

Anal. Calcd. for $C_{19}H_{12}ClNO_4 \cdot 3/2\ H_2O$: C, 60.00; H, 3.94. Found: C, 59.69; H, 4.05.

The perchlorate was obtained as red needles from dimethylformamide and methanol, decomposing from 350°.

Anal. Calcd. for $C_{19}H_{12}ClNO_8$: C, 54.61; H, 2.87; N, 3.35. Found: C, 54.50; H, 3.21; N, 3.75.

2,3,9,10-Bismethylenedioxydibenzo[a,g]quinolizidine (tetrahydrocoptisine, ±-stylopine, IV). The above salt (II. X = Cl) was hydrogenated in the usual way and the free base was crystallized twice from methanol. The tetrahydrocoptisine (XIV) was obtained as colorless needles, m.p. 217–218° dec. (lit.,[9,15,16] m.p. 219°, 227–228°, 215–216°); yield 50%. It was found that a solution of the base in glacial acetic acid slowly turned green on addition of a drop of concentrated sulfuric acid, while the further addition of a drop of dilute nitric acid produced a red color. Tetrahydrocoptisine was reported to behave similarly.[9]

Anal.[24] Calcd. for $C_{19}H_{17}NO_4$: C, 70.57; H, 5.30; N, 4.33. Found: C, 70.64; H, 5.14; N, 4.56.

DURHAM, N. C.

[CONTRIBUTION NO. 656 FROM THE CENTRAL RESEARCH DEPARTMENT, EXPERIMENTAL STATION, E. I. DU PONT DENEMOURS AND CO.]

Trimerization of Acetylenes

F. W. HOOVER, O. W. WEBSTER, AND C. T. HANDY

Received December 12, 1960

The trimerization of monovinylacetylene and the cotrimerization of divinylacetylene with acetylene and with methylacetylene have been effected under mild conditions using triisobutylaluminum/titanium tetrachloride catalyst to give trivinylbenzenes and *o*-divinylbenzenes, respectively.

The thermal trimerization of acetylene to benzene was reported almost one hundred years ago by Berthelot.[1] Since then, such catalysts as metal carbonyls,[2] triphenylphosphinenickel carbonyl,[3] trialkylchromium,[4] diborane-activated silicaalumina,[5] and triisobutylaluminum–titanium tetrachloride[6] have been shown to facilitate the trimerization of acetylenes. Trialkylaluminum–titanium tetrachloride catalysts are well known for their ability to catalyze the polymerization of olefins,[7] and have been used to polymerize 1-hexyne to linear conjugated structures.[8]

Although vinylacetylenes might thus be expected to give complex products with trialkylaluminum–titanium tetrachloride catalysts, we have found that these catalysts promote trimerization of monovinylacetylene and cotrimerization of divinylacetylene with acetylene readily at −10 to 50° to give vinylbenzenes in modest to good yields.

At −10°, monovinylacetylene gave a mixture of 1,2,4- and 1,3,5-trivinylbenzenes in 74% yield. The yield at 50° was only 10%. The composition of this mixture as determined by ultraviolet analysis of the hydrogenated products was 90% 1,2,4-trivinylbenzene and 10% 1,3,5-trivinylbenzene. Statistically, one would expect a product containing 75% of 1,2,4-trivinylbenzene. 1,3,5-Trivinylbenzene has been prepared by another method,[9] but apparently the 1,2,4-isomer has not been reported.

The 1,2,4- and 1,3,5-trivinylbenzenes were separated by gas chromatography although considerable polymerization occurred on the column. The retention time of the 1,2,4-isomer was slightly shorter than that of the 1,3,5-isomer.

The infrared spectra of 1,3,5-trivinylbenzene and of the mixture of trivinylbenzenes were in general those expected for vinylbenzenes. The spectrum of 1,2,4-trivinylbenzene showed a strong band at 11.98 μ which was absent in the spectrum of 1,3,5-trivinylbenzene. As would be expected, the trivinylbenzenes absorb strongly in the ultraviolet, $\lambda_{max}^{C_2H_5OH}$ 246 mμ (ε = 31,000).

(1) M. Berthelot, *Compt. rend.*, **62**, 905–909 (1866).

(2) W. Hübel and C. Hoogzand, *Chem. Ber.*, **93**, 103–115 (1960).

(3) W. Reppe and W. J. Schweckendick, *Liebigs Ann. Chem.*, **560**, 104 (1948).

(4) H. H. Zeiss and W. Herwig, *J. Am. Chem. Soc.*, **80**, 2913 (1958).

(5) I. Shapiro and H. G. Weiss, *J. Am. Chem. Soc.*, **79**, 3294 (1957).

(6) B. Franzus, P. J. Canterino, and R. A. Wickliffe, *J. Am. Chem. Soc.*, **81**, 1514 (1959).

(7) N. G. Gaylord and H. F. Mark, *Linear and Stereoregular Addition Polymers*, Interscience, New York, 1959.

(8) G. Natta, *et al.*, *Gazz. chim. ital.*, **89**, 465–94 (1959).

(9) D. T. Mowry and E. L. Ringwald, *J. Am. Chem. Soc.*, **72**, 2037 (1950).

o-Divinylbenzene and dimethyl-*o*-divinylbenzene isomers are readily obtained by cotrimerization of divinylacetylene with acetylene and with methylacetylene, respectively. With acetylene in large excess, *o*-divinylbenzene was obtained in about 30% yield based on divinylacetylene. In limited process studies, the yields were increased to about 60% *o*-divinylbenzene when nearly stoichiometric proportions of acetylene were used.[10] The cotrimerization of divinylacetylene and acetylene has also been effected with triphenylphosphinenickel tricarbonyl and with bis(triphenylphosphine)nickel dicarbonyl. With these catalysts the yields were somewhat lower and the products were more difficult to purify.

Gas chromatographic analysis of the mixture of dimethyl-1,2-divinylbenzenes obtained from methyl acetylene and divinylacetylene showed three components representing approximately 5%, 85%, and 10% of the total. The identity of these isomers was not established. As 3,5-dimethyl-1,2-divinylbenzene is favored statistically, it would be expected to predominate, particularly because it was shown that the statistically favorable isomer was the main product in the case of the trivinylbenzene synthesis.

EXPERIMENTAL

Trimerization of vinylacetylene. Vinylacetylene (120 g.), scrubbed with 30% aqueous sodium bisulfite and with 20% aqueous sodium hydroxide, and dried with calcium chloride and anhydrous calcium sulfate, was added to a mixture of 1000 ml. of toluene, 6.4 g. of triisobutylaluminum, and 2.0 g. of titanium tetrachloride over a period of 75 min. (scrupulously dried equipment was used). The temperature was maintained at −10° by cooling. Methanol (400 ml.) was added to destroy the catalyst and to precipitate methanol-insoluble products. Distillation of the filtrate gave 15 g. of recovered monovinylacetylene and 78 g. of trivinylbenzenes,[11] b.p. 90° at 5 mm., n_D^{25} 1.6050, corresponding to a conversion of 65% and yield of 74%. In a similar run at 29–52°, the yield was only 10%.

Anal. Calcd. for $C_{12}H_{12}$: C, 92.25; H, 7.75; Hydrogenation No. 0.0385; mol. wt. 156. Found: C, 91.72; H, 8.07; Hydrogenation No. 0.0400, 0.0408; mol. wt. 156 (by mass spectrometry).

Hydrogenation of the trivinylbenzene fraction was carried out in ethanol at 33° under atmospheric pressure using a platinum oxide catalyst. Ultraviolet analysis of the hydrogenated product indicated that it contained 90% 1,2,4-triethylbenzene and 10% 1,3,5-triethylbenzene.

Gas chromatographic analysis of the trivinylbenzene isomers was carried out using a 1-m. stainless steel column (O.D.—0.25 in.) containing polypropylene glycol (20%) on Columnpak at 160° with a preheater temperature of 220° and a helium flow of 75 ml./min. The chromatogram showed a large peak (about 75% of total) at a retention time of 35 min. and a smaller peak (25%) at 38 min. The 38-min. peak was shown to be due to 1,3,5-trivinylbenzene by comparison with the chromatogram of an authentic sample.[9] Attempts to use preparative-scale gas chromatography resulted in nearly complete polymerization of the trivinylbenzenes on the column. As polymerization does occur on the column, the quantitative interpretations of the gas chromatographic analysis may be subject to considerable error.

The ultraviolet spectrum of the trivinylbenzene fraction showed strong absorption in the ultraviolet region, $\lambda_{max}^{C_2H_5OH}$ 246 mμ (ε 31,000). The infrared absorption spectrum showed bands at 3.25 μ, 3.35 μ (unsaturated carbon-hydrogen bonds), 6.15 μ (conjugated olefinic —C=C—), 6.30 μ (aromatic —C=C—), 10.15 μ and 11.02 μ (CH deformations, —CH=CH_2), 11.37 μ (out-of-plane C—H deformation vibration in 1,3,5-trivinylbenzene), and 11.98 μ (out-of-plane CH deformation vibration in 1,2,4-trivinylbenzene).

The infrared spectrum of an authentic sample[9] of 1,3,5-trivinylbenzene was very similar except it did not show the strong band at 11.98 μ.

o-Divinylbenzene. A. *Catalyst: Triisobutylaluminum/titanium tetrachloride.* To a dry, 1-l. reaction flask equipped with a mechanical stirrer, condenser, dropping funnel for addition of divinylacetylene (DVA),[12] gas addition tube, and a thermometer there was added 150 ml. of toluene dried over sodium. The reaction system was flushed with nitrogen and 10 ml. of triisobutylaluminum and 1 ml. of titanium tetrachloride were added in turn by means of a hypodermic syringe. The catalyst solution was cooled in ice water and acetylene was passed into the system at the rate of 0.8 mole per hr. A solution of 16 g. of divinylacetylene in 30 ml. of toluene was added over the course of 2 hr. The temperature of the reaction solution was maintained at 15–20° by means of a water bath. Methanol (50 ml.) containing a trace of *N*-phenyl-β-naphthylamine to inhibit polymerization was added. The solution was filtered and the filtrate was distilled. *o*-Divinylbenzene,[13] 8 g., 30% yield, n_D^{25} 1.5740, b.p. 52°/3 mm., $\lambda_{max}^{C_2H_5OH}$ 229 mμ (ε 20,400), was collected. The infrared spectrum of this product was identical with that of a sample prepared with triphenylphosphinenickel tricarbonyl as catalyst.

B. *Catalyst: Triphenylphosphinenickel tricarbonyl.* A 1-l., creased, five-necked flask was equipped with a mechanical stirrer, condenser, two 500-ml. addition funnels, and a gas addition tube. The reaction system was flushed with dry oxygen-free nitrogen. *N,N*-Dimethylacetamide, 200 ml., and 4 g. of calcium carbide were placed in the reaction flask. A solution of 30 g. of triphenylphosphinenickel tricarbonyl in 150 ml. of dimethylacetamide was placed in one additional funnel. A solution of 95 g. of divinylacetylene in 100 ml. of *N,N*-dimethylacetamide (inhibited with 0.5 g. of phenothiazine) was placed in the other addition funnel. A portion of the catalyst solution was added to the reaction vessel and acetylene passed into the mixture at approximately 0.5 mole per hr. The temperature of the catalyst solution was gradually raised to 95°. At this temperature, the acetylene flow rate was increased to 2 moles per hr. The divinylacetylene solution was added dropwise over the course of 5 hr. The temperature was maintained at 100–110° by means of a cooling bath. Catalyst solution was added as necessary to maintain acetylene absorption. The product was distilled and the fraction, b.p. 25–60°/5 mm., was collected, diluted with pentane, and washed with water. The product was then dried and distilled through a two-foot spinning-band column. Two major fractions were obtained: 1) styrene, 8 g., b.p. 25°/5 mm., n_D^{25} 1.5432, characterized by its infrared spectrum; 2) *o*-divinylbenzene, 34.5 g., 22% yield, b.p. 59–60°/4.5 mm., n_D^{25} 1.5740, (lit.[14] b.p. 73.5°/11 mm., n_D^{21} 1.5760, b.p. 73–74°/12 mm., n_D^{22} 1.5759). The infrared spectrum of the product showed absorption at 3.23, 3.25, 3.30 (hydrogen attached to unsaturated carbon), 6.14 (conjugated carbon-carbon double bond), 6.75, 6.88, 7.05 (aromatic ring vibrations), 10.14,

(10) We are indebted to Dr. R. W. Keown of E. I. du Pont de Nemours & Co. for this information.

(11) F. W. Hoover, U. S. patent 2,951,884, September 6, 1960.

(12) As divinylacetylene readily forms explosive peroxides when exposed to air, all reactions with this substance should be conducted in an inert atmosphere.

(13) F. W. Hoover, U. S. patent 2,933,541, April 19, 1960.

(14) R. Deluchat, *Ann. Chim.* (11), 1, 181 (1934); K. Fries, H. Bestian, and W. Klauditz, *Ber.*, 69B, 715 (1936).

10.95 (vinyl hydrogen), and 13.20 μ (four adjacent hydrogens on an aromatic ring). The NMR spectrum was in agreement with the assigned structure, *o*-divinylbenzene.

Cotrimerization of divinylacetylene and methylacetylene. To a dry 500-ml. reactor equipped with a mechanical stirrer, condenser, dropping funnel, gas addition tube (open-end type extended below liquid level) and a thermometer, there was added 200 ml. of toluene dried with calcium hydride. Triisobutylaluminum (5 ml.) was added to the reactor under nitrogen by means of a hypodermic syringe, followed by titanium tetrachloride (1.5 ml.). Methylacetylene, dried by passing it through a tower containing Drierite, was added at the rate of 1.2 moles per hour. Concurrently, a solution of 15.6 g. (0.2 mole) of divinylacetylene in 50 ml. of toluene was added dropwise over a period of 80 min. Throughout the reaction, the temperature was maintained between 9° and 16° by means of an ice bath. Ten minutes after completion of the addition of the divinylacetylene, the catalyst was deactivated by addition of 50 ml. of methanol. On distillation there was obtained 40 g. of a trimethylbenzene isomer mixture, b.p. 32°/2 mm., and 9 g. (28% yield) of dimethyl-*o*-divinylbenzene[12] isomer mixture, b.p. 50–51°/0.2 mm., n_D^{25} 1.5598 and $\lambda_{max}^{C_2H_5OH}$ 228 mμ (ϵ 23,200).

Anal. Calcd. for $C_{14}H_{16}$: C, 91.14; H, 8.86; mol. wt., 158. Found: C, 90.73; H, 9.13; mol. wt., 158 (by mass spectrometry).

Gas chromatographic analysis of the product using a 1-m. Perkin Elmer Column R at 168° (preheat 220°) with a helium flow of 75 ml./min. showed three components with retention times of 11.7 min., 14.2 min., and 17.2 min., representing approximately 5%, 85%, and 10%, respectively, of the total. The three isomers were not identified.

Acknowledgment. We wish to thank Professor A. C. Cope, Dr. R. E. Benson, and Dr. V. A. Engelhardt for helpful suggestions during this work.

WILMINGTON 98, DEL.

[CONTRIBUTION FROM THE LABORATORY OF BIOCHEMISTRY, NATIONAL CANCER INSTITUTE[1]]

Replacement and Elimination of Bromine in Bromonitrofluorenones. The Preparation of 2,3- and 1,2,3-Substituted Fluorenes and Fluorenones

KAZUO SUZUKI,[2] ELIZABETH K. WEISBURGER, AND JOHN H. WEISBURGER

Received August 11, 1960

The oxidation by peracetic acid of 2-amino-3-bromofluorene and 2-amino-3-bromofluorenone, and of 1,3-dibromo-2-fluorenamine furnished the corresponding nitro derivatives. In the nitrobromofluorenones the bromine was readily replaced by amino groups in ethanolic ammonia. Ethanolic potassium hydroxide introduced a hydroxyl group into these compounds, but in one case elimination of bromine in the 1-position with substitution by hydrogen occurred. Potassium hydroxide in pyridine substituted a hydroxyl for a bromine at the 3-, but not at the 1-position in 1,3-dibromo-2-nitrofluorenone. These replacement reactions led to the facile preparation of a number of new 2,3- and 1,2,3-substituted fluorenones, and fluorenes.

The recent description[3] of a procedure for the oxidation of a primary aromatic amine by peracetic acid to the corresponding nitro derivative has suggested its use for the purpose of activating halogens *ortho* to the nitro group, thereby permitting the selective replacement of the halogen by other functional groups. The present paper deals with the application of this method to the convenient preparation of a number of otherwise difficultly available 2,3- and 1,2,3-substituted fluorene and fluorenone derivatives.

Bromination of 2-aminofluorenone by bromine afforded the 3-bromo derivative. The use of *tert*-butyl bromide in dimethyl sulfoxide[4] in addition produced 2-amino-3-bromo-9-fluorenol. Reduction of 2-amino-3-bromofluorenone by the Wolff-Kishner reaction resulted in good yields of 3-bromo-2-fluorenamine, provided that the reaction was performed in the absence of alkali. If alkali was added, halogen elimination ensued so that the product was 2-fluorenamine.

The action of peracetic acid on the 2-amino-3-bromofluorene and 2-amino-3-bromofluorenone readily gave the nitro derivatives. In the resulting nitrobromofluorenone bromine was easily replaced by amino, or by hydroxyl to yield the corresponding 2-nitro-3-amino-9-fluorenone or 2-nitro-3-hydroxy-9-fluorenone. This latter material served as a good source for the otherwise difficultly prepared 2-amino-3-fluorenol.[5] In fact, this aminohydroxyfluorene could be made in a single sequence of operations directly from 2-nitro-3-bromo-9-fluorenone by first treating with alkali under mild conditions, followed by addition of hydrazine and raising the temperature, thus effecting the Wolff-Kishner reaction. This new, short sequence of steps would appear to be the procedure of choice for the preparation of 2-amino-3-fluorenol.

Attempts to replace the bromine by fluorine in 2-nitro-3-bromo-9-fluorenone in acetamide as solvent gave the expected elimination of bromine, but under these conditions fluorine did not enter

(1) National Institutes of Health, Public Health Service, Department of Health, Education and Welfare.

(2) Visiting Scientist, National Cancer Institute. On leave of absence from Yamaguchi University, Ube, Japan.

(3) W. L. Mosby and W. L. Berry, *Tetrahedron*, 5, 93 (1959).

(4) T. L. Fletcher and H. L. Pan, *J. Am. Chem. Soc.*, 78, 4812 (1956). T. L. Fletcher, M. J. Namkung, and H. L. Pan, *Chem. and Ind.*, 660 (1957).

(5) E. K. Weisburger and J. H. Weisburger, *J. Org. Chem.*, 19, 964 (1954).

the molecule. Instead, a hydroxyl group and an amino group were introduced, even though the reactants had been rigorously dried. The amino group possibly resulted from the partial dissociation of acetamide. Indeed, when dimethylsulfoxide was used under mild conditions, only the hydroxy compound was formed. In none of the many attempts could a fluorine-containing compound be detected.[6] Likewise, although the bromine atom was eliminated, there was no evidence for the formation of a bifluorene derivative in this reaction.

The authentic bifluorene was prepared in poor yield by the action of activated copper on 2-nitro-3-bromo-9-fluorenone. In this instance as well, loss of halogen with production of 2-nitrofluorenone was the main reaction. Dehalogenation during the Ullmann reaction has been observed by Longo and Pirona.[7]

Peracetic acid likewise smoothly oxidized 1,3-dibromo-2-fluorenamine to the nitro derivative. Some 1,3-dibromo-2-nitro-9-fluorenone was also produced. In the latter compound both halogens proved susceptible to replacement by amino groups, thus yielding a 1,2,3-nitrogen substituted fluorenone derivative. On the other hand, refluxing 1,3-dibromo-2-nitrofluorenone with aqueous ethanolic alkali did not give the expected dihydroxy compound, but furnished instead 2-nitro-3-hydroxy-9-fluorenone. The halogen at the 1-position was eliminated under the influence of alkali, just as in the case of the Wolff-Kishner reaction of 3-bromo-2-aminofluorenone in the presence of potassium hydroxide, discussed above. Performance of the reaction in pyridine and alkali, however, led to the replacement of the bromine at the 3- position only, giving 1-bromo-2-nitro-3-hydroxyfluorenone. This compound also lost the halogen under the influence of ethanolic alkali.

It was of some interest to investigate whether the replacement of halogen by other functions in these fluorenones was mediated as a result of activation by the nitro group, or whether the keto group played a major role.[8] To this end, exchange reactions of 1,3-dibromo-2-nitrofluorene with ethanolic ammonia and ethanolic potassium hydroxide were performed as described for the fluorenone derivative. In the case of ammonia, about 30% of the starting material was recovered, and in addition a small amount of 1,3-dibromo-3-nitro-9-fluorenone was also isolated. Silver bromide equivalent to a 13% replacement of halogen was found. The potassium hydroxide reaction gave only a trace of alkali-soluble product. In addition, a number of unidentified substances were observed in both reactions. All of these exhibited a band in the infrared which indicated the presence of a keto function, suggesting that the exchange of halogen for another substituent occurs only when the keto group is present. Apparently the single nitro group does not activate an *ortho* halogen sufficiently in the fluorene ring system. Bradley and Williams also noted the inertness of 2-nitrofluorene to the action of potassium hydroxide in pyridine under conditions where 2-nitrofluorenone reacted.[9]

EXPERIMENTAL

The melting points were determined in a capillary tube and are not corrected. In a few cases, high melting points were taken on a Kofler apparatus. The ultraviolet spectra were recorded by Mr. P. H. Grantham on a Cary recording spectrophotometer as $5 \times 10^{-5} M$ solutions in ethanol and the infrared spectra on a Perkin-Elmer spectrophotometer, model 21, as solids in potassium bromide disks. We are indebted to the staff of the NIH Microanalytical Laboratory for the analyses.

2-Amino-3-bromo-9-fluorenone. A. 2-Amino-9-fluorenone (12 g.) in 200 ml. acetic acid reacted with 3.16 ml. bromine at 20° to yield 2-amino-3-bromo-9-fluorenone (11.9 g., 71%), m.p. 210° (from ethanol) (lit.[4] m.p. 216°).

B. 2-Amino-9-fluorenone (7.6 g.) in 196 ml. dimethyl sulfoxide was treated with 4.45 ml. of *t*-butyl bromide at 105° for 1.5 hr. and poured into water.[4] Extraction of the product by refluxing benzene gave upon cooling 1.9 g. of brick-red 2-amino-3-bromo-9-fluorenone, m.p. 210°. Extraction of the benzene-insoluble material with hot 1*N* hydrochloric acid and subsequent neutralization gave 1.5 g. of *2-amino-3-bromo-9-fluorenol*,[10] m.p. 198° (raised to 205–206°, from ethanol and benzene). Thus, reduction of the keto function in a position *para*- to the entering bromo group was a concomitant reaction.

Anal. Calcd. for $C_{13}H_{10}BrNO$: C, 56.54; H, 3.65; N, 5.79; Br, 28.93. Found: C, 56.80; H, 3.74; N, 5.27; Br, 28.36.

3-Bromo-2-fluorenamine. A Wolff-Kishner reduction of 5.5 g. of 2-amino-3-bromo-9-fluorenone, 20 ml. of 85% hydrazine hydrate, and 40 ml. of diethylene glycol afforded in 2 hr. 4.8 g. (91%), of 3-bromo-2-fluorenamine, m.p. 137–139° (colorless plates from cyclohexane) (lit.[4] m.p. 142.5°).

In the presence of potassium hydroxide the only product isolated was 2-fluorenamine. Thus, 550 mg. of ketone, 2 ml. of hydrazine hydrate, 170 mg. of alkali, and 5 ml. of glycol gave 462 mg. of product, m.p. 115°, which was sublimed *in vacuo* and recrystallized from cyclohexane: 185 mg. (51%) of 2-fluorenamine, m.p. and mixed m.p. 124° (lit.[11] m.p. 127.5°).

2-Nitro-3-bromofluorene. 3-Bromo-2-fluorenamine (4.2 g.) in 60 ml. 40% peracetic acid was refluxed for 10 min. (color changes through green to brown) and cooled. The crude product was sublimed *in vacuo* at 130° and the sublimate crystallized from acetic acid: 2-Nitro-3-bromofluorene (1.6 g., 35%), m.p. 130–131°. From the sublimation residues and the mother liquors 1 g. (20%) of 2-nitro-3-bromofluorenone, m.p. 250° was isolated. λ_{max} 260 mμ (ϵ = 12,910); 307 (10,-180); λ_{min} 239 (8860), 275 (7000).

Anal. Calcd. for $C_{13}H_5BrNO_2$: C, 53.81; H, 2.78. Found: C, 54.15; H, 3.07.

(6) We are grateful to Dr. C. G. Finger, Illinois State Geological Survey, Urbana, Ill., for valuable discussions regarding the introduction of fluorine into aromatic compounds by exchange reactions.

(7) B. Longo and M. Pirona, *Gazz. chim. ital.*, **77**, 117 (1947).

(8) P. E. Fanta, *Chem. Revs.*, **38**, 139 (1946).

(9) W. Bradley and F. P. Williams, *J. Chem. Soc.*, 1205 (1959).

(10) Catalytic reduction of 2-amino-3-bromofluorenone over platinum oxide in ethanol also furnished the fluorenol, m.p. and mixed m.p. 205°.

(11) W. E. Kuhn, *Org. Syntheses*, Coll. Vol. II, 447 (1943).

2-Nitro-3-bromofluorenone. 2-Amino-3-bromo-9-fluorenone (5.05 g.) in 100 ml. of 40% peracetic acid was refluxed for 3 hr. (color change to dark yellow). A small amount of potassium bichromate was added and refluxing continued briefly to give upon cooling 5.3 g. of product, m.p. 254° (m.p. 255–257°, from benzene or acetic acid) λ_{max} 260 mμ (ε = 36,830); λ_{min} 226(9140).

Anal. Calcd. for $C_{13}H_6BrNO_3$: C, 51.34; H, 1.99. Found: C, 51.25; H, 2.37.

2-Nitro-3-amino-9-fluorenone. 2-Nitro-3-bromo-9-fluorenone (304 mg.) in 70 ml. of absolute ethanol, saturated at 0° with ammonia, was heated in a pressure bottle for 24 hr. at 60° (green solution) to give upon cooling 240 mg. of brownish yellow crystals, m.p. 312–313° (m.p. 313–314°, Kofler, from benzene) λ_{max} 236.5 mμ (ε 11,210); 273 (13,270), 307.5 (19,520); 402 (7770); λ_{min} 244 (7950), 281 (12, 170), 359 (4640).

Anal. Calcd. for $C_{13}H_8N_2O_3$: C, 65.00; H, 3.36; N, 11.66. Found: C, 64.92; H, 3.73; N, 11.40.

A Wolff-Kishner reduction of 312 mg. of this compound in 2.5 ml. of hydrazine hydrate and 5 ml. of diethylene glycol produced 122 mg. of *2,3-fluorenediamine*, m.p. and mixed m.p. 193° (lit.[12] m.p. 192°), (from cyclohexane and dilute ethanol).

Refluxing 240 mg. of 2-nitro-3-aminofluorenone in 50 ml. of acetic anhydride for 7 hr. yielded 210 mg. of *N-(2-nitro-9-oxo-3-fluorenyl) acetamide*, m.p. 187°, after chromatography on alumina in benzene and crystallization from ethanol, (m.p. 190–191°, from ethanol, or cyclohexane-ethanol), λ_{max} 255 mμ (ε 25,790), 303.5 (30,640), 363 (6160); λ_{min} 232 (12,710), 276.5 (18,600); 347.5 (5840).

Anal. Calcd. for $C_{15}H_{10}N_2O_4$: C, 63.82; H, 3.57; N, 9.93. Found: C, 63.55; H, 3.76; N, 9.65.

2-Nitro-3-hydroxy-9-fluorenone. 2-Nitro-3-bromo-9-fluorenone (912 mg.) in 30 ml. each of ethanol and 2*N* potassium hydroxide was refluxed for 1 hr. (color change from yellow to red). The solution was diluted with water, filtered, and acidified, giving 594 mg. (82%) of product, m.p. 245° [from benzene; 247–248° (lit.[9] 248–249°) from benzene and ethanol]. λ_{max} 247.5 mμ (ε = 28,010); 296.5 (31,920); 357.5 (9170); λ_{min} 266(15,950); 333.5 (7780)

2-Amino-3-fluorenol. A. A Wolff-Kishner reduction of 241 mg. of 2-nitro-3-hydroxy-9-fluorenone in 2 ml. of hydrazine hydrate and 4 ml. of diethylene glycol yielded 180 mg. (91%) of 2-amino-3-fluorenol, m.p. and mixed m.p. 211–212° (lit.[6] 209–210°), from benzene.

B. 2-Nitro-3-bromo-9-fluorenone (304 mg.) and 170 mg. of potassium hydroxide in 5 ml. of diethylene glycol was heated for 2 hr. on a steam bath. After cooling, 2 ml. of hydrazine hydrate was added and a Wolff-Kishner reaction performed: 2-amino-3-fluorenol (187 mg., 95%), m.p. 212–213°.

Reaction of 2-nitro-3-bromo-9-fluorenone with potassium fluoride. A. The fluorenone (4.86 g.), 50 g. of dry acetamide (sublimed and recrystallized), and 3.6 g. of oven-dried potassium fluoride was heated to 170–175° with stirring for 7.5 hr. Extraction of the brown product with water, acidification of the solution with nitric acid, and addition of silver nitrate precipitated 2.67 g. (89%) of silver bromide.

Extraction of the residue with hot sodium bicarbonate and acidification gave 0.88 g. of 2-nitro-3-hydroxyfluorenone, m.p. 249–250°. The residue was further extracted in a Soxhlet apparatus for 11 days with benzene. Extraction of the benzene solution with sodium bicarbonate furnished another 0.17 g., m.p. 248°.

Further extraction of the residue with ethanol for 3 days, and concentration of the ethanol solution produced 0.43 g. of brownish crystals, m.p. 280–300°, which yielded 0.25 g. of 2-nitro-3-aminofluorenone, m.p. 309–310° (from pyridine). The black residue, m.p. > 360°, weighed 2.14 g.[13]

B. In dimethyl sulfoxide. 2-Nitro-3-bromofluorenone (608 mg.), 354 mg. of oven-dried potassium fluoride in 50 ml. of vacuum-distilled dimethyl sulfoxide was stirred at 115° for 78 hr. and diluted with 200 ml. water to give a yellow precipitate (465 mg.), m.p. 238–242°. A chloroform solution of this material was extracted with sodium bicarbonate and the aqueous layer acidified to give 2-nitro-3-hydroxy-9-fluorenone (401 mg.), m.p. and mixed m.p. 248°. No evidence for the 3-fluorine-substituted material was found in the chloroform layer.

2,2′-Dinitro-3,3′-bifluoren-9-one. 2-Nitro-3-bromofluorenone (1.5 g.) in 70 ml. of dry xylene was refluxed for 20 hr. with 2 g. of iodine-activated copper powder.[14] The solution was filtered, and cooled to give a small amount of crystalline material, m.p. > 360°. The filtrate was chromatographed on alumina. A faster yellow band was extracted with benzene to give 2-nitrofluorenone (0.45 g.), m.p. and mixed m.p. 218°. A slower brown band extracted with pyridine furnished a solid, which was combined with a pyridine extract of the copper powder, and the high melting product above to give yellow 2,2′-dinitro-3,3′-bifluoren-9-one (69 mg.) m.p. >360°, from pyridine. λ_{max} 270 mμ (ε = 35,310); λ_{min} 226 (17,340); inflection pt. 360.

Anal. Calcd. for $C_{26}H_{12}N_2O_6$: C, 69.64; H, 2.70; N, 6.25. Found: C, 69.00; H, 3.08; N, 6.33.

3,3′-Bis-2,2′-fluorenamine. A Wolff-Kishner reduction of 896 mg. of dinitrobifluorenone, 150 ml. of diethylene glycol, and 60 ml. of hydrazine hydrate produced a gray precipitate. Chromatography on alumina in benzene and crystallization from ethyl acetate and pyridine left 450 mg. of yellow diamine, m.p. 314–316°. λ_{max} 270 mμ (ε = 48,360); 367 (26,630); 389 (23,930); λ_{min} 234 (20,220); 310 (10,010); 380 (22,030).

Anal. Calcd. for $C_{26}H_{20}N_2$: C, 86.63; H, 5.59; N, 7.77. Found: C, 87.03; H, 4.66; N, 7.97.

The *diacetyl derivative* was prepared in benzene with acetic anhydride as pale yellow crystals, m.p. 284–285°, from ethyl acetate. λ_{max} 277 mμ (ε = 36,180); 304 (23,230); λ_{min} 235 (22,230); 302 (23,230); shoulder 258 mμ.

Anal. Calcd. for $C_{30}H_{24}N_2O_2$: C, 81.06; H, 5.44; N, 6.30. Found: C, 80.47; H, 5.39; N, 6.33.

1,3-Dibromo-2-nitrofluorene. 1,3-Dibromo-2-fluorenamine[4] (13.6 g.) was refluxed for 40 min. in 272 ml. of 40% peracetic acid and 120 ml. of acetic acid (color from green to red to golden yellow). The reaction was terminated at this point to avoid extensive oxidation to the fluorenone. Dilution with water gave a product which was chromatographed on alumina in benzene to give colorless 1,3-dibromo-2-nitrofluorene (8.5 g.) m.p. 163° (m.p. 164–165°, from cyclohexane or ethanol). This compound is sensitive to light in solution and in the solid state, being altered to a violet product. λ_{max} 270 mμ (ε = 15,760); 297 (7820); 307.5 (6300); λ_{min} 245 (8380); 295 (7760); 305 (5830).

Anal. Calcd. for $C_{13}H_7Br_2NO_2$: C, 42.31; H, 1.91; Br, 43.31. Found: C, 42.01; H, 2.06; Br, 43.26.

Elution of the alumina column, above, with 10% ethanol, in benzene gave 1.15 g. of 1,3-dibromo-2-nitrofluorenone, m.p. 248° (see below). The fluorene derivative could also be separated from the smaller amounts of the fluorenone compound by reason of the virtual insolubility of the latter compound in cyclohexane.

1,3-Dibromo-2-nitrofluorenone. 1,3-Dibromo-2-nitrofluorene (3.7 g.) and 3 g. of potassium bichromate in 110 ml. of acetic acid were refluxed for 5 hr. and poured into water to give 1,3-dibromo-2- nitrofluorenone (2.8 g., 82%), m.p. 251–252°, from benzene. A sample, chromatographed on alumina in benzene, was eluted with ethanol from the segment containing the yellow band to give material with m.p. 253–254°, from benzene and acetic acid. λ_{max} 269 mμ (ε = 7220); 306 (550); 321 (400); 335.5 (300); λ_{min} 233 (1250); 300.5 (460); 317 (390); 332 (295).

(12) E. K. Weisburger and J. H. Weisburger, *J. Org. Chem.*, **23**, 1193 (1958).

(13) The infrared spectrum of this material was unlike that of the bifluorene derivative described below, but exhibited instead some of the features of a 2,3-substituted fluorenone.

(14) E. C. Kleiderer and R. Adams, *J. Am. Chem. Soc.*, **55**, 4219 (1933).

Anal. Calcd. for $C_{13}H_6Br_2NO_3$: C, 40.76; H, 1.32; N, 3.66; Br, 41.73. Found: C, 40.99; H, 1.46; N, 3.39; Br, 41.67.

1,3-Diamino-2-nitrofluorenone. A suspension of 0.57 g. of finely powdered 1,3-dibromo-2-nitrofluorenone in 90 ml. of absolute ethanol was saturated with gaseous ammonia at 0°, heated in a pressure bottle to 60° for 48 hr. and cooled to give orange needles, 0.28 g., m.p. 205° (Kofler block), from benzene or ethanol. λ_{max} 248 mμ (ϵ = 15,750); 264 (14,890); 292 (17,450); 304 (16,010); 355 (22,930); 455.5 (4790); λ_{min} 225 (11,070); 255 (14,100); 273.5 (12,830); 301 (15,850); 330 (9110); 417 (3110).

Anal. Calcd. for $C_{13}H_9N_3O_3$: C, 61.17; H, 3.56; N, 16.46. Found: C, 61.05; H, 3.76; N, 16.37.

The diacetyl derivative, *N, N'(2-nitro-9-oxo-1,3-fluorenylene) bisacetamide*, 102 mg., m.p. 325°, was prepared by refluxing 100 mg. of the amine for 8 hr. with 10 ml. each of acetic acid and acetic anhydride. Chromatography in benzene on alumina, and recrystallization from a mixture of benzene and ethanol, or from acetic acid gave colorless needles, m.p. 328° (Kofler). λ_{max} 265.5 mμ (ϵ = 25,970); λ_{min} 235 (14,310).

Anal. Calcd. for $C_{17}H_{13}N_3O_5$: C, 60.18; H, 3.86; N, 12.38. Found: C, 59.75; H, 4.24; N, 12.37.

1,2,3-Triacetylaminofluorene. 1,3-Diamino-2-nitro-9-fluorenone (0.8 g.) was subjected to a Wolff-Kishner reaction with 24 ml. of hydrazine hydrate and 40 ml. of diethylene glycol in a nitrogen atmosphere. Dilution with 100 ml. of oxygen-free water gave a precipitate which dissolved in 1*N* hydrochloric acid and reprecipitated by hydrazine hydrate yielded 530 mg. of crude 1,2,3-fluorenetriamine, m.p. 204°. This somewhat unstable compound was immediately acetylated by acetic anhydride in benzene to give a white triacetyl derivative (400 mg.), m.p. 285–287°, from acetic acid and benzene. λ_{max} 217 mμ(ϵ=34,890), 244 (31,340), 272.5 (23,160); λ_{min} 231 (22,260); 259 (18,270); shoulder 310 mμ (7310).

Anal. Calcd. for $C_{19}H_{19}N_3O_3$: C, 67.64; H, 5.68; N, 12.46. Found: C, 67.37; H, 5.82; N, 12.41.

Reaction of 1,3-dibromo-2-nitro-9-fluorenone with ethanolic alkali. A suspension of 497 mg. of 1,3-dibromo-2-nitrofluorenone in 70 ml. each of ethanol and 2*N* aqueous potassium hydroxide was refluxed for 35 hr. giving a red solution, which was diluted with water and acidified. The precipitate was dissolved in alkali (Norit) and reprecipitated with acid to give yellow 2-nitro-3-hydroxy-9-fluorenone (284 mg., 91%), m.p. and mixed m.p. 247°, from ethanol and benzene.

Anal. Calcd. for $C_{13}H_7NO_4$: C, 64.73; H, 2.93; N, 5.81. Found: C, 64.86; H, 3.33; N, 5.36.

1-Bromo-2-nitro-3-hydroxy-9-fluorenone. 1,3-Dibromo-2-nitrofluorenone (1.1 g.) in 35 ml. each of pyridine and 1*N* aqueous potassium hydroxide was refluxed for 1 hr. (color dark green), poured into water, acidified, and extracted with ether. The ether layer was shaken with bicarbonate and the aqueous layer acidified to give 1-bromo-2-nitro-3-hydroxyfluorenone (0.5 g.), m.p. 257° (raised to 257–258°, from benzene, acetic acid, ethanol, and dilute ethanol), positive Beilstein test. λ_{max} 258 mμ (ϵ = 30,630); 263 (30,720); 299 (31,030); 410 (2900); λ_{min} 228 (12,180); 260 (30,610); 296 (9800); 387 (2700).

Anal. Calcd. for $C_{13}H_6BrNO_4$: C, 48.77; H, 1.89; Br, 24.97. Found: C, 48.99; H, 2.13; Br, 25.67.

Further refluxing of this compound for 5.5 hr. in equal volumes of pyridine and 4*N* potassium hydroxide resulted in the recovery of the starting material. However, when 0.5 g. of compound was refluxed for 2 hr. in 25 ml. each of ethanol and 6*N* aqueous potassium hydroxide, 346 mg. (92%) of 2-nitro-3-hydroxyfluorenone, m.p. and mixed m.p. 248° was obtained.

BETHESDA 14, MD.

[CONTRIBUTION FROM THE LABORATORY OF BIOCHEMISTRY, NATIONAL CANCER INSTITUTE[1]]

Derivatives of 3-Fluorofluorene by the Pschorr Synthesis

KAZUO SUZUKI,[2] ELIZABETH K. WEISBURGER, AND JOHN H. WEISBURGER

Received August 11, 1960

The reaction of *p*-fluorophenylmagnesium iodide with 6-oxo-2-methyl-4,5-benz-1,3-oxazine (from acetic anhydride and anthranilic acid) gave 2-(4'-fluorobenzoyl)acetanilide, which was hydrolyzed to the amine. A Pschorr reaction on the latter afforded 3-fluorofluorenone, which in turn was readily reduced to 3-fluorofluorene. The intermediate aminofluorobenzophenone was also prepared by a Hofmann reaction on the corresponding amide. A Curtius reaction on *o*-benzoylbenzoic acid in the presence of pyridine yielded moderate amounts of 2-aminobenzophenone, but without pyridine the main product was *N*-phenylphthalimide. From the dinitration of 3-fluorofluorene the 2,7-dinitro derivative was obtained in good yield. Reduction of this compound by hydrogen sulfide gave a mixture of amines from which 3-fluoro-7-nitro-2-fluorenamine was isolated and characterized.

In connection with the preparation of fluorinated derivatives of the carcinogen *N*-2-fluorenylacetamide, a number of approaches to the synthesis of the required intermediates, especially 3-fluorofluorene, were explored. In a previous publication[3] the preparation of this compound from 3-fluorenamine was described. The present paper deals with two other routes giving 3-fluorofluorene from commercially available starting material. In addition, the dinitration of 3-fluorofluorene, and products related thereto will be described. Furthermore, some observations bearing on the chemistry of *ortho*-substituted benzophenones will be discussed.

One method leading to 3-fluorofluorenone consisted in the inverse addition of a Grignard reagent from *p*-fluoroiodobenzene to 6-oxo-2-methyl-4,5-benz-1,3-oxazine, itself readily available from acetic anhydride and anthranilic acid. The product, 2-(4'-fluorobenzoyl)acetanilide was converted to the corresponding amine, 2-amino-4'-fluorobenzophenone, which in turn was subjected to a Pschorr reaction with production of 3-fluorofluorenone. This

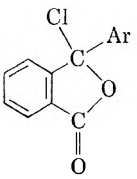
(1) National Institutes of Health, Public Health Service, Department of Health, Education and Welfare.

(2) Visiting Scientist, National Cancer Institute. On leave of absence from Yamaguchi University, Ube, Japan.

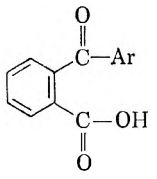
(3) K. Suzuki, E. K. Weisburger, and J. H. Weisburger, *J. Org. Chem.*, **24**, 1511 (1959).

compound was reduced in good yield to the fluorene derivative by a Wolff-Kishner reaction.

Another path to the intermediate 2-amino-4′-fluorobenzophenone involved a Hofmann reaction[4] on 2-(4′-fluorobenzoyl)benzamide. This amide was prepared from the acid *via* the ethyl ester. It could not be made *via* the acid[5] chloride, presumably because of the predominance of the pseudo form of the acid chloride, indicated by an infrared peak at 5.58 μ.[6] In contrast, the acid, ester, and amide existed primarily in the normal form, as evidenced by the similarity of their infrared peaks



Pseudo form



Normal form

of 5.90 and 5.97, 5.86 and 5.99, and 5.86 and 6.01 μ, respectively.

Further evidence for the existence of normal and pseudo forms of certain derivatives of *o*-benzoylbenzoic acid was provided by the attempts to obtain 2-amino-4′-fluorobenzophenone from the corresponding acid by means of a modified Curtius reaction, successfully used in a number of other such conversions.[7] Thus, preparation of the azide, *via* the acid chloride, yielded an oil which when decomposed in the presence of acetic anhydride led mainly to *N*-(4′-fluorophenyl)phthalimide, and also gave small amounts of other, not precisely identified materials. Some parallel studies with *o*-benzoylbenzoic acid itself entirely confirmed the findings of Bhatt, of Arcus and associates, and of Badger *et al.*[8] who reported benzoylanthranilic acid, 6-oxo-2-phenyl-4,5-benzo-1,3-oxazine and chiefly *N*-phenylphthalimide as products of the Schmidt reaction on this acid. We have observed, however, that decomposition of the azide in a Curtius reaction in the presence of pyridine also led to moderate yields of the expected 2-aminobenzophenone, in addition to the above materials.

Another route to 3-fluorofluorene was by way of the corresponding diphenylmethane derivatives. The crucial intermediate 2-(4′-fluorobenzyl)benzoic acid,[9] m.p. 124°, was prepared best in two steps from the benzophenone derivative: (*1*) A reduction to the lactone, 3-(*p*-fluorophenyl)phthalide, m.p. 101°, with zinc and ammonia, (*2*) a reduction of this compound with phosphorus and hydrogen iodide. The use of the latter step alone on the benzophenone derivative yielded the dilactone, and only 50% of the desired acid. Likewise, a Wolff-Kishner reduction was unsuitable, for ring closure with production of 1-(2H)-2-(4′-fluorophenyl)-phthalazinone was the preponderant reaction taking place.

The modified Curtius reaction on 2-(4′-fluorobenzyl)benzoic acid gave excellent yields of the expected amine, 2-(4′-fluorobenzyl)aniline, *via* the intermediate acetyl and diacetyl derivatives, in contrast to the behavior in the benzophenone series. However, the Pschorr reaction on this amine afforded only traces of the fluorene derivatives, probably because of steric factors in the diphenylmethane derivative. Owing to the tetrahedral nature of the configuration around the methylene carbon, the phenyl rings are not coplanar and ring closure is thus not favored. On the other hand, benzophenones are coplanar, and ring closure is generally facile.[10]

The dinitration of 3-fluorofluorene, not previously studied, in acetic acid with fuming nitric acid led to the 2,7-dinitro derivative, in analogy with the reaction of fluorene. A mixture of amines was obtained by the action of hydrogen sulfide on this compound. The pure compound isolated from this reduction was 3-fluoro-7-nitro-2-fluorenamine, as proved by the isolation of 3-fluoro-7-nitrofluorene upon deamination.

EXPERIMENTAL

The melting points were determined in a capillary tube and are not corrected. The ultraviolet spectra were recorded by Mr. P. H. Grantham on a Cary recording spectrophotometer as 5×10^{-5} *M* solutions in ethanol and the infrared spectra on a Perkin-Elmer spectrophotometer, model 21, as solids in potassium bromide disks. We are indebted to the staff of the NIH Microanalytical Laboratory for the analyses.

Ethyl 2-(4′-fluorobenzoyl)benzoate. 2-(4′-Fluorobenzoyl)-benzoic acid[5] (84.7 g.), m.p. 138–139°, and 3 ml. of concd. sulfuric acid in 230 ml. of absolute ethanol was refluxed for 6 hr. Dilution with water gave 76.5 g. of the ester, m.p. 78–80°, from cyclohexane (lit.[5] m.p. 80°). λ_{max} 246.5 mμ (ϵ = 6990); λ_{min} 228 (5600).

Anal. Calcd. for $C_{16}H_{13}FO_3$: C, 70.58; H, 4.81. Found: C, 70.48; H, 5.01.

2-(4′-Fluorobenzoyl)benzamide. Ethyl 2-(4-fluorobenzoyl)-benzoate (12.8 g.) in 70 ml. of absolute ethanol, saturated

(4) K. Suzuki, S. Kajigaeshi, and M. Sano, *Yûki Gôsei Kagaku Kyôkai Shi*, 16, 82 (1959).

(5) F. C. Hahn and E. E. Reid, *J. Am. Chem. Soc.*, 46, 1645 (1924).

(6) W. Graf, E. Girod, E. Schmid, and W. G. Stoll, *Helv. Chim. Acta*, 42, 1085 (1959).

(7) E. K. Weisburger and J. H. Weisburger, *J. Org. Chem.*, 23, 1193 (1958).

(8) M. V. Bhatt, *Chem. and Ind.*, 1390 (1956); C. L. Arcus and M. M. Coombs, *J. Chem. Soc.*, 3698 (1953); C. L. Arcus and R. E. Marks, *J. Chem. Soc.*, 1627 (1956); G. M. Badger, R. T. Howard, and A. Simons, *J. Chem. Soc.*, 2849 (1952).

(9) Hahn and Reid[5] reported a m.p. of 148–149° for this compound, prepared by reducing the benzophenone derivative with copper sulfate activated zinc dust in aqueous ammonium hydroxide or sodium hydroxide. The discrepancy in the melting point is not clear. The single analysis for fluorine shown by Hahn and Reid for this substance exhibits a larger deviation from theoretical (found 7.78%, calcd. 8.26%) than any of the other compounds listed in their paper. In our hands the use of ethanolic ammonium hydroxide and ordinary zinc dust led to the lactone, m.p. 101°.

(10) D. F. DeTar, *Org. Reactions*, 9, 409 (1957).

with ammonia gas at 0°, was heated in a pressure bottle for 24 hr. at 50°, and the solvent evaporated. The residue extracted with dilute sodium hydroxide gave a recovery of 1.5 g. of 2-(4′-fluorobenzoyl)benzoic acid. The alkali-insoluble part recrystallized from benzene yielded 8.3 g. of the amide, m.p. 174° (raised to 177–178°). λ_{max} 270 mμ (ϵ = 1230); 285 (450); λ_{min} 268 (1140); general absorption below 260 mμ.

Anal. Calcd. for $C_{14}H_{10}FNO_2$: C, 69.13; H, 4.14. Found: C, 69.36; H, 4.22.

2-Amino-4′-fluorobenzophenone. To an ice-cold solution of 0.7 g. of bromine and 1.5 g. of potassium hydroxide in 20 ml. of water, 1.09 g. of powdered amide was added slowly with stirring. After 2 hr., 2.25 g. of potassium hydroxide in 2.25 ml. of water was introduced and the mixture was heated at 100° for 45 min. to give a light yellow amine (0.57 g., 59%), m.p. 124–125° (raised to 127–128°), from cyclohexane. λ_{max} 234 mμ (ϵ = 13,660); 375 (5600).

Anal. Calcd. for $C_{13}H_{10}FNO$: C, 72.69; H, 4.92. Found: C, 72.40; H, 4.77.

The hydrochloride melted at 187–188° dec. Acetylation of the amine in benzene with acetic anhydride gave *2-(4′-fluorobenzoyl)acetanilide*, m.p. 98–100°, from methanol, identical with the material described below.

3-Fluorofluorenone. Finely powdered sodium nitrite (1.77 g.) was stirred into an ice-cold solution of 4.73 g. of the amine in 440 ml. of 50% sulfuric acid over 1 hr. After 2–3 hr. at 25°, and 0.5 hr. at 100° the mixture was cooled. An ether extract was washed with sodium bicarbonate and the ether was evaporated. The residue was sublimed *in vacuo* to give yellow 3-fluorofluorenone (3.72 g., 85%) m.p. 124–126° (raised to 128–129°), from cyclohexane. λ_{max} 249 mμ (ϵ = 46,770); 257 (65,560); 280 (2700); 290.5 (3970); 309 (1430); λ_{min} 250 (46,140); 272.5 (1740); 286.5 (2380); 305 (1190).

Anal. Calcd. for $C_{13}H_7FO$; C, 78.77; H, 3.56. Found: C, 79.29; H, 4.09.

Acidification of the bicarbonate extract in some runs gave a precipitate of *4′-fluoro-2-hydroxy-3(or 5)-nitrobenzophenone*, m.p. 99–100°. This compound presumably is the result of the action of excess nitrite on the phenol produced initially. λ_{max} 250 mμ (ϵ = 14,790); λ_{min} 225 (11,400).

Anal. Calcd. for $C_{13}H_8FNO_4$: C, 59.77; H, 3.09; N, 5.36. Found: C, 60.30; H, 3.79; N, 5.40.

3-Fluorofluorene. 3-Fluorofluorenone (3.6 g.) and 11 ml. of 85% hydrazine hydrate in 25 ml. of diethylene glycol was refluxed for 1.5 hr. The condenser was removed until the temperature rose to 185°, then refluxing was continued for 2 hr. The product collected on dilution with water was sublimed *in vacuo* and chromatographed on alumina in benzene: 3-Fluorofluorene (2.5 g., 75%), m.p. 80°, from cyclohexane, (lit.[3] m.p. 77–78°).

2-(4′-Fluorobenzoyl)acetanilide. This method was based on that of Lothrop and Goodwin.[11] A benzoxazine, m.p. 77–80°, was isolated from the reaction of acetic anhydride on anthranilic acid. A filtered Grignard reagent, from 13 g. of *p*-fluoroiodobenzene, 1.52 g. of magnesium, and 35 ml. of ether, was dropped into a cold solution of 9.4 g. of the benzoxazine in 216 ml. of dry benzene during 1.5 hr., and stirred 1 hr. more. After 15 hr. the reaction mixture was decomposed with 150 ml. of 3*N* sulfuric acid, the upper layer washed with water, the solvents evaporated, and the product chromatographed on alumina in benzene to give colorless needles (8.5 g., 57%), m.p. 96–97° (raised to 99–101°), from methanol. λ_{max} 235 mμ (ϵ = 21,900); 324 (2400) λ_{min} 220.5 (15,600), 294 (1700).

Anal. Calcd. for $C_{15}H_{12}FNO_2$: C, 70.03; H, 4.70. Found: C, 70.26; H, 4.93.

Hydrolysis of 0.5 g. of the acetylamino derivative in 1.5 ml. of 12*N* hydrochloric acid and 5 ml. of ethanol, and neutralization gave 0.38 g. (90%) of amine, m.p. 124–126° (from ethanol), undepressed by admixture of the amine obtained in the Hofmann reaction.

2-(4′-Fluorobenzyl)benzoic acid. A. The following is the preferred procedure. 2-(4′-Fluorobenzoyl)benzoic acid (9.7 g.) in 120 ml. of ethanol and 50 ml. of ammonium hydroxide was refluxed for 2 hr. with 25 g. of zinc dust. After removal of the zinc and concentration, 8.95 g. of the *lactone* (4-fluorophenyl)phthalide, m.p. 100–101°, crystallized. λ_{max} 264 mμ (ϵ = 1240); 270 (1420); 281 (1300); λ_{min} 248 (500), 267.5 (1160), 278 (1100); general absorption below 230 mμ.

Anal. Calcd. for $C_{14}H_9FO_2$: C, 73.68; H, 3.97. Found: C, 73.67; H, 4.21.

The lactone (8.95 g.) was refluxed for 5 hr. in 80 ml. of acetic acid and 15 ml. of hydriodic acid with 3 g. red phosphorus and diluted with water. Solution in bicarbonate and reprecipitation with acid gave 8.6 g. (over-all yield 93%) of *2-(4′-fluorobenzyl)benzoic acid*, m.p. 122–124°, from cyclohexane. λ_{max} 266.5 mμ (ϵ = 1940); 273 (2010); λ_{min} 254 (1250); 270 (1520); general absorption below 240 mμ.

Anal. Calcd. for $C_{14}H_{11}FO_2$: C, 73.03; H, 4.82. Found: C, 72.79; H, 5.09.

B. 2-(4′-Fluorobenzoyl)benzoic acid (18 g.) was refluxed in 100 ml. of acetic acid, 40 ml. of 50% hydroiodic acid, and 1 g. of red phosphorus for 9 hr. Dilution with water gave a precipitate extracted with bicarbonate. Acidification produced 8.9 g. (52%) of 2-(4′-fluorobenzyl)benzoic acid, m.p. 123°. The portion insoluble in bicarbonate was the *dilactone*, bis-(4-fluorophenyl)phthalide, 7.9 g. m.p. 272–273°, from benzene. λ_{max} 265 mμ (ϵ = 2920); 269.5 (3100); 277(3400); 284 (3660); λ_{min} 255 (2320), 267 (2900), 273 (3000), 281 (3300); general absorption below 240 mμ.

Anal. Calcd. for $C_{28}H_{16}F_2O_4$: C, 74.00; H, 3.55. Found: C, 73.60; H, 3.60.

The dilactone was converted in about 50% yield to the phthalide derivative, m.p. 100°, by refluxing for 1 hr. in ethanolic potassium hydroxide.

1(2H)-4-(4′-Fluorophenyl)phthalazinone. A white precipitate increasing with time appeared as 2.4 g. of 2-(4′-fluorobenzoyl)benzoic acid, 11 ml. of hydrazine hydrate and 25 ml. of diethylene glycol was refluxed for 1 hr. Dilution with water gave 2.4 g. of compound, m.p. 257–264° (raised to 267–268.5°), from acetic acid, ethyl acetate, or *n*-butyl alcohol. λ_{max} 292.5 mμ (7900); λ_{min} 269 (5600).

Anal. Calcd. for $C_{14}H_9FN_2O$: C, 69.99; H, 3.78; N, 11.66. Found: C, 69.76; H, 4.00; N, 11.63.

Modified Curtius reaction on 2-(4′-fluorobenzyl)benzoic acid. The finely powdered acid (11.5 g.) stood 18 hr. in 100 ml. of thionyl chloride at 25°. The excess thionyl chloride was distilled *in vacuo* and traces removed by three further codistillations with petroleum ether. Sodium azide (4 g.) in 4 ml. of water was added to the residual acid chloride, m.p. 36–38°, in 100 ml. of dry acetone at −40°. After 2 hr. the mixture was poured into cold water and extracted with benzene. The dry (calcium chloride at 5°) benzene layer was distilled *in vacuo* leaving the azide as a light yellow oil.

The oil in 100 ml. of acetic anhydride was heated until gas evolution stopped, then poured into ice water. Extraction of the product with ether, and evaporation of the solvent yielded 10.6 g. (75%) of colorless *2′′-(4′′′-fluorobenzyl)diacetanilide* or 2-diacetylamino-4′-fluorodiphenylmethane, m.p. 67–69°, from petroleum ether. λ_{max} 260.5 mμ (ϵ = 1220); 266 (1510); 272 (1350); λ_{min} 247 (800), 262 (1200), 270 (850).

Anal. Calcd. for $C_{17}H_{16}FNO_2$: C, 71.56; H, 5.65; N, 4.91. Found: C, 71.74; H, 5.59; N, 4.80.

The ether-insoluble portion, 2.1 g. (17%), m.p. 152–154°, was *2-(4′-fluorobenzyl)acetanilide*, m.p. 155–156°, from benzene.

Anal. Calcd. for $C_{15}H_{14}FNO$: C, 74.05; H, 5.80; N, 5.76. Found: C, 73.68; H, 5.85; N, 5.87.

Both mono- and diacetylamino derivatives were hydrolyzed to 2-(4′-fluorobenzyl)aniline, m.p. 56–57°, from cyclohexane, in 85–90% yields by refluxing for 1.5 hr. in 12*N*

(11) W. C. Lothrop and P. A. Goodwin, *J. Am. Chem. Soc.*, 65, 363 (1943); *cf.* A. Mustafa, *et al.*, *J. Am. Chem. Soc.*, 77, 1612 (1955); A. Morrison and T. P. C. Mulholland, *J. Chem. Soc.*, 2702 (1958); E. D. Bergmann and R. Barshai, *J. Am. Chem. Soc.*, 81, 5641 (1959).

hydrochloric acid, followed by neutralization. Direct hydrolysis of the crude mixture of mono- and diacetyl derivatives gave an over-all yield of 93% of amine. λ_{max} 235 mμ (ε = 7250); 266.5 (1900); 272.5 (2200); 287 (2280) λ_{min} 225 (6170), 262 (1500), 269 (1560), 276.5 (1800).

Anal. Calcd. for $C_{13}H_{12}FN$: C, 77.58; H, 6.01; N, 6.96. Found: C, 77.41; H, 6.16; N, 7.14.

Direct hydrolysis of the azide was not so useful. Thus, the azide from 2.3 g. of acid was refluxed for 1 hr. with 12*N* hydrochloric acid. The acid-soluble product yielded 220 mg. (11%) of amine, m.p. 56°. The acid-insoluble material was *sym-di[2-(4'-fluorobenzyl)phenyl]urea*, 0.49 g., m.p. 229–230° from benzene. λ_{max} 247 mμ (ε = 17,000), 272 (5600); λ_{min} 230 (10,600), 270.5 (5400).

Anal. Calcd. for $C_{27}H_{22}F_2N_2O$: C, 75.68; H, 5.18; N, 6.54. Found: C, 76.08; H, 5.50; N, 6.68.

The amine (200 mg.) in 500 ml. of ice-cold 60% sulfuric acid was diazotized with 100 mg. of sodium nitrite during 1.5 hr., refluxed 40 min., diluted with water, and extracted with benzene. The benzene solution was washed with 1*N* potassium hydroxide, evaporated, and the residue sublimed *in vacuo* giving 10 mg. of 3-fluorofluorene, m.p. 69–71° (raised to m.p. and mixed m.p. 74°, from petroleum ether).

Attempted Curtius reaction on 2-(4'-fluorobenzoyl)benzoic acid. The acid chloride, from 34.2 g. acid and 100 ml. of thionyl chloride, in 300 ml. cold, dry acetone was treated with 11 g. of sodium azide in 30 ml. water. The azide, extracted into cold benzene after dilution with ice water, was freed of solvent. After refluxing in 250 ml. of acetic anhydride for 3 hr. the solution was poured into water. The oily product was dissolved in 250 ml. of hot ethanol and the solution concentrated to give white felt-like *4'-fluorophenylphthalimide* (11.9 g.), m.p. 180–181.5°, from ethanol.

Anal. Calcd. for $C_{14}H_8FNO_2$: C, 69.71; H, 3.34. Found: C, 69.90; H, 3.42.

Modified Curtius reaction on benzophenone-2-carboxylic acid. The acid chloride, from 22.6 g. of acid and thionyl chloride at 25°, reacted in 300 ml. of cold acetone and 10 ml. of pyridine with 8 g. of sodium azide in 20 ml. of water. The azide was extracted into benzene, freed of solvent *in vacuo*, and refluxed with 150 ml. of acetic anhydride for 1.5 hr. *N-Phenylphthalimide* (6 g.) m.p. 199–201°, formed upon addition of water.

The filtrate taken to *p*H 6 with bicarbonate gave an oily precipitate, which was dissolved in ether. The solution extracted with bicarbonate and the latter acidified gave 1 g. of *N-benzoylanthranilic acid*, m.p. 185–188°. The ether solution, evaporated and the residue chromatographed in benzene on alumina, gave 6.7 g. of oily material which was refluxed for 3 hr. with equal volumes of 12*N* hydrochloric acid and ethanol. Neutralization and dilution with water gave 4.5 g. of *2-aminobenzophenone*, m.p. 102°. 2-Aminobenzophenone could not be isolated if pyridine was omitted during the formation and decomposition of the azide.

2,7-Dinitro-3-fluorofluorene. Powdered 3-fluorofluorene (9.2 g.) was vigorously stirred into 75 ml. of acetic and 75 ml. of fuming nitric acid (d = 1.5) over 15 min. The temperature rose to 55°. Upon cooling, 9.0 g. (66%) of yellow 2,7-dinitro-3-fluorofluorene, m.p. 274° (raised to 278–279°), from acetic acid, was collected. λ_{max} 329 mμ (ε = 24,980); λ_{min} 255 (3800).

Anal. Calcd. for $C_{13}H_7FN_2O_4$: C, 56.93; H, 2.57. Found: C, 56.63; H, 2.73.

In addition, 93 mg. of 7-nitro-3-fluorofluorene, m.p. and mixed m.p. 197° was isolated from the mother liquor.

3-Fluoro-2,7-fluorenediamine. Low-pressure catalytic reduction of 548 mg. of the dinitro compound over platinum oxide in 80 ml. of ethanol gave 310 mg. of diamine, m.p. 178° (raised to 181–182°), from cyclohexane. λ_{max} 293.6 mμ (ε = 23,840); 337 (9350); λ_{min} 247 (2660), 325 (8390).

Anal. Calcd. for $C_{13}H_{11}FN_2$: N, 13.08. Found: N, 12.81.

3-Fluoro-7-nitro-2-fluorenamine. A hot suspension of 8.3 g. of 2,7-dinitro-3-fluorofluorene in 400 ml. of ethanol and 140 ml. of 15*N* ammonium hydroxide was treated with hydrogen sulfide over 160 min. Dilution with water and repeated extraction of the resulting precipitate with 2900 ml. of 0.5*N* hydrochloric acid gave 4.6 g. of a crude mixture of amines. Orange 3-fluoro-7-nitro-2-fluorenamine (0.9 g.), m.p. 240° (raised to 242–243°) was obtained after crystallization from benzene, and from acetic acid as the acid sulfate[12]; λ_{max} 253 mμ (ε = 11,350), 390 (18,620); λ_{min} 227.5 (6610); 298 (2380).

Anal. Calcd. for $C_{13}H_9FN_2O_2$: C, 63.93; H, 3.71. Found: C, 64.07; H, 3.91.

Deamination of this compound (0.66 g.) by 3.8 ml. of hypophosphorous acid, after diazotization in 13 ml. of acetic acid, 1.4 ml. of water, and 0.5 ml. of sulfuric acid with 0.18 g. of sodium nitrite in 0.4 ml. of water, gave a crude product (0.62 g.) m.p. 192°. Vacuum sublimation at 160° gave 0.47 g. (75%) of 7-nitro-3-fluorofluorene (2-nitro-6-fluorofluorene), m.p. and mixed m.p. 197°, from acetic acid. Thus, the amino group in the compound, m.p. 243° described above, was in the 2- position.

2,7-Dinitro-3-fluoro-9-fluorenone. 2,7-Dinitro-3-fluorofluorene (5 g.) in 350 ml. of acetic acid was refluxed for 12 hr. while 57 ml. of red fuming nitric acid was added dropwise. Dilution with water gave 3.8 g. of yellow needles, m.p. 235–236°, from acetic acid. λ_{max} 281.5 mμ (ε = 35,020); 325.5 (8300); 340 (8170); λ_{min} 231.5 (13,450); 319 (7970); 334 (7550).

Anal. Calcd. for $C_{13}H_5FN_2O_5$: C, 54.18; H, 1.75; N, 9.72. Found: C, 53.93; H, 2.01; N, 9.63.

The same compound was also obtained by addition of 1 ml. of fuming nitric acid to a cooled solution of 0.9 g. of 7-nitro-3-fluorofluorenone in 12 ml. of concd. sulfuric acid. After 1 hr. the mixture was poured onto ice to give needles (0.6 g.), m.p. and mixed m.p. with the product above, 235–236°, from acetic acid.

6-Fluoro-2-amino-9-fluorenone. Hydrogen sulfide and 1.2 g. of 7-nitro-3-fluorofluorenone in 100 ml. of boiling ethanol and 60 ml. of ammonium hydroxide for 1 hr. followed by extraction of the crude product with dilute hydrochloric acid gave 0.52 g. of violet needles, m.p. 200° (raised to 210–211°, from benzene). λ_{max} 277 mμ (ε = 44,320); 327 (7270); λ_{min} 230 (6390); 315 (6740).

Anal. Calcd. for $C_{13}H_8FNO$: C, 73.23; H, 3.78; Found: C, 73.42; H, 3.99.

BETHESDA 14, MD.

(12) J. H. Weisburger and E. K. Weisburger, *J. Org. Chem.*, **21**, 514 (1956).

[CONTRIBUTION FROM THE CHEMISTRY RESEARCH LABORATORY OF THE DEPARTMENT OF SURGERY, UNIVERSITY OF WASHINGTON, SCHOOL OF MEDICINE]

Derivatives of Fluorene. XV. Fluorofluorenes. IV[1]

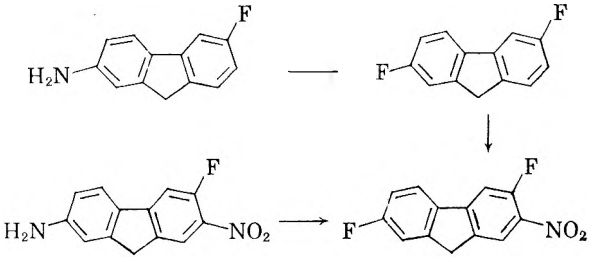
MOSES J. NAMKUNG AND T. LLOYD FLETCHER[2]

Received October 24, 1960

New difluorinated derivatives of fluorene are described, particularly 1,7- and 3,7-difluoro-2-acetamidofluorene, for cancer research. These are of interest because blocking metabolic hydroxylation sites may lead to more potent carcinogens and to metabolic products pertinent to the origin of cancer.

Previously[3] we discussed the importance of fluorinated *N*-2-(fluorenyl)acetamides in carcinogenicity studies being done by Drs. J. A. and E. C. Miller,[4] and described preparation of six new monofluoro-2-acetamidofluorenes[3,5,6] We felt that difluoro-2-acetamidofluorenes, with one fluorine atom in the 7-position,[7] the major hydroxylation site, might have enhanced carcinogenicity. Additionally, if the positions *ortho* to the acetamido group were to be blocked, thus preventing N—OH[8] to ring —OH migration, the metabolic picture as related to carcinogenicity might be clarified.

We synthesized 2-nitro-3,7-difluorofluorene in two ways:



By an improved procedure using tetrahydrofuran[9] 6-fluoro-2-fluorenamine[6] was diazotized in fluoboric acid. Decomposition of the salt in boiling xylene gave 2,6-difluorofluorene. Nitration of the latter gave a good yield of 2-nitro-3,6-difluorofluorene which was also obtained from 3-fluoro-2-nitro-7-fluorenamine.[6] Reduction[10] and acetylation gave *N*-2-(3,7-difluorofluorenyl)acetamide.

2-Nitro-1,7-difluorofluorene was prepared by Schiemann decomposition of the diazonium salt[9] of 1-fluoro-2-nitro-7-fluorenamine.[5] Nitration of 1,7-difluorofluorene (from 8-fluoro-2-fluorenamine[5]) gave a mixture which seemed difficult to separate by crystallization and chromatography. Its infrared spectrum, however, showed that the mixture was chiefly 2-nitro-1,7-difluorofluorene.

EXPERIMENTAL[11]

2,6-Difluorofluorene. 6-Fluoro-2-fluorenamine[6] (11 g., 0.055 mole) was dissolved in 100 ml. of tetrahydrofuran[9] (warm) and 200 ml. of 48–50% fluoboric acid was added. A white precipitate came out upon cooling. To the cooled mixture (0°), an aqueous solution of 4 g. (0.059 mole) of sodium nitrite was added dropwise with stirring. After 15 min. (0°), the salt was filtered and washed with cold 5% fluoboric acid, methanol, and ether and dried, giving 15 g., dec. 120°. The diazonium salt was decomposed in boiling xylene. After filtration from a small amount of residue, the solvent was evaporated and the product was recrystallized from petroleum ether (b.p. 30–60°), giving 7.1 g. (63% based on the amine), m.p. 46–48°. One more recrystallization from petroleum ether gave an analytical sample, m.p. 48–49°; λ_{max} 255 mμ (ϵ 1.48 × 10^4), 260 (1.49 × 10^4), 264 (1.47 × 10^4), 281 (6.05 × 10^3), 287 (5.37 × 10^3), 293 (8.2 × 10^3), 298 (7.70 × 10^3), 305 (1.12 × 10^4); C—F stretching: 8.23 μ, 8.51 μ.

Anal. Calcd. for $C_{13}H_8F_2$: C, 77.22; H, 3.99; F, 18.79. Found: C, 77.22; H, 4.05; F, 18.60.

2-Nitro-3,7-difluorofluorene. (a) To a cooled (0°) mixture of 1.5 g. (0.061 mole) of 3-fluoro-2-nitro-7-fluorenamine[6] and 30 ml. of fluoboric acid (50%) and 60 ml. of 85% phosphoric acid, a saturated aqueous solution of 0.5 g. (0.072 mole) of sodium nitrite was added dropwise with stirring. After stirring for 10 min., the diazonium salt was treated as above, giving 1.5 g. (73%) of salt, dec. 135–140°. Decomposition of the salt in boiling xylene, evaporation of the solvent and recrystallization from alcohol (Darco) gave 0.75 g. (50%, based on the amine) of 2-nitro-3,7-difluorofluorene, m.p.

(1) This work was supported in part by research grant C-1744 from the National Cancer Institute of the U. S. Public Health Service.

(2) To whom communications regarding this manuscript should be addressed.

(3) T. L. Fletcher, W. H. Wetzel, M. J. Namkung, and H. L. Pan, *J. Am. Chem. Soc.*, **81**, 1092 (1959).

(4) McArdle Memorial Laboratory, The University of Wisconsin.

(5) T. L. Fletcher, M. J. Namkung, H. L. Pan, and W. H. Wetzel. *J. Org. Chem.*, **25**, 996 (1960).

(6) T. L. Fletcher, M. J. Namkung, W. H. Wetzel, and H. L. Pan, *J. Org. Chem.*, **25**, 1342 (1960).

(7) J. A. Miller, R. B. Sandin, E. C. Miller, and H. P. Rusch, *Cancer Research*, **15**, 188 (1955).

(8) J. A. Miller, J. W. Cramer, and E. C. Miller, *Cancer Research*, **20**, 950 (1960).

(9) T. L. Fletcher and M. J. Namkung, *Chem. & Ind.*, 179, (1961).

(10) T. L. Fletcher and M. J. Namkung, *J. Org. Chem.*, **23**, 680 (1958).

(11) Melting points were taken on a Fisher-Johns block and are corrected to standards. Analyses were done by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y., and Alfred Bernhardt, Mülheim (Ruhr), Germany. Miss Barbara Bigley gave us valuable assistance in preparation and purification of starting compounds. Ultraviolet spectra were obtained on a DK-1 recording spectrophotometer ($3 \times 10^{-5}M$ in absolute ethanol for all except acetamido-compounds which were $2 \times 10^{-5}M$). Infrared spectra were taken on a Beckman IR-5.

182–187°. Recrystallization from benzene raised the m.p. to 186–187°. An analytical sample was prepared by sublimation at 180° (1 mm.), m.p. 187–187.5°; λ_{max} 288 mμ (ε 8.20 × 10^3), 327 (1.38 × 10^4); C–F stretching: 8.17 μ, 8.32 μ.

Anal. Calcd. for $C_{13}H_7F_2NO_2$: C, 63.16; H, 2.85; N, 5.67. Found: C, 63.39; H, 3.29; N, 5.92.

(b) To a solution of 2.02 g. (0.01 mole) of 2,6-difluorofluorene in 8 ml. of glacial acetic acid at 50°, 2 ml. of nitric acid (d. 1.42) was added, the mixture was heated to 70° and 4 drops of concd. sulfuric acid were added with stirring. An exothermic reaction occurred with formation of a yellow precipitate. The temperature of the mixture was kept 85° for 5 min., then allowed to drop to 25°. The precipitate was filtered, washed with cold acetic acid and water, and dried, giving 2.2 g. (89%) of crude product, m.p. 182–186°. One recrystallization from benzene (Darco) gave 1.8 g. (73.5%) of the pure compound, m.p. 186–187°. A mixture melting point with the Schiemann decomposition product of 3-fluoro-2-nitro-7-fluorenamine was undepressed, and the infrared spectra of the two compounds were identical.

2-Amino-3,7-difluorofluorene. An alcoholic solution (50 ml.) of 0.46 g. (0.002 mole) of 2-nitro-3,7-difluorofluorene was reduced with 0.5 ml. of 100% hydrazine hydrate and Raney nickel[10] giving 0.38 g. (95%) of the amine, m.p. 124–124.5°. One recrystallization from alcohol gave an analytical sample, m.p. 124–124.5°; λ_{max} 279 mμ (ε 1.97 × 10^4), 326 (8.75 × 10^3), C—F stretching: 8.01 μ, 8.56 μ.

Anal. Calcd. for $C_{13}H_9F_2N$: N, 6.45. Found: N, 6.28.

N-2-(3,7-Difluorofluorenyl)acetamide. The foregoing compound was acetylated quantitatively with acetic anhydride on the steam bath for 10 min. The product was recrystallized from alcohol (Darco), m.p. 240–240.5°; λ_{max} 274 mμ (ε 2.03 × 10^4), 308 (1.49 × 10^4), $\lambda_{shoulder}$ 280 mμ, 286 μ; C–F stretching: 8.08 μ, 8.57 μ.

Anal. Calcd. for $C_{15}H_{11}F_2NO$: C, 69.49; H, 4.28; F, 14.66; N, 5.40. Found: C, 69.68; H, 4.28; F, 14.47; N, 5.40.

1,7-Difluorofluorene. A solution of 4.3 g. (0.026 mole) of 1-fluoro-7-fluorenamine[5] in 25 ml. of tetrahydrofuran[9] and 25 ml. of 48–50% fluoboric acid (0°) was diazotized. After 30 min., the salt was filtered and washed giving 5.9 g. (91%), dec. 170°. This was suspended in *o*-dichlorobenzene and heated gradually to the boiling point. Upon evaporating the solvent and recrystallizing the residue from petroleum ether (b.p 30–60°), 2.7 g. (62%, based on the amine) of product was obtained, m.p. 64–66°. Two recrystallizations from cyclohexane followed by sublimation (75°, 1 mm.) gave an analytical sample, m.p. 73.5–74.5°; λ_{max} 261 mμ (ε 1.84 × 10^4), 278 (7.60 × 10^3), 287 (3.67 × 10^3), 299 (3.27 × 10^3), $\lambda_{shoulder}$ 216 mμ, 255, 271, 292; C—F stretching : 8.03 μ, 8.13 μ.

Anal. Calcd. for $C_{13}H_8F_2$: C, 77.22; H, 3.99; F, 18.79. Found: C, 77.35; H, 4.08; F, 18.67.

Nitration of 1,7-difluorofluorene. The foregoing compound (2 g., 0.001 mole) was nitrated in the same manner as above, giving 2.2 g. of crude product, m.p. 125–128°, three recrystallizations from alcohol raised the m.p. to 127–130°. A benzene solution of this was percolated through alumina and upon evaporating the solvent, 1.72 g. was recovered with melting point unchanged. The infrared spectrum of this material was almost the same as that of 2-nitro-1,7-difluorofluorene, described in the following section, with a few additional bands.

2-Nitro-1,7-difluorofluorene. To a solution of 3.85 g. (0.017 mole) of 1-fluoro-2-nitro-7-fluorenamine[5] in 30 ml. of tetrahydrofuran[9] 50 ml. of 50% fluoboric acid was added to form a thick white salt. This was cooled to 0° and a saturated aqueous solution of 2 g. (0.029 mole) of sodium nitrite was added dropwise with stirring. The resulting diazonium salt was filtered, washed as above, and dried, giving 4.5 g. (90%), dec. 140°. Upon decomposition in boiling xylene, evaporation of the liquid and recrystallization from alcohol (Darco) 2.8 g. (71% based on the amine) of the 2-nitro-1,7-difluorofluorene was obtained, m.p. 164–165°. An analytical sample was prepared by sublimation at 150° (1 mm.), m.p. 165.5–166°; λ_{max} 230 mμ (ε 1.27 × 10^4), 319 (1.77 × 10^4); C—F stretching: 8.05 μ, 8.18 μ.

Anal. Calcd. for $C_{13}H_7F_2NO_2$: C, 63.16; H, 2.85; N, 5.67. Found: C, 63.44; H, 3.24; N, 5.63.

1,7-Difluoro-2-fluorenamine. The foregoing compound was reduced[10] in quantitative yield, m.p. 124–125°. One recrystallization from alcohol gave an analytical sample, m.p. 125–125.5°; λ_{max} 287 mμ (ε 2.58 × 10^4); C–F stretching: 8.1 μ, 8.21 μ.

Anal. Calcd. for $C_{13}H_9F_2N$: N, 6.45. Found: N, 6.48.

N-2-(1,7-Difluorofluorenyl)acetamide. Acetylation in benzene with acetic anhydride gave a quantitative yield, m.p. 198–199°. One recrystallization from alcohol (Darco) gave an analytical sample, m.p. 199–199.5°; λ_{max} 275 mμ (ε 3.17 × 10^4), 285 (3.00 × 10^4), $\lambda_{shoulder}$ 298 mμ; C—F stretching: 8.08 μ, 8.29 μ.

Anal. Calcd. for $C_{15}H_{11}F_2NO$: C, 69.49; H, 4.28; F, 14.66; N, 5.40. Found: C, 69.59; H, 4.32; F, 14.63; N, 5.50.

SEATTLE 5, WASH.

[CONTRIBUTION FROM THE CHEMISTRY RESEARCH LABORATORY OF THE DEPARTMENT OF SURGERY, UNIVERSITY OF WASHINGTON SCHOOL OF MEDICINE]

Derivatives of Fluorene. XVI. *N*-9-Fluorenylmaleamic Acids and Maleimides[1]

HSI-LUNG PAN AND T. LLOYD FLETCHER[2]

Received November 7, 1960

Several *N*-9-fluorenylmaleamic acids, maleimides, and some new intermediates are described. Cyclization of three *N*-9-fluorenylmaleamic acids is effected in boiling glacial acetic acid. Acetic anhydride with fused sodium acetate, in the usual cyclization procedure, gives highly colored mixtures.

In a recent paper we described the preparation of a number of *N*-(ring)-fluorenylmaleamic acids and maleimides.[3] The end- products described beloware *N*-aralkylmaleimides. Various substituents on the rings might be expected, among other effects,

(1) Supported in part by a research grant (C-1744) from the National Cancer Institute, National Institutes of Health.

(2) To whom correspondence regarding this paper should be addressed.

(3) T. L. Fletcher and H. L. Pan, "Derivatives of Fluorene. XIV," submitted for publication.

to alter susceptibility to RS-H saturation of the carbon-carbon double bond. These compounds are being tested elsewhere for various biological properties including tumor inhibition screening.

In this study several *N*-9-fluorenylmaleamic acids and maleimides were synthesized, starting with 9-fluorenamine prepared by zinc dust reduction of fluorenone oxime.[4] Trifluoroacetylation gave a high yield of *N*-9-fluorenyltrifluoroacetamide. Schmidt and Stützel[5] reported that nitration of *N*-9-fluorenylacetamide in boiling nitric acid gave 1,8-dinitrofluorenone, and Bennett and Noyes[6] nitrated the same compound by means of nitric and sulfuric acid mixture obtaining a compound designated as 1,8-dinitro-9-acetamidofluorene. However, *N*-9-fluorenyltrifluoroacetamide when nitrated under mild conditions gave good yields of *N*-9-(2-nitrofluorenyl)trifluoroacetamide. The position of the nitro group was established by dichromate oxidation to 2-nitrofluorenone.

Acid hydrolysis of *N*-9-(2-nitrofluorenyl)trifluoroacetamide gave 2-nitro-9-fluorenamine. Reaction of the latter with maleic anhydride gave *N*-9-(2-nitrofluorenyl)maleamic acid which was cyclized to the corresponding maleimide in boiling glacial acetic acid. Attempts to close the maleamic acid, in acetic anhydride in the presence of fused sodium acetate, led to a dark purple solid which could not be purified by crystallization or by chromatography on alumina.

Reduction[7] of 2-nitro-9-trifluoroacetamidofluorene gave the 2-amine which was acetylated. The latter compound was hydrolyzed by brief boiling in dilute sodium hydroxide solution giving 2-acetamido-9-fluorenamine, an unstable compound. This amine was also obtained by zinc dust–acetic acid reduction of 2-acetamidofluorenone oxime. In neither case were we able to prepare an analytical sample. However, upon crystallization from acetone, *N*-2-(9-isopropylidenaminofluorenyl)acetamide was obtained as shown by microanalyses and infrared spectrum.

The above amine reacted with maleic anhydride giving an almost quantitative yield of *N*-9-(2-acetamidofluorenyl)maleamic acid. Attempted cyclization in acetic anhydride with fused sodium acetate led to a purple solid which decomposed upon attempted purification. Closure was effected by prolonged refluxing in glacial acetic acid with anhydrous sodium acetate. In addition to the maleimide, a high-melting white solid was obtained.

N-9-Fluorenylmaleamic acid, prepared from the 9-amine, also gave a dark purple intractable solid when heated in acetic anhydride with fused sodium acetate. The corresponding maleimide was obtained by refluxing a mixture of 9-fluorenamine, maleic anhydride, and anhydrous sodium acetate in glacial acetic acid. This maleimide gave an addition compound when treated with *N*-2-(α-thiolnaphthyl)acetamide.

9-Trifluoroacetamido-2-fluorenamine gave *N*-2-(9-trifluoroacetamidofluorenyl)maleamic acid, which cyclized in the acetic anhydride procedure. Upon alkaline hydrolysis, this maleamic acid gave the supposed *N*-2-(9-aminofluorenyl)maleamic acid (not characterized) which was treated with acetic anhydride and sodium acetate. A yellow crystalline solid resulted which was not the expected 9-acetamidomaleimide. Further characterization has not been attempted.

Attempts to prepare 2,9-dimaleimidofluorene from 2,9-diaminofluorene[6] were not successful. With an excess or an equivalent amount of maleic anhydride, the diamine gave a compound of unknown structure.

EXPERIMENTAL[8]

N-9-Fluorenyltrifluoroacetamide. To a cooled (10°) mixture of 9-aminofluorene hydrochloride (21.8 g., 0.1 mole) and pyridine (80 ml.), trifluoroacetic anhydride (23.1 g., 0.11 mole) was added with stirring over a period of 5 min. The reaction mixture was allowed to stand at room temperature for 0.5 hr. then heated on a steam bath for 0.25 hr. and cooled. After water dilution the precipitated product weighed 23.9 g. (87%), m.p. 251–252.5°. Recrystallization from methanol gave an analytical sample, m.p. 252–253° (preheated block). $\lambda_{max}^{C_2H_5OH}$: 224 mμ (log ε 4.40), 232 (4.24), 268 (4.34), 292 (3.80), 304 (3.59). ν_{N-H} 3290, 1550; $\nu_{C=O}$ 1700; ν_{C-F} 1180 cm.$^{-1}$ (broad).

Anal. Calcd. for $C_{15}H_{10}F_3NO$: C, 64.98; H, 3.64; N, 5.05. Found: C, 65.34; H, 3.69; N, 4.85.

N-9-(2-Nitrofluorenyl)trifluoroacetamide. A mixture of nitric acid (*d.* 1.42) (0.7 ml., ~ 0.011 mole) and glacial acetic acid (1.5 ml.) was added portionwise (10 min.) to a stirred suspension of *N*-9-fluorenyltrifluoroacetamide (1.9 g., 0.007 mole) in glacial acetic acid (15 ml.) and concd. sulfuric acid (1 ml.) at 75°. The temperature was kept at 75–80° for 5 min., with stirring, and then allowed to drop to room temperature. After water dilution and filtration the crude product, 2.2 g. (98%), was recrystallized from methanol-benzene giving 1.6 g. (71%), m.p. 234.5–235.5°. Further crystallization gave an analytical sample, m.p. 236–237°. ν_{N-H} 3300, 1550; $\nu_{C=O}$ 1710; ν_{NO_2} 1345; ν_{C-F} 1180 cm.$^{-1}$ (broad).

Anal. Calcd. for $C_{15}H_9F_3N_2O_3$: C, 55.91; H, 2.82; N, 8.69. Found: C, 55.96; H, 2.83; N, 8.78.

Oxidation of N-9-(2-nitrofluorenyl)trifluoroacetamide. A mixture of the trifluoroacetamide (0.1 g.), potassium dichromate (0.3 g.), 9*N* sulfuric acid (4 ml.), and glacial acetic acid (4 ml.) was refluxed for 1 hr. and the reaction mixture then diluted with water. There was obtained 0.05 g. (70%)

(4) C. K. Ingold and C. L. Wilson, *J. Chem. Soc.*, 1493 (1933).

(5) J. Schmidt and H. Stützel, *Ann.*, **370**, 1 (1909).

(6) C. W. Bennett and W. A. Noyes, *J. Am. Chem. Soc.*, **52**, 3437 (1930).

(7) T. L. Fletcher and M. J. Namkung, *J. Org. Chem.*, **23**, 680 (1958).

(8) Melting points were taken on a Fisher-Johns block and are corrected to standards. The analyses were done by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.; A. Bernhardt, Mülheim (Ruhr); and W. Manser, Zürich. The ultraviolet absorptions were measured with a Beckman DK-1 Recording Spectrophotometer. The solutions had been prepared immediately before the measurements were made. The infrared spectra were run on a Beckman IR-5 (potassium bromide disk).

of 2-nitrofluorenone, m.p. and mixture m.p. 225–226°. The infrared spectrum of this substance was identical with that of authentic 2-nitrofluorenone.

Acid hydrolysis of N-9-(2-nitrofluorenyl)trifluoroacetamide. The amide (2 g., 0.006 mole) was refluxed for 9 hr. in a mixture of concd. hydrochloric acid (8 ml.) and absolute ethanol (50 ml.) and the solvent was distilled under reduced pressure until crystallization of the amine hydrochloride took place. This was filtered, washed with 6*N* hydrochloric acid, and dried giving 1.55 g. (96%). The product started melting with decomposition at 206°, but no definite melting point was observed.

N-9-(2-Nitrofluorenyl)maleamic acid. A suspension of 2-nitro-9-fluorenamine hydrochloride (0.5 g., 0.002 mole) in glacial acetic acid (20 ml.) and anhydrous sodium acetate (0.2 g., 0.002 mole) was heated until most of the amine hydrochloride went into solution. The hot mixture was then added in one portion to a rapidly stirred solution of maleic anhydride (0.3 g., 0.003 mole) in glacial acetic acid (5 ml.). After 30 min. of stirring the reaction mixture was set aside for 1 hr. then diluted with water. The product 0.55 g. (90%), melted (dec.) at 203–205°. Crystallization from acetone gave an analytical sample, m.p. 208.5–209.5° dec. $\lambda_{max}^{C_2H_5OH}$: 329 mμ (log ε 4.23). ν_{N-H} 3250, 1550; $\nu_{C=O}$ 1710; ν_{NO_2} 1340 cm.$^{-1}$

Anal. Calcd. for $C_{17}H_{12}N_2O_5$: C, 62.96; H, 3.73; N, 8.64. Found: C, 63.30; H, 3.77; N, 8.80.

N-9-(2-Nitrofluorenyl)maleimide. (a) A mixture of *N*-9-(2-nitrofluorenyl)maleamic acid (0.5 g.), fused sodium acetate (0.1 g.), and acetic anhydride (5 ml.) was heated on a steam bath for 15 min. with frequent shaking. The deep purple reaction solution was treated with dilute sodium carbonate and a resinous solid (0.5 g.) was obtained. Attempts to purify this solid, both by crystallization and chromatography on alumina, were unsuccessful.

(b) *N*-9-(2-Nitrofluorenyl)maleamic acid (0.5 g.) was refluxed in glacial acetic acid (25 ml.) under an air condenser for 7 hr. and the solvent distilled. The residual oil solidified upon cooling and was recrystallized from 95% ethanol giving 0.33 g., m.p. 218–223°. Further crystallization from ethanol gave an analytical sample, m.p. 242.5–243.5°. $\lambda_{max}^{C_2H_5OH}$: 328 mμ (log ε 4.25). $\nu_{C=O}$ 1715; ν_{NO_2} 1340 cm.$^{-1}$

Anal. Calcd. for $C_{17}H_{10}N_2O_4$: C, 66.66; H, 3.29; N, 9.15. Found: C, 66.54; H, 3.59; N, 9.10.

N-9-(2-Aminofluorenyl)trifluoroacetamide. N-9-(2-Nitrofluorenyl)trifluoroacetamide (3 g.) was reduced[7] in boiling 95% ethanol (150 ml.) with hydrazine hydrate (100%), (1.5 ml.) and Raney nickel, giving 2.6 g. (97%) of the amine, m.p. 267–268°.

N-Acetyl derivative: m.p. 297.5–299° dec. $\lambda_{max}^{C_2H_5OH}$: 224 mμ (log ε 4.56), 238 (shoulder), 293 (4.43), 304 (shoulder). ν_{N-H} 3270, 1550; $\nu_{C=O}$ 1710, 1665; ν_{C-F} 1190 cm.$^{-1}$ (broad).

Anal. Calcd. for $C_{17}H_{13}F_3N_2O_2$: C, 61.08; H, 3.92; N, 8.38. Found: C, 61.20; H, 4.19; N, 8.19.

Hydrolysis of the latter derivative (0.1 g.) by boiling for 1 min. in a mixture of 95% ethanol (1 ml.) and 2% sodium hydroxide (4 ml.) gave 2-acetamido-9-fluorenamine identical with the compound prepared by reduction of 2-acetamidofluorenone oxime. Recrystallization of this amine from acetone gave the azomethine, described below, obtained from the recrystallization of the reduction product of 2-acetamidofluorenone oxime.

2-Acetamidofluorenone oxime. A mixture of hydroxylamine hydrochloride (9 g., 0.13 mole) and anhydrous sodium acetate (13.1 g., 0.16 mole) was dissolved in water (40 ml.). To the solution 2-acetamidofluorenone (15.8 g., 0.07 mole) and ethanol (100 ml.) were added with stirring. The whole was then refluxed for 10 min., cooled, diluted with water, and the product filtered, giving 15.3 g. (92%), m.p. 237–238.5° dec.

Recrystallization from methanol gave an analytical sample, m.p. 238–239° dec.

Anal. Calcd. for $C_{15}H_{12}N_2O_2 \cdot CH_3OH$: C, 67.60; H, 5.67; N, 9.86. Found: C, 68.14; H, 5.76; N, 10.26.

N-2-(9-Aminofluorenyl)acetamide. Reduction of the oxime (2 g.) in acetic acid–water (12:1) (13 ml.) with zinc dust (2.6 g.) at 90–95° (bath) (20 min.) gave 1.9 g. (quant.), m.p. 160–163° dec.

Recrystallization from acetone gave *N-2-(9-isopropylidenaminofluorenyl)acetamide,* m.p. 209–211° dec. The infrared spectrum (potassium bromide disk, cm.$^{-1}$) showed no absorption corresponding to a primary amino group but intense absorption at 2970, 2870 (CH_3); 1680 (C=N); and 1665 (C=O of the acetamido group). $\lambda_{max}^{C_2H_5OH}$: 213 mμ (shoulder), 236 (shoulder), 282 (shoulder), 291 (log ε 4.52), 306 (shoulder).

Anal. Calcd. for $C_{18}H_{18}N_2O$: C, 77.67; H, 6.52; N, 10.07. Found: C, 77.82; H, 6.86; N, 10.06.

N-9-(2-Acetamidofluorenyl)maleamic acid. To a stirred solution of maleic anhydride (3 g., 0.03 mole) in glacial acetic acid (20 ml.), *N*-2-(9-aminofluorenyl)acetamide (6.8 g., 0.03 mole) in glacial acetic acid (60 ml.) was added over a period of 20 min. The resulting thin paste was stirred for 2 hr. then filtered. The product was washed with acetic acid and dried on the funnel giving 8.7 g. (95%), m.p. 209.5–212° dec. Recrystallization from acetone gave an analytical sample, m.p. 213–214° dec. $\lambda_{max}^{C_2H_5OH}$: 214 mμ (log ε 4.63), 238 (shoulder), 282 (shoulder), 292 (4.48), 307 (shoulder). ν_{N-H} 3280, 1550; $\nu_{C=O}$ 1710, 1667 cm.$^{-1}$

Anal. Calcd. for $C_{19}H_{16}N_2O_4$: C, 67.85; H, 4.80; N, 8.33. Found: C, 67.70; H, 4.82; N, 8.44.

N-9-(2-Acetamidofluorenyl)maleimide. The foregoing maleamic acid (2 g.) was refluxed 22 hr. in glacial acetic acid (50 ml.) with anhydrous sodium acetate (2 g.). The excess solvent was distilled and the residual solid triturated in ice water, filtered, and washed with water. When dry the solid was extracted with boiling benzene and the extract evaporated to an oily solid which was crystallized from acetone. A small amount of white solid (m.p. > 280°) of unknown composition was removed. The first crop was recrystallized successively from acetone-water, benzene-cyclohexane (twice), and benzene (twice) giving yellowish white prisms, 0.2 g., m.p. 221–223°. $\lambda_{max}^{C_2H_5OH}$: 237 mμ (shoulder), 281 (log ε 4.64), 291 (4.62). ν_{N-H} 3390, 1540; $\nu_{C=O}$ 1705, 1670 cm.$^{-1}$

Anal. Calcd. for $C_{19}H_{14}N_2O_3$: C, 71.69; H, 4.43; N, 8.80. Found: C, 71.83; H, 4.59; N, 8.80.

N-9-Fluorenylmaleamic acid. 9-Aminofluorene (9.05 g., 0.05 mole) was dissolved in warm glacial acetic acid (40 ml.) and added slowly (15 min.) to a stirred solution of maleic anhydride (5.5 g., 0.055 mole) in glacial acetic acid (20 ml.). After a half hour of stirring the reaction mixture was heated on a steam bath for 15 min. and cooled. Upon water dilution there was obtained 13.6 g. (98%) of the maleamic acid, m.p. 201–203.5° dec. (preheated block). $\lambda_{max}^{C_2H_5OH}$: 224 mμ (log ε 4.49), 232 (4.33), 268 (4.33), 292 (3.77), 304 (3.62). ν_{N-H} 3260, 1540; $\nu_{C=O}$ 1700 cm.$^{-1}$

Anal. Calcd. for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.02. Found: C, 73.28; H, 4.99; N, 4.72.

N-9-Fluorenylmaleimide. Maleic anhydride (1.1 g., 0.011 mole) was added to a mixture of 9-aminofluorene hydrochloride (2.18 g., 0.01 mole; Aldrich Chemical Co., Milwaukee, Wis.), glacial acetic acid (23 ml.), and anhydrous sodium acetate (0.9 g., 0.011 mole). The whole was shaken and refluxed under an air condenser for 2 hr. and cooled. After water dilution the gummy solid was recrystallized from methanol-water and from benzene-ligroin (*d.* 0.67–0.69). A small amount of the maleamic acid was first removed by filtration. Evaporation of solvent gave a second crop which was recrystallized from methanol-water giving lustrous white needles (0.2 g.), m.p. 171–173°. Further crystallization from the same solvent gave an analytical sample, m.p. 174–175°. $\lambda_{max}^{C_2H_5OH}$: 224 mμ (log ε 4.51), 232 (4.34), 268 (4.28), 279 (shoulder), 293 (3.73), 304 (3.62). The ultraviolet absorption in cyclohexane was quite similar. $\nu_{C=O}$ 1700 cm.$^{-1}$

Anal. Calcd. for $C_{17}H_{11}NO_2$: C, 78.15; H, 4.24; N, 5.36. Found: C, 78.19; H, 4.34; N, 5.55.

N-9-Fluorenyl-α-S-[1′-(2′-acetamidonaphthyl)]mercapto-

succinimide. The foregoing maleimide (0.05 g.) was dissolved in acetone (3 ml.). To the solution *N*-2-(α-thiolnaphthyl)-acetamide (1.1 equivalents) in acetone (3 ml.) was added dropwise (5 min.). The reaction solution was stirred for 20 min. and concentrated to an oil. Methanol was added to the oil and the mixture was concentrated until crystallization of a white substance took place. After filtration and recrystallization from acetone-methanol, 0.08 g., m.p. 208–209° was obtained. Two recrystallizations from acetone-water gave an analytical sample, m.p. 211–212°.

Anal. Calcd. for $C_{29}H_{22}N_2O_3S$: N, 5.85; S, 6.70. Found: N, 5.83; S, 6.56.

N-2-(9-Trifluoroacetamidofluorenyl)maleamic acid. *N*-9-(2-Aminofluorenyl)trifluoroacetamide (0.2 g., 0.7 mmole) reacted with maleic anhydride (0.14 g., 1.4 mmoles) in glacial acetic acid (10 ml.) giving a quantitative yield (0.27 g.) of the maleamic acid, m.p. 223–225° dec. An analytical sample was prepared by stirring the product with boiling acetone and filtering, m.p. 225–227° dec. $\lambda_{max}^{C_2H_5OH}$: 276 mμ (log ε 4.14), 319 (4.22). ν_{N-H} 3310, 1550; $\nu_{C=O}$ 1710; ν_{C-F} 1175 cm.$^{-1}$ (broad).

Anal. Calcd. for $C_{19}H_{13}F_3N_2O_4$: C, 58.47; H, 3.36; N, 7.18. Found: C, 58.54; H, 3.63; N, 714.

N-2-(9-Trifluoroacetamidofluorenyl)maleimide. The above maleamic acid (7.8 g.) was cyclized in acetic anhydride (30 ml.), in the presence of fused sodium acetate (1.2 g.), giving 7.1 g. (96%) of the maleimide, m.p. 255–259°. Recrystallization from benzene gave an analytical sample, m.p. 262–263°. $\lambda_{max}^{C_2H_5OH}$ 234 mμ (shoulder), 277 (log ε 4.36), 306 (3.83). ν_{N-H} 3330, 1550; $\nu_{C=O}$ 1730, 1710; ν_{C-F} 1180 cm.$^{-1}$ (broad).

Anal. Calcd. for $C_{19}H_{11}F_3N_2O_3$: C, 61.30; H, 2.98; N, 7.53. Found: C, 61.44; H, 2.98; N, 7.78.

Attempted preparation of N-2-(9-acetamidofluorenyl)-maleimide. *N*-2-(9-Trifluoroacetamidofluorenyl)maleamic acid (4 g.) was dissolved in 1*N* sodium hydroxide (50 ml.), heated on a steam bath for 3 min., and cooled. A small amount of fluffy precipitate was removed. The alkaline solution was chilled in ice and acidified to *p*H 4 with hydrochloric acid. The yellow precipitate was filtered, washed once with ice water, and dried giving 3.3 g., m.p. 185–190° dec.

The latter compound (1 g.) was mixed with fused sodium acetate (0.15 g.) and acetic anhydride (6 ml.) and heated on a steam bath, with shaking, for 15 min. and cooled to room temperature. The pasty mixture was stirred in 10% sodium acetate and the excess acetic anhydride destroyed with 5% sodium carbonate. The yellow solid was filtered, washed with water, and dried, giving 0.9 g. Recrystallization from acetone-benzene-ligroin gave 0.85 g., m.p. 190–192° dec. Three recrystallizations from acetone-water gave an analytical sample, m.p. 209–211° (glassy).

Anal. Found: C, 69.19; H, 5.09; N, 8.86.

Attempted preparation of N,N'-2,9-fluorenedimaleamic acid. 2,9-Diaminofluorene[6] (1.96 g., 0.01 mole) in warm glacial acetic acid (10 ml.) was added dropwise to a warm solution of maleic anhydride (2.94 g., 0.03 mole) in glacial acetic acid (15 ml.) over a period of 20 min. The reaction mixture was stirred at room temperature for 30 min. then heated (steam bath) for 10 min. and cooled. Water dilution of the mixture gave 3.8 g. (97.5%) of an acidic substance, m.p. ~ 212° dec.

Recrystallization from acetone-methanol gave a sample, m.p. 210–211° dec. (preheated block).

Anal. Found: C, 61.44; H, 4.91; N, 5.68.

SEATTLE 5, WASH.

[CONTRIBUTION NO. 304 FROM THE JACKSON LABORATORY, ORGANIC CHEMICALS DEPARTMENT, E. I. DU PONT DE NEMOURS AND CO., INC.]

m-Dioxanes and Other Cyclic Acetals

CHRISTIAN S. RONDESTVEDT, JR.

Received November 10, 1960

An extensive series of substituted *m*-dioxanes has been prepared by acetalization of 1,3-glycols. Some 1,3-dioxolanes, 1,3-oxathianes, and 1,3-dioxolanes have been synthesized for comparison. Differences in the ease of acetalization have been noted.

The study of catalytic reactions of *m*-dioxanes[1] required the preparation of a variety of *m*-dioxanes and related acetals. Although the basic synthetic method, direct acid-catalyzed reaction of 1,3-diols (or in a few cases, 1,2- or 1,4-diols) with aldehydes or ketones has long been known, it was necessary to develop refinements of this procedure to obtain satisfactory yields of certain acetals.

Some unstable aldehydes—*e.g.*, chloroacetaldehyde and malonaldehyde—are marketed as their methyl or ethyl acetals. These were conveniently converted to the *m*-dioxanes by interchange with the diol in the presence of boron trifluoride or *p*-toluenesulfonic acid. The lower alcohol was distilled during the interchange to shift the equilibrium.

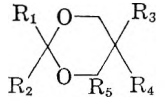
Although quantitative kinetic experiments were not performed, the qualitative effects of substituents on the rate and equilibria were noted. The aromatic aldehydes reacted very rapidly, with simple aliphatic aldehydes next in line. Ketones seemed to react rapidly, but the equilibrium position was less favorable. With acetone, very little product was formed (infrared) until the water was removed from the distillate by drying it with calcium chloride. It was surprising to find that the cyclopentanone ketal (#11)[2] was hydrolyzed rapidly by distilled water, in which the dissolved carbon dioxide must function as the acid catalyst. This was not the case with the acetone (#10) and cyclohexanone (#12) ketals. These results are in line with the prediction from the I-strain principle,[3] which teaches that reactions in which a ring carbon atom changes from

(1) C. S. Rondestvedt, Jr., and G. J. Mantell, *J. Am. Chem. Soc.*, **82**, 6419 (1960).

(2) The arabic numerals are those assigned to the acetals in the tables.

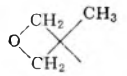
(3) H. C. Brown, R. S. Fletcher, and R. B. Johannessen, *J. Am. Chem. Soc.*, **73**, 212 (1951).

TABLE I. *m*-DIOXANES



Acetal No.	R_1	R_2	R_3	R_4[a]	B.P., Mm.	n^{25}_D (M.P.) (Cryst. Solv.[b])	Yield, %	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
1	H	H	CH_3	CH_3	126.5/atm.	1.4190	97	$C_6H_{12}O_2$[e]				
2	CH_3	H	H	H	109–110/atm.	1.4119	63	$C_5H_{10}O_2$[d]				
3	CH_3	H	CH_3	CH_3	130–131/atm.	1.4134	88	$C_7H_{14}O_2$	64.58	10.84	64.5, 64.7	10.8, 10.7
4	$(CH_3)_2CH$	H	CH_3	CH_3	165–167/atm. 70/30	1.4227	85	$C_9H_{18}O_2$[e]	68.4	11.4	68.6, 68.3	10.9, 11.0
5[f]	$(CH_3)_2CH$	H	CH_3	$CH_3CH_2CH_2$	114–116/45	1.4332	79	$C_{11}H_{22}O_2$	71.0	11.8	71.1, 71.0	11.9, 11.9
6	$CH_2{=}CH$	H	CH_3	CH_3	83–86/70	1.4349	63	$C_8H_{14}O_2$	67.57	9.92	67.6, 67.5	10.0, 10.3
7		H	CH_3	CH_3	80–81/1.5	1.4708	High	$C_{12}H_{20}O_2$	73.42	10.27	73.3, 73.3	10.3, 10.1
8	$ClCH_2$	H	CH_3	CH_3	104–105/49	1.4476	95	$C_7H_{12}ClO_2$	51.07	7.90	50.8, 50.8	7.9, 7.9[g]
9	Cl_3C	H	CH_3	CH_3	—	(129.0–129.5) (H-B)	30	$C_7H_{11}Cl_3O_2$	36.00	4.75	36.0, 36.1	4.9, 4.9[h]
10	CH_3	CH_3	CH_3	CH_3	144–145/atm.	1.4178	>73	$C_8H_{16}O_2$	66.62	11.19	66.7, 66.5	11.4, 11.3
11	—$(CH_2)_4$—		CH_3	CH_3	103–105/36	1.4520	67	$C_{10}H_{18}O_2$	70.55	10.66	70.6, 70.7	10.6, 10.5
12	—$(CH_2)_5$—		CH_3	CH_3	116–118/34	1.4610	87	$C_{11}H_{20}O_2$	71.69	10.94	71.7, 72.0	11.0, 10.9
13	C_6H_5	H	CH_3	CH_3	134–137/7	1.5021[i] (33) (M-W)	95	$C_{12}H_{16}O_2$[j]	—	—	—	—
14	*p*-$CH_3C_6H_4$	H	CH_3	CH_3	106/1.7	(40.8–41.0) (M-W)	88	$C_{13}H_{18}O_2$	75.69	8.79	75.7, 75.6	8.9, 8.9
15	*p*-$(CH_3)_2CHC_6H_4$	H	CH_3	CH_3	136/4	1.5017	87	$C_{15}H_{22}O_2$	76.88	9.47	76.9, 76.6	9.6, 9.5
16[f]	*p*-$CF_3C_6H_4$	H	CH_3	CH_3	—	(73) (H)	49	$C_{13}H_{15}F_3O_2$	60.0	5.8	60.1, 60.2	6.0, 5.0
17	*p*-ClC_6H_4	H	CH_3	CH_3	—	1.5050 (55.5–56.5) (H)[k]	75	$C_{12}H_{15}ClO_2$	63.54	6.67	63.7, 63.5	6.6, 6.9[l]
18[m]	2,4-$Cl_2C_6H_3$	H	CH_3	CH_3	—	(57.0–57.5)	—	$C_{12}H_{14}Cl_2O_2$	55.19	5.40	55.15	5.41
19[m]	3,4-$Cl_2C_6H_3$	H	CH_3	CH_3	—	(45–46)	—	$C_{12}H_{14}Cl_2O_2$	55.19	5.40	55.00	5.38
20[m]	2,6-$Cl_2C_6H_3$	H	CH_3	CH_3	—	(120–121)	—	$C_{12}H_{14}Cl_2O_2$	55.19	5.40	54.96	5.48
21	*p*-$CH_3OC_6H_4$	H	CH_3	CH_3	—	(81.5–82.0) (H or M)	>80	$C_{13}H_{18}O_3$	70.24	8.16	70.2, 70.0	8.0, 8.0
22	*p*-$(CH_3)_2NC_6H_4$	H	CH_3	CH_3	—	(98.0–98.5) (B, D)	>75	$C_{14}H_{21}NO_2$	71.45	9.00	71.4, 71.1	9.0, 8.8[n]
23	*m*-$NO_2C_6H_4$	H	CH_3	CH_3	—	(48.0–49.0) (H, D)	86	$C_{12}H_{15}NO_4$	60.84	6.37	60.9, 60.5	6.6, 6.5
24[o]	CH_3	H	CH_2OH	CH_3	125–135/33	1.4508	79	$C_7H_{14}O_3$	—	—	—	—
25	CH_3	H	CH_2O Tosyl	CH_3	—	(86–87) (H-B)	89[p]	$C_{14}H_{20}O_5S$	55.98	6.71	55.9, 55.9	6.7, 6.7
25a	CH_3	H	CH_2O Tosyl	CH_3	—	(61–62) (H-B)		$C_{14}H_{20}O_5S$	55.98	6.71	56.1, 55.9	6.4, 6.7
26	$(CH_3)_2CH$	H	—CH_2OCH_2—		86–89/8	1.4524	59	$C_9H_{16}O_3$	62.76	9.37	62.9, 62.8	9.2, 9.2
27	$(CH_3)_2CH$	H	—$OCH_2CH_2CH_2$—		112–114/26	1.4495	87[p]	$C_{10}H_{18}O_3$	64.48	9.74	64.6, 64.8	9.6, 9.3
27a	$(CH_3)_2CH$	H	—$OCH_2CH_2CH_2$—		138–139/25	1.4592		$C_{10}H_{18}O_3$	64.48	9.74	63.8, 63.7	10.4, 10.2

TABLE I (*Continued*)

Acetal No.	R_1	R_2	R_3	R_4[a]	B.P., Mm.	n_D^{25} (M.P.) (Cryst. Solv.[b])	Yield, %	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
28		H	CH_3	CH_3	110–112/17	1.4438 (42.0–42.5) (M-W)	68	$C_{10}H_{18}O_3$	64.48	9.74	64.1, 64.2	9.8, 9.6
29		H	CH_3	CH_3	107–109/12	1.4558	82	$C_{10}H_{18}O_3$	64.48	9.74	64.2, 64.7	9.4, 9.5
30	$(CH_3)_2CH$	H	$CH_2OCH_2CH{=}CH_2$	C_2H_5	106–108/6	1.4470	90	$C_{13}H_{24}O_3$	68.38	10.59	68.2, 68.2	10.6, 10.8
31	$CH_3CH_2CH_2$	H	$CH_2{=}CH$	CH_3	75–78/12	1.4408	100	$C_{10}H_{18}O_2$	70.54	10.65	70.6, 70.4	10.7, 10.9
32	$(CH_3)_2CH$	H	NO_2	CH_3	142–144/18	(56–57) (H-D)	68	$C_8H_{15}NO_4$[p]	50.78	7.99	51.1, 51.1	8.3, 8.3[q]
32a	$(CH_3)_2CH$	H	NO_2	CH_3	107–137/18	1.4443–1.4460	18	$C_8H_{15}NO_4$[p]	50.78	7.99	51.5, 51.4	8.1, 8.1[r]
33	$(CH_3)_2CHCH_2O$-$CH_2C(CH_3)_2$	H	CH_3	CH_3	130–132/23	1.4314	84	$C_{14}H_{28}O_3$	68.81	11.55	68.9, 69.0	11.4, 11.4
34	n-$C_{11}H_{23}$[s]	H	CH_3	CH_3	137–143/2.2	1.4441	77	$C_{17}H_{34}O_2$	75.50	12.67	75.3, 75.5	12.8, 13.0
35	$(CH_3)_2CH$	H	CH_3	CH_3[a]	98–102/26	1.4310	>80	$C_{12}H_{24}O_2$	71.95	12.08	71.8, 72.1	12.1, 12.0
36	C_6H_5	H	CH_3	CH_3[a]	133–134/7	1.4995	90	$C_{18}H_{22}O_2$	76.88	9.47	76.7, 77.0	9.3, 9.6
37	$(CH_3)_2CH$	H	—$CH_2CH{=}CHCH_2CH_2$—		98.5–100/6	1.4730	94	$C_{12}H_{20}O_2$	73.42	10.27	73.46	10.27
38	$(CH_3)_2CH$	H	—$CH_2CH_2CH_2CH_2CH_2$—		99–100.5/6	1.4635	100	$C_{12}H_{22}O_2$	72.68	11.19	73.4, 73.5	11.0, 11.0
39	$(CH_3)_2CH$	H	C_6H_5	C_6H_5	—	(96.5–97.5) (H)	64	$C_{19}H_{22}O_2$	80.81	7.86	80.5, 80.7	7.9, 7.8

[a] R_5 = H, except for Nos. 35 and 36, where R_5 = isopropyl. [b] Solvents—A = ethanol; B = benzene; C = cyclohexane; D = decolorized with Darco G-60; E = ethyl acetate; H = hexane; M = methanol; W = water. [c] M. Apel and B. Tollens, *Ann.*, **289**, 44 (1896), report b.p. 126°. [d] A. Lochert, *Ann. chim.*, [6] **16**, 48 (1889), reports b.p. 110–112°/768 mm. [e] R. Dworzak and T. M. Lasch, *Monatsh.*, **51**, 67 (1929), report b.p. 159–161°. [f] These acetals were prepared by Harold W. Pier, to whom I am indebted. [g] % Cl—calcd., 21.54; found, 20.1, 20.0. [h] % Cl—calcd., 45.55; found, 46.8, 46.8. [i] n_D^{59}. [j] A. Francke and E. Gigerl, *Monatsh.*, **49**, 14 (1928), report b.p. 123–124°/10 mm., m.p. 35°, 68% yield. [k] n_D^{35}. [l] % Cl—calcd., 15.64; found, 15.5, 15.8. [m] These acetals were prepared by Dr. John Harvey, to whom I am indebted. [n] % N—calcd., 5.96; found (Kjeldahl), 5.93, 5.97. Dumas nitrogen analyses were very erratic with this compound. [o] Trojan Powder Company, Technical Bulletin on Trimethylolethane, report b.p. 217–221°/atm. The boiling range of our product indicates it is a mixture of stereoisomers. [p] M. S. Newman, B. J. Magerlein, and W. B. Wheatley, *J. Am. Chem. Soc.*, **68**, 2112 (1946), report m.p. 46°, b.p. 98–103°/0.5 mm., 73% yield. There was no mention of another stereoisomer. [q] % N—calcd., 7.40; found (Dumas), 7.7, 7.2. [r] % N—calcd., 7.40; found (Dumas), 7.2, 7.2. [s] The available dodecanal was contaminated with small amounts of (apparently) higher and lower aldehydes. The acetal thus contains small amounts of homologs, to judge from the VPC analysis.

tetrahedral (the ketal) to trigonal (the cyclic ketone) are energetically more favorable with cyclopentanone derivatives than with those of cyclohexanone.

Chloral was very sluggish in its reaction with 2,2-dimethyl-1,3-propanediol, in keeping with the accepted mechanism of acetalisation.[4] Formation of the stabilized carbonium ion intermediate from the hemiacetal will be drastically inhibited by the powerful electron withdrawal by the chlorine atoms. It was necessary to use a considerable amount of concentrated sulfuric acid to promote formation of acetal #9.

When either component of the acetal contained an additional ether oxygen, the reaction was somewhat retarded. Though only slight with an aliphatic ether (#30, 33), retardation was quite noticeable with the more basic oxygen in a tetrahydrofuran ring (#27, 29). This effect was probably also present with the two compounds containing an oxetane ring (#26, 28), but with these two a competitive reaction supervened, apparently a moderately rapid stoichiometric reaction of the acid catalyst with the oxetane ring to destroy the catalyst. A considerable quantity of polymeric ether was formed from both of these compounds.

m-Dioxanes with two different substituents at each of two positions will exist as diastereoisomeric racemates.[5] In the present work, three acetals (#25, 27, and 32) were separated into the diastereoisomers, and one (#5) was demonstrated by vapor-phase chromatography to be a mixture of roughly equal parts of two isomers. In the other cases where stereoisomerism was possible (#24, 30, 31, 35, and 36), separation was not accomplished by distillation. From conformational analysis, one would predict that bulky groups would assume equatorial positions in the chair conformation of the *pseudo*-cyclohexane ring. It should be possible to find examples in which one isomer predominates strongly because of the greatly disparate steric requirements of the groups at C-5. That did not appear to be the case in the compounds studied in this work, for polar effects are probably responsible for the preponderance of the solid isomer of the nitro acetal #32.

EXPERIMENTAL[6]

In most cases, the diols and carbonyl compounds were high-grade commercial chemicals, and were used without purification after inspection of the infrared spectrum.

Procedure for acetalization. Approximately equimolar quantities of carbonyl compound and diol were placed in a flask surmounted by a Dean-Stark moisture trap and a reflux condenser. In some cases, an excess of the cheaper component was used when it could readily be removed during workup. Hexane as an azeotropic solvent (about 100–150 ml. per mole)[7] and 0.5 mole % of *p*-toluenesulfonic acid were added, and the mixture was refluxed, cautiously at first until any sudden exothermic reaction was spent, until the water evolution had stopped, then for an additional half hour. The cooled mixture was shaken with sodium bicarbonate solution and with water until the infrared spectrum showed no diol. Any acid present in the original aldehyde sample was removed by this procedure. After drying with potassium carbonate, the product was distilled, though in many cases the residue after removal of hexane was sufficiently pure for use. The product could sometimes be crystallized directly from the hexane solution by concentration and cooling.

The acetals prepared by this method are listed in Tables I to III without comment. Variations from this procedure are described below, using the acetal number given in the Tables. It may be noted that many of these cyclic acetals proved extraordinarily difficult to burn completely in a standard microanalytical train. Ultimately, the acetals were routinely burned at higher temperatures.[8]

Acetal #6. Acrolein reacts with alcohols to form acetals of β-alkoxypropionaldehydes. To minimize this addition to the double bond, various tricks have been proposed.[9] In this work, the azeotroping solvent was petroleum ether (b.p. 30–60°) and only 0.003 mole % of *p*-toluenesulfonic acid was used, according to Meyers, Magerlein, and Staffen[9g]; water evolution ceased after 7.5 hr. of reflux.

Acetal #8. Diethyl chloroacetal (Union Carbide Chemicals) was refluxed with an equimolar amount of neopentyl glycol (2,2-dimethyl-1,3-propanediol, Tennessee Eastman) under a fractionating column in the presence of 1 mole-% of *p*-toluenesulfonic acid. Ethanol was collected overhead. When most of the ethanol had been removed (about 2 hr.), benzene was added and the remaining ethanol was removed as the benzene azeotrope. The catalyst was destroyed with solid potassium carbonate and the product was distilled.

Acetal #9. Anhydrous chloral (Eastman Kodak) (0.72 mole) was refluxed with a slight excess of neopentyl glycol in hexane solution. *p*-Toluenesulfonic acid was not effective as catalyst. When 25 ml. of concd. sulfuric acid was added, the mixture darkened rapidly. The solution was refluxed gently for 1 hr. and allowed to stand overnight. The dark, crystalline mass was dissolved by warming with benzene, transferred to a separatory funnel, and 25 ml. was withdrawn from the bottom and discarded. (The mixture was so dark that no phase separation was visible.) The upper layer was shaken with 40 g. of sodium hydroxide in 600 ml. of ice water which lightened the color at once. The benzene layer was washed and dried, concentrated to 250 ml., and diluted with an equal volume of hexane. The crystalline acetal was recrystallized from 1:2 benzene-hexane. The low yield could doubtless be

(4) E. R. Alexander, *Principles of Ionic Organic Reactions*, Wiley, New York, 1950, p. 215.

(5) Some previous stereoisomers were isolated by M. Senkus, *J. Am. Chem. Soc.*, **65**, 1656 (1943) and by authors therein cited.

(6) The author is indebted to Wallace Buskirk and James Chestnut for efficient and imaginative technical assistance. Melting points and boiling points are uncorrected. Infrared spectra were obtained with the Perkin Elmer Model 21, 221, and "Infracord" Model 137 Spectrophotometers.

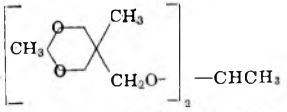
(7) Occasionally benzene or toluene was used as azeotropic solvent, but hexane was preferred because most of the diols were so sparingly soluble in it that removal of excess diol was readily accomplished by water-washing the final solution. In a few cases, sulfuric, hydrochloric, or oxalic acid was used as catalyst.

(8) C. A. Rush, S. S. Cruikshank, and E. J. H. Rhodes, *Mikrochim. Acta*, No. **416**, 858 (1956).

(9) (a) R. H. Hall and E. S. Stern, *J. Chem. Soc.*, **1955**, 2657; **1954**, 3383. (b) J. A. Van Allan, *Org. Syntheses*, **32**, 5 (1952). (c) D. I. Weisblat, *et al.*, *J. Am. Chem. Soc.*, **75**, 5893 (1953). (d) F. J. Bellinger and T. Bewley, Brit. Pat. **713,833**. (e) J. Habeshaw and C. J. Geach, Brit. Pat. **715,794** and **702,206**. (f) D. G. Thomas, U. S. Pat. **2,691,049**. (g) D. R. Meyers, B. J. Magerlein, and G. W. Staffen, U. S. Pat. **2,678,950** and Brit. Pat. **713,088**.

TABLE II

BIS-*m*-DIOXANES

Acetal No.	Structure[a]	B.P., Mm.	n_D^{25} (M.P., Cryst. Solv.)	Yield, %	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
41	R—R	125/7	(165.5–166.5) (E)	61	$C_{12}H_{22}O_4$	62.58	9.63	62.4, 62.5	10.0, 9.8
42	RCH_2R	152/15	(119.5–120.5) (E-C)	85	$C_{13}H_{24}O_4$	63.90	9.90	63.88	9.94[b]
43	RCH_2CH_2R	—	(74–75) (E-C)	>83	$C_{14}H_{26}O_4$	65.1	10.1	64.8, 64.9	10.3, 10.3
44	$RCH_2CH_2CH_2R$	—	(69.8–70.5) (M-W)	76	$C_{15}H_{28}O_4$	66.1	10.2	66.1, 65.9	10.2, 10.0
45		—	(210.5–212.0) (E)	84	$C_{18}H_{26}O_4$	70.56	8.55	70.4, 70.4	8.5, 8.6
46		120–135/2[c]	1.4490	37	$C_{16}H_{30}O_6$	60.35	9.50	59.6, 60.1	9.3, 9.0
47	Pentaerythritol diformal[d]	86/0.8	(50)	88	$C_7H_{12}O_4$[e]	—	—	—	—
48	Pentaerythritol diisobutyral[d]	110/0.8	(89–90) (B-C)	92	$C_{13}H_{24}O_4$[f]	—	—	—	—
49	Pentaerythritol dibenzal[d]	—	(158.5–159.0) (E)	>80	$C_{19}H_{20}O_4$[g]	—	—	—	—

[a] R=$(CH_3)_2$  . [b] Calcd.: O, 26.20; mol. wt., 244. Found: O, 27.2, 26.9; mol. wt. 246, 237. [c] Trojan Powder Co., Technical Bulletin on Trimethylolethane, report b.p. 142–145°/1 mm. for trimethylolethane sesquiacetal. [d] The *Chemical Abstracts* name of the ring system  is 4,9-dialkyl-3,5,8,10-tetraoxaspiro[5,5]-undecane. In this paper, the acetals are named as pentaerythritol derivatives. [e] Supplied by Hercules Powder Co., used as received. [f] A. Skrabal and M. Zlateva, *Z. phys. chem.*, **119**, 305 (1926), report m.p. 95°. [g] M. Apel and B. Tollens, *Ann.*, **289**, 34 (1896), report m.p. 160°.

TABLE III

MISCELLANEOUS ACETALS

Acetal No.	Acetal	B.P., Mm.	n_D^{25} (M.P., Cryst. Solv.)	Yield, %	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
51	2,4,4-Trimethyl-1,3-dioxolane	98–100/atm.	1.3921	69	$C_6H_{12}O_2$[a]	—	—	—	—
52	2-Isopropyl-1,3-dioxepane	163–166/atm.	1.4312	58	$C_8H_{16}O_2$	66.62	11.18	66.4, 66.5	11.2, 11.2
53	2-Isopropyl-1,3-dioxep-5-ene	94–99/90	1.4470	38	$C_8H_{14}O_2$[b]	67.57	9.92	67.8, 67.6	9.9, 9.9
54	2-Phenyl-1,3-dioxepane	118–119/11	1.5210	38	$C_{11}H_{14}O_2$	74.13	7.92	74.4, 73.9	7.9, 7.9
55	2-Isopropyl-5,5-diethyl-1,3-oxathiane[c]	127–130/18	1.4809	45	$C_{11}H_{22}OS$	65.29	10.96	64.8, 65.0	10.9, 11.3[d]
56	2-Phenyl-5,5-diethyl-1,3-oxathiane[c]	—	(52–54) (M)	80	$C_{14}H_{20}OS$	71.13	8.52	70.9, 70.8	8.3, 8.5[e]
57	1,6-Dioxapiro[4,4]nonane[f]								
58	2,2-Dimethoxypropane[g]								
59	4,4-Dimethyl-*m*-dioxane[h]								

[a] M. G. Voronkov and E. S. Titlinova, *Zhur. Obshchei Khim.*, **24**, 613 (1954) [*Chem. Abstr.*, **49**, 5484a (1955)], report b.p. 100.1°/762 mm., n_D^{20} 1.3938. [b] K. C. Bannock and G. R. Lappin, *J. Org. Chem.*, **21**, 1366 (1956), report b.p. 170.0–170.6°/735 mm., n_D^{20} 1.4484. [c] The required 3-mercapto-2,2-diethyl-1-propanol was prepared by the method of C. S. Rondestvedt, *J. Org. Chem.*, in press. [d] % S—calcd., 15.85; found, 15.7, 15.8. [e] % S—calcd., 13.57; found, 13.5, 13.4. [f] Supplied by Quaker Oats Co., used as received. [g] Supplied by Dow Chemical Co., used as received. [h] Supplied by Atlantic Refining Co., used as received.

improved by decreasing the quantity of sulfuric acid, and by moderating the temperature.

Acetal #10. The distillate, consisting of benzene, acetone, and water, did not separate into two phases. Accordingly, the mixture was refluxed into a Soxhlet extractor containing a large thimble full of calcium chloride to dehydrate the distillate. The calcium chloride was renewed as it became exhausted. The catalyst was destroyed with solid potassium carbonate before the product was fractionated.

Acetal #11. When the hexane solution was washed with bicarbonate and water, the quantity of aqueous layer was larger than the volume of water added, and "schlieren" were evident at the interface. This suggests a rapid hydrolysis of the ketal by neutral water. Although the theoretical quantity of water had been removed during the reflux period, 16% of cyclopentanone was recovered when the organic layer was distilled. Omission of the water wash should materially improve the yield.

Acetals #25 and 25a. The alcohol (acetal #24) in excess pyridine reacted somewhat exothermically with *p*-toluenesulfonyl chloride added portionwise. The mixture was stirred overnight at room temperature, diluted with benzene, filtered to remove the theoretical quantity of pyridine hydrochloride, and washed thoroughly with water to remove the excess pyridine; the benzene was removed by distillation, ultimately at 10 mm., pot temperature 140°. The residue, which crystallized slowly, amounted to 91% yield. It was crystallized from hexane containing a little benzene to yield first the high-melting acetal #25. Concentration of the mother liquors yielded the impure low-melting isomer 25a. In order to recrystallize 25a, it was necessary that the hexane-benzene solution be saturated at no higher than 35°; then very slow cooling with seeding yielded crystalline material. The two isomers are present in roughly equal amounts.

Acetal #26. Oxetane-3,3-dimethanol[10] and a slight excess of isobutyraldehyde in benzene reacted rapidly in the presence of *p*-toluenesulfonic acid to liberate about 10% of the theoretical water; water evolution then stopped abruptly. Several additional portions of *p*-toluenesulfonic acid were added, with repetition of this behavior. Ultimately about 90% of the theoretical water was collected. The mixture was then processed by the general procedure. Some unchanged diol was present in the still residue. This peculiar behavior suggests that the oxetane ring is slowly cleaved by a stoichiometric reaction with *p*-toluenesulfonic acid, thus destroying the catalyst.

Acetals #27 and 27a. The acetals were prepared by the general procedure from tetrahydrofuran-2,2-dimethanol (Quaker Oats Co.) and separated readily by fractional distillation. The infrared spectrum of the lower-boiling acetal has a wealth of fine structure in the region 6.8–11.0 μ absent from that of the higher-boiling isomer. Bands at 11.4 w, 11.6 vw, 12.95 w, and 14.1 μs in the former are much weaker in the latter, while a strong band at 12.8 μ in the latter is absent from the former. The two isomers were essentially pure by VPC.

Acetal #28. Oxalic acid at room temperature converted an equimolar mixture of 3-formyl-3 methyloxetane[11] and neopentyl glycol in hexane to hemiacetal (infrared). Only half of the theoretical water was obtained on prolonged refluxing. *p*-Toluenesulfonic acid promoted loss of a small additional amount of water, but it was necessary to add several small portions of sulfuric acid to force the reaction to completion. A substantial amount of viscous residue remained after distillation of the acetal, showing that acid-catalyzed polymerization of the oxetane ring had taken place to some extent.

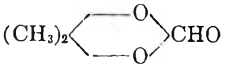
Acetal #31. The *p*-toluenesulfonic acid was not neutralized before distillation. A substantial amount of unchanged diol[12] was recovered, despite nearly complete removal of water. The yield of acetal was quantitative when allowance was made for unreacted diol.

Acetals #32 and 32a. Although an acetal of this structure has been reported,[13] there was no mention of stereoisomers; the reported physical constants (m.p. 46°, b.p. 98–103°/0.5 mm.) did not agree with ours. Our liquid isomer was undoubtedly contaminated with other materials; it exhibited infrared bands at 9.69, 10.22, 12.46, and 13.0 μvs not in the solid acetal, which in turn has bands at 8.10, 11.97, and 13.6 μ, as well as much stronger absorption at 11.56 and 11.71 μ.

Acetal #33. The isobutoxypivalaldehyde was a roughly distilled pyrolyzate of acetal #4, containing about 25% of unchanged acetal. The contaminants were readily separated from acetal #33 by fractionation, and the yield figure given in the Table takes these contaminants into account.

Acetal #39. 2,2-Diphenyl-3-hydroxypropanoic acid was prepared from diphenylacetic acid by the Ivanov reaction and reduced to 2,2-diphenyl-1,3-propanediol with lithium aluminum hydride by the method of Blicke.[14] The acetal prepared by the general procedure with a slight excess of isobutyraldehyde was contaminated with unchanged diol which was difficult to remove by crystallization. The crude acetal was dissolved in a minimum quantity of carbon disulfide, separated from the insoluble diol, and then recrystallized from hexane. Though the yield of crude material was high, purification was attended by considerable loss. Use of a larger excess of isobutyraldehyde would very likely have given better results.

Acetal #41. A mixture of 625 g. (6 moles) of neopentyl glycol, 625 g. (500 ml., 3.23 moles) of 30% aqueous glyoxal (Union Carbide Chemicals), 500 ml. of benzene, and 2.2 g. of *p*-toluenesulfonic acid was refluxed while removing the water. In 3.5 hr., 300 ml. was removed, and an additional 132 ml. distilled in 3 hr. more. Then 300 ml. of benzene was removed to pot temperature 127°. An infrared spectrum of the residue showed strong OH and medium carbonyl. An additional gram of *p*-toluenesulfonic acid was added and a further 56 ml. of water was collected in 2 hr. more. The OH and carbonyl absorptions were much weaker, but still present. The volatile materials were removed at 200 mm., pot temperature 100°, then 800 ml. of ethyl acetate was added to the hot residue. The mixture was chilled rapidly with stirring to yield 330 g. of diacetal, m.p. 161–163°. The analytical sample was crystallized twice more from ethyl acetate. Recrystallization and processing of the mother liquors yielded a total of 422 g. of acetal, 61% yield. The mother liquors were distilled, yielding 163 g. of pale yellow liquid, b.p. 73–108°/mm. The temperature then rose rapidly to 146°, and a second cut was obtained from 146–200°/1 mm., 150 g., containing a little of the solid acetal. The infrared spectrum of the first cut showed a weak OH, a very strong carbonyl at 5.75 μ (5.55 μsh), but only a trace of aldehyde CH absorption at 3.7 μ. There were also strong bands at 8.2, 9.0, and 9.7 μ, and a medium band at 12.65 μ doubtless resulting from the *m*-dioxane structure. No further effort was expended on identifying this liquid fraction. It may contain some monoacetal (although the absence of the 3.7 μ



band argues against this structure), or a glycolate ester of some type may be present.

Acetal #42. The starting material was either 1,1,3,3-tetraethoxypropane (Union Carbide Chemicals) or 1-methoxy-1,3,3-triethoxypropane (Kay-Fries). Either

(10) D. B. Pattison, *J. Am. Chem. Soc.*, 79, 3455 (1957).

(11) R. K. Miller, U. S. Pat. 2,923,645.

(12) 3,3-Dihydroxymethyl-1-butene from Celanese Corp.

(13) M. S. Newman, B. J. Magerlein, and W. B. Wheatley, *J. Am. Chem. Soc.*, 68, 2112 (1946).

(14) F. F. Blicke and H. Raffelson, *J. Am. Chem. Soc.*, 74, 1730 (1952). Our product melted at 105.7–106.2°, in agreement with these authors.

acetal reacted smoothly with two equivalents of neopentyl glycol in the presence of a little boron fluoride etherate. The theoretical quantity of ethanol (or methanol-ethanol mixture) was collected by slow distillation through a short column, and the residue was distilled directly in an apparatus for distilling solids.

Acetal #43. A mixture of 2,5-diethoxytetrahydrofuran (Union Carbide Chemicals), two equivalents of neopentyl glycol, and a little concentrated hydrochloric acid was warmed until homogeneous and allowed to stand overnight. The solid product was recrystallized from cyclohexane.

Acetal #44. A mixture of 1 mole of 2-ethoxy-3,4-dihydro-2-H-pyran (Union Carbide Chemicals), 2 moles of neopentyl glycol, and 5 ml. of concd. hydrochloric acid warmed spontaneously to about 60°; the clear solution rapidly became cloudy. On cooling, the product solidified. It was dissolved in about 1.2 l. of cyclohexane, 31 ml. of aqueous layer was separated, and the cyclohexane was dried with solid potassium carbonate. The solution was concentrated and crystal crops were taken.

Acetal #46. Reaction of one mole of trimethylolethane (2-hydroxymethyl-2-methyl-1,3-propanediol) (Heyden-Newport) and 1.5 moles of acetaldehyde in the presence of *p*-toluenesulfonic acid led only to the monoacetal #24. The monoacetal with *p*-toluenesulfonic acid and two additional moles of acetaldehyde liberated no more water. Finally, one-fourth mole of calcium chloride was added and the mixture allowed to stand for 3 days. Distillation then yielded the sesquiacetal which still had a weak hydroxyl absorption.

Acetals #52, 53, 54. The acid catalyst was removed before distillation, so that considerable pot residue (linear polyacetals) remained. The yields could have been improved by distillation in the presence of acid.[15]

WILMINGTON 99, DEL.

(15) K. C. Brannock and G. R. Lappin, *J. Org. Chem.*, 21, 1366 (1956).

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF LEPETIT S.P.A.]

Reactions with α-Substituted β-Propiolactones. I. 4,4-Disubstituted 2-Oxazolidinones

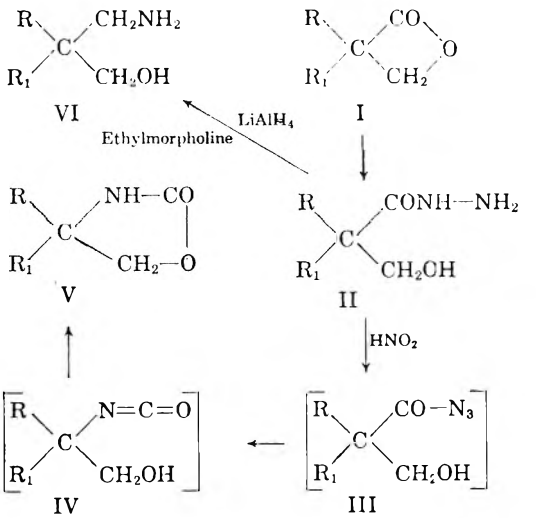
Research on Compounds Active on the Central Nervous System. XXIII[1a]

BRUNO I. R. NICOLAUS, LUIGI MARIANI, GIANGUALBERTO GALLO,[1b] AND EMILIO TESTA

Received October 31, 1960

Several 4-mono- and 4,4-disubstituted 2-oxazolidinones have been prepared by the action of nitrous acid on the substituted β-hydroxypropionic acid hydrazides, which were obtained by the action of hydrazine on β-propiolactones. This reaction also proves the constitution of these hydrazides. The infrared spectra of the 2-oxazolidinones are discussed. The reduction of the foregoing hydrazides by lithium aluminum hydride in ethylmorpholine leads to amino alcohols under cleavage of the N—N bond. Some preliminary pharmacological results are also reported.

During our investigation on compounds active on the central nervous system we carried out a new and general synthesis of α-substituted β-propiolactones.[2-4] In fact, if the easily obtained α-substituted β-aminopropionic acids are diazotized, β-propiolactones are obtained in good yield as colorless (alkyl derivatives) or greenish-yellow (aryl derivatives) fluids (only in a few cases solid compounds were obtained), having an itching action on skin and mucosae.[5] β-Lactones easily react with hydrazine hydrate[4,6] and substituted hydrazines, thus almost generally producing the hydrazides of α-substituted β-hydroxypropionic acids.[7] The latter compounds, the structure of which were previously suggested by chemical analysis (titration of the radical —CO—NH—NH_2, acetylation, etc.) and by infrared spectra (typical bands of the group —CO—NH— at 1650 cm.$^{-1}$),



(1) (a) Previous paper (note XXII): E. Testa, L. Fontanella, and V. Aresi, *Ann.*, in press. (b) Physical Chemical Department of Lepetit S.p.A.

(2) E. Testa, L. Fontanella, G. F. Cristiani, and F. Fava, *Ann.*, 619, 47 (1958).

(3) E. Testa, L. Fontanella, and L. Mariani, *J. Org. Chem.*, 25, 1812 (1960).

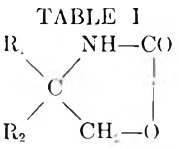
(4) E. Testa, L. Fontanella, G. F. Cristiani, and L. Mariani, *Ann.*, 639, 166 (1961).

(5) A good review on β-lactones has been given by Zaugg in *Org. Reactions*, VIII, 305 (1954).

(6) B. F. Goodrich, Brit. Patent 648,886; *Chem. Abstr.*, 45, 8031 (1951).

(7) The research in this field is under investigation. We have seen that under special conditions the corresponding α-substituted β-hydrazinepropionic acids may be isolated.

TABLE I



R_1	R_2	Formula	M.P. or B.P.	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Yield, %	Lit.
C_2H_5	C_2H_5	$C_7H_{13}O_2N$	160–170°/0.6 mm.	58.71	9.15	9.78	58.41	9.31	9.65	30	—
C_6H_5	C_6H_5	$C_{15}H_{13}O_2N$	178–179°	75.29	5.48	5.85	75.36	5.80	6.12	62.5	21
C_6H_5	CH_3	$C_{10}H_{11}O_2N$	78–79°	67.78	6.26	7.91	67.78	6.52	7.92	91	21
C_6H_5	C_2H_5	$C_{11}H_{13}O_2N$	80–81°	69.08	6.85	7.32	69.32	7.01	7.29	88.8	—
C_6H_5	$(CH_3)_2CH$	$C_{12}H_{15}O_2N$	139–140°	70.22	7.37	6.82	70.4	7.6	7.03	73.9	—
C_6H_5	$C_6H_5CH_2$	$C_{16}H_{15}O_2N$	106–107°	75.85	5.97	5.53	76.0	5.99	5.35	62	—
C_6H_5	H	$C_9H_9O_2N$	137–139°	66.24	5.56	8.58	66.13	5.71	8.20	40	21
iso-C_4H_9	H	$C_7H_{13}O_2N$	130–140°/0.2 mm.	58.72	9.15	9.78	58.9	9.31	10.04	28	—

show very irregular melting points. Consequently, it seemed desirable to gain further evidence for the proposed chemical structure.

In fact, by diazotization of II, azide III was obtained. III was not isolated, but extracted with benzene and by subsequent heating it lost nitrogen and isomerized to the isocyanate IV. This latter compound, by intramolecular reaction, gave in good yield 4-substituted oxazolidine-2-ones. Thus structure II, proposed for the compounds obtained by reaction of β-lactones with hydrazine, is definitively demonstrated.

The class of 2-oxazolidinones has already been investigated and can be obtained by two general methods of synthesis: a) the action of ethyl carbonate or phosgene on β-aminoethanol derivatives [8–10,21] and b) diazotization of hydrazides of β-hydroxypropionic acid derivatives.[13–18,20]

Some procedures are suitable for preparation of peculiar derivatives.[11–13,19,22,23] However only a few 4,4-disubstituted compounds are known.[10,13,21] Perhaps this is because β,β-disubstituted β-aminoethanol derivatives and α,α-disubstituted β-hydroxypropionic acid derivatives are obtained with difficulty. Particularly, the esters of the latter compounds, as we have already observed,[24] do not react with hydrazine.

As the synthesis of α-substituted β-propiolactones is a general one, the method for preparing 4-mono- and 4,4-disubstituted 2-oxazolidinones, which is the object of our present publication, can also become of general use. We have prepared eight 2-oxazolidinones by our method. They are listed in Table I. Five of them appear to be new, and except for two of them, they are crystalline, easily recrystallizable white solids.

The infrared spectra of the synthesized oxazolidine-2-ones were measured using a Perkin-Elmer Model 12 C single beam spectrophotometer fitted with a sodium chloride prism. The compounds were examined as such when liquid and in a Nujol mull when solid. The most typical bands shown by all the oxazolidine-2-ones were selected and assigned as arising from the vibrations of the chemical bonds of the structure. The limits in which fall the frequencies of the bands and the vibrations from which the bands take origin have been suggested in the following way according to Bellamy[25]: 3250–3200 cm.$^{-1}$ (NH stretching), 1750–1730 cm.$^{-1}$ (C=O stretching), 1280–1240 cm.$^{-1}$ (5-1 C—O stretching), 1060–1035 cm.$^{-1}$ (2-1 C—O stretching).

In connection with this work we submitted some hydrazides (α,α-diphenyl-, α,α-diethyl-, α-phenyl-α-ethyl-β-hydroxypropionic acid hydrazides), to the action of lithium aluminum hydride. In ether and tetrahydrofuran, even after prolonged refluxing, no reaction occurred and hydrazides were recovered unaltered; in ethylmorpholine at a temperature

(8) A. H. Homeyer, U. S. Patent 2,399,118; *Chem. Abstr.*, **40**, 4084 (1946).
(9) S. Fränkel and M. Cornelius, *Ber.*, **51**, 1662 (1918).
(10) A. H. Homeyer, U. S. Patent 2,437,390; *Chem. Abstr.*, **42**, 4613 (1948).
(11) J. Cason and F. S. Prount, *J. Am. Chem. Soc.*, **71**, 1218 (1949).
(12) A. T. Blomquist, U. S. Patent 2,485,855; *Chem. Abstr.*, **44**, 3516 (1950).
(13) W. J. Close, *J. Am. Chem. Soc.*, **73**, 95 (1951).
(14) E. D. Bergmann, *et al.*, *J. Org. Chem.*, **16**, 84 (1951).
(15) H. E. Zimmerman and J. English, *J. Am. Chem. Soc.*, **76**, 2285 (1954).
(16) D. Shapiro, *J. Org. Chem.*, **15**, 1027 (1950).
(17) W. S. Ide and R. Baltzly, *J. Am. Chem. Soc.*, **70**, 1084 (1948).
(18) A. E. Ardis, R. Baltzly, and W. Schoen, *J. Am. Chem. Soc.*, **68**, 591 (1946).
(19) E. Katchalski and Dov Ben Ishai, *J. Org. Chem.*, **15**, 1067 (1950).
(20) M. S. Newman and A. Kutner, *J. Am. Chem. Soc.*, **73**, 4199 (1951).
(21) M. S. Newman and W. M. Edwards, *J. Am. Chem. Soc.*, **76**, 1840 (1954).
(22) G. Gever, G. O'Keefe, G. Drake, F. Ebetino, J. Michels, and K. Hayes, *J. Am. Chem. Soc.*, **77**, 2277 (1955).
(23) G. F. Hennion and F. X. O'Shea, *J. Org. Chem.*, **23**, 662 (1958).
(24) R. Fusco and E. Testa, *Il Farmaco (Pavia), Ed. Sc.*, **12**, 828 (1957).
(25) L. K. Bellamy, *The Infrared Spectra of Complex Molecules*, Methuen and Co., London, 1958.

between 80° and 100° reduction of the carboxylic function took place, accompanied by the breaking of the N—N bond and the formation of β,β-disubstituted γ-amino alcohols. In the same solvent no reaction occurred when the temperature did not reach 70°. This behavior of primary hydrazides is different from that of secondary and tertiary ones, which leads to the corresponding hydrazines, and as far as we know, has not yet been described.

The prepared compounds, when subjected to broad pharmacological screening, showed some activity on the central nervous system. All compounds revealed convulsant properties, while some of them, at lower dosages, protected mice from electroshock seizures. The convulsant activity was particularly evident for 4,4-diethyl- 2-oxazolidinones, thus paralleling the observation made on the previously described 5,5-diethyl-tetrahydro-1,3-oxazine-2,4-dione.

EXPERIMENTAL

2-Oxazolidinones. To a stirred suspension of 0.01 mole of hydrazide (II) in 30 ml. of water at 0° a solution of 0.03 mole of hydrochloric acid in 30 ml. of water was added. Some of the resulting hydrochlorides were soluble, others were sparingly soluble or insoluble. The solution or suspension of the hydrazide hydrochlorides was diazotized with a solution of 0.011 mole of sodium nitrite in 10 ml. of water at 0–5°. The oil which precipitated during the reaction was extracted with benzene and dried over sodium sulfate. The clear solution was gently refluxed for 0.5 hr. While heating a gas evolution was observed. After concentration *in vacuo* the residue was recrystallized from ligroin, ether–petroleum ether, or ethyl acetate–petroleum ether. The two oily compounds (Table I. No. 1 and 8) were distilled by Ronco's technique.[26]

Reductions with lithium aluminum hydride. 1) γ-Amino-β,β-diphenylpropanol. A mixture of 8.5 g. of α,α-diphenyl-β-hydroxypropionic acid hydrazide, 7 g. of lithium aluminum hydride, and 70 ml. of ethylmorpholine was heated for 4 hr. at 100°. The mixture was cautiously treated with water and extracted with ether. After evaporation of the ether the residue was recrystallized from isopropyl ether; yield, 5.1 g.; m.p. 103–105°. After a further recrystallization from diluted ethyl alcohol the m.p. reached 105–106°.

Anal. Calcd. for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.52; H, 7.64; N, 5.87.

N,O-Diacetyl derivative m.p. 134–136°.

Anal. Calcd. for $C_{19}H_{21}NO_3$: C, 73.28; H, 6.80; N, 4.50. Found: C, 73.10; H, 7.04; N, 4.83.

Picrate, m.p. 213–216°.

Anal. Calcd. for $C_{21}H_{20}N_4O_8$: N, 12.28. Found: N, 11.93.

2) γ-Amino-β-phenyl-β-methylpropanol. A mixture of 9.7 g. of α-phenyl-α-methyl-β-hydroxypropionic acid hydrazide, 9.5 g. of lithium aluminum hydride, 150 ml. of ethylmorpholine, and 150 ml. of tetrahydrofuran was refluxed for 24 hr. and worked up further as described in 1). The oily residue was distilled according to Ronco's technique[26]; yield, 4.4 g., b.p. 120–128° at 0.6 mm.

Anal. Calcd. for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.80; H, 9.30; N, 8.63. Acetylation equivalent: 98.8%.

3) γ-Amino-β,β-diethylpropanol. A mixture of 8.0 g. of α,α-diethyl-β-hydroxypropionic acid hydrazide, 9.5 g. of lithium aluminum hydride and 150 ml. of ethylmorpholine was heated at 100–110° for 24 hr. and worked up further as described in 1). The oily residue was distilled according to Ronco's technique[26]; yield 2.3 g. b.p. 85–87° at 0.6 mm.

Anal. Calcd. for $C_7H_{17}NO$: C, 64.07; H, 13.06; N, 10.68. Found: C, 64.08; H, 13.30; N, 10.52. Acetylation equivalent: 99.1%.

Acknowledgment. We are indebted to Prof. R. Fusco for the very useful discussion on this subject during the experimental work; and to Miss. Dr. G. Pelizza and Mr. A. Restelli for organic and microanalysis.

We thank Prof. Dr. G. Maffii and co-workers of the Pharmacological Department of Lepetit S.p.A. for the preliminary pharmacological results, which will be published elsewhere.

MILAN, ITALY

(26) K. Ronco, B. Prijs, and H. Erlenmeyer, *Helv. Chim. Acta*, **39**, 2094 (1957).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ROCHESTER]

Synthesis and Properties of Bicyclic Oxetanes[1]

A. ROSOWSKY[2] AND D. S. TARBELL

Received September 13, 1960

The bicyclic oxetanes 7-oxabicyclo[4.2.0]octane and 1-oxaspiro[3.5]nonane were prepared by internal nucleophilic displacement reactions of the appropriate glycol derivatives. The structure assigned to these compounds is supported by their physical properties, as well as by chemical reactions typical of simpler oxetanes, such as acid-catalyzed methanolysis and lithium aluminum hydride reduction, which occur predictably by attack on the least substituted carbon.

Among models once considered in connection with the antibiotic fumagillin[3] were structures containing an oxetane unit attached to a cyclohexane ring. The present paper will be concerned with two of these models, 7-oxabicyclo[4.2.0]-octane[4,5] (I) and 1-oxaspiro[3.5]nonane (II), the latter of which has not been reported previously.

(1) This research was supported in part by Grant E-1138 of the U. S. Public Health Service.

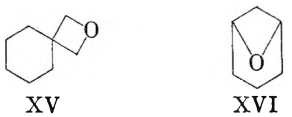
(2) Abbott Laboratories Fellow, 1959–1960.

(3) D. S. Tarbell *et al.*, *J. Am. Chem. Soc.*, **82**, 1005 (1960).

(4) (a) The synthesis of this compound was reported in a preliminary account to the 136th A. C. S. Meeting, Atlantic City, N. J., Sept. 1959, page 67P of the abstract; see also Ref. 5. (b) For the results of a similar study, published after the submission of this manuscript, see H. B. Henbest and B. B. Millward, *J. Chem. Soc.*, 3575 (1960).

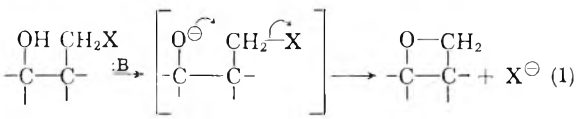
I II

The literature dealing with bicyclic oxetanes has not been very extensive. Rupe and Klemm[4] claimed to have prepared I by acid-catalyzed intramolecular dehydration of 2-hydroxymethylcyclohexanol, but gave only scant chemical proof for their structure. In our hands several attempts to effect such cyclizations were unsuccessful. An oxetane closely related to II is 2-oxaspiro[3.5]nonane (III), which was recently reported by two groups of investigators.[6,7] The elusive bridged oxetane 6-oxabicyclo[3.1.1]heptane (IV) has thus far defied synthesis in at least four laboratories.



XV XVI

Synthesis of oxetanes. The general method followed by us in the preparation of I and II can be represented by equation (1),



(1)

where: B is a base and X = —Cl or Bs (*p*-bromobenzenesulfonate). It has been stated[7,8] that chlorohydrins are precursors of choice in this type or internal nucleophilic displacement, and our experience is in accord with this view, as will be seen below.

The starting materials for the above cyclizations, accessible in a straightforward manner, were subjected to the reactions shown in Charts I and II.

The glycol III, previously shown to possess a *cis* configuration[11] was converted to monobrosylate IV and then to *cis*-2-chloromethylcyclohexanol (V) with lithium chloride in ethanol.[8] Cyclization to I could be accomplished in any of three ways: 1) treatment of IV with potassium *tert*-butoxide in *tert*-butyl alcohol at 0°,[9] 2) treatment of IV with sodium hydride in ether at reflux temperature, or 3) treatment of V with solid potassium hydroxide at elevated temperatures, with simultaneous removal

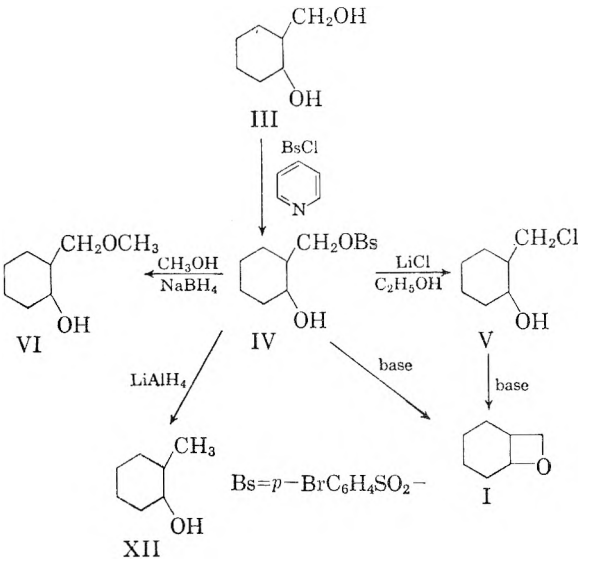


Chart I. Synthesis of 7-oxabicyclo[4.2.0]octane

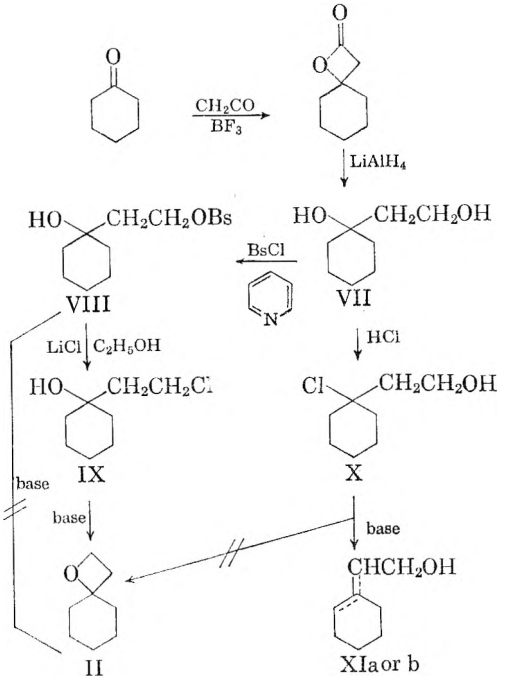


Chart II. Synthesis of 1-oxaspiro[3.5]nonane

of the product from the reaction zone.[6,8] Evidence of the 1,3-cleavage reaction observed in similar instances by other workers[9,10,12] was obtained by infrared spectroscopy for the reaction of IV with potassium hydroxide or sodium methoxide in methanol.

For the preparation of II, cyclohexanone was treated with ketene in ether, using a catalytic amount of boron trifluoride etherate, as described by Nazarov and Kuznetsov.[13] The resulting β-lactone was not purified, but was reduced directly

(5) H. Rupe and O. Klemm, *Helv. Chim. Acta*, 21, 1538 (1938).

(6) S. Searles, Jr., E. F. Lutz, and M. Tamres, *J. Am. Chem. Soc.*, 82, 2932 (1960).

(7) E. L. Wittbecker, H. K. Hall, Jr., and T. W. Campbell, *J. Am. Chem. Soc.*, 82, 1218 (1960).

(8) M. F. Clarke and L. N. Owen, *J. Chem. Soc.*, 2103, 2108 (1950).

(9) R. B. Clayton and H. B. Henbest, *J. Chem. Soc.*, 1982 (1957).

(10) F. V. Brutcher, Jr., and H. J. Cenci, *Chem. & Ind.*, 1295 (1957).

(11) A. T. Blomquist and J. Wolinsky, *J. Am. Chem. Soc.*, 79, 6025 (1957).

(12) S. Searles, Jr., R. G. Nickerson, and W. K. Witsiepe, *J. Org. Chem.*, 24, 1839 (1959).

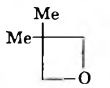
(13) I. N. Nazarov and N. V. Kuznetsov, *J. Gen. Chem., U.S.S.R.*, 29, 754 (1959).

with lithium aluminum hydride to the glycol VII. The monobrosylate VIII of this glycol was converted to 1-(β-chloroethyl)cyclohexanol (IX) with lithium chloride in ethanol,[8] and this was in turn cyclized to II without prior purification by heating over potassium hydroxide as above.[6,8] When the related chlorohydrin X, prepared from VII by shaking with concentrated hydrochloric acid, was heated with potassium hydroxide, however, the product isolated appeared to be an unsaturated alcohol XIa or XIb, or a mixture of the two. The monobrosylate VIII, in contrast to IV, could *not* be cyclized with sodium hydride, polymerization occurring instead.

Physical properties. Oxetanes I and II are highly volatile compounds with a characteristic odor and a tendency to foam on distillation.[14] They are readily identified by intense absorption bands in the 10 μ region of the infrared, in accord with the findings of Searles, *et al.*[6,15] A bathochromic shift has been associated[6] with strain of the oxetane ring, and so the noticeable displacement of the 10 μ band of I and II relative to trimethylene oxide caused no surprise. The position of this band, along with other physical properties, is shown in Table I, three other oxetanes being included for comparison.

TABLE I

PHYSICAL PROPERTIES OF OXETANES

Compound	B.P.	n_D	Infrared, Main Peak
	44.5–45° (9–10 mm.)	1.4625[a]	10.4 μ
	78–79° (34–35 mm.)	1.4520[a]	10.4 μ
	64° (14 mm.)[c]	1.4602[b]	10.1 μ[b]
	70° (1 atm.)[d]	1.3878[d]	10.4 β[d]
	76–78° (1 atm.)[d]	1.3956[e]	10.2 μ[d]

[a] n_D^{25}. [b] n_D^{20}, taken from Ref. 6. [c] Taken from Ref. 7. [d] n_D^{25}, taken from Ref. 15. [e] n_D^{25}, taken from Ref. 16.

Oxetanes I and II were further characterized by their NMR spectra, which are summarized in Table II. Trimethylene oxide itself has been reported to have a τ-value[17] of 5.4 for the α-CH_2 protons.[18a] The τ-values, splitting patterns, and

TABLE II

NMR SPECTRA OF OXETANES

Compound	Protons	τ-values[18]	Splitting
	—CH_2—O	5.41, 5.1	Quartet, quartet
	—CH—O	6.10	Quartet
	—CH—CH_2	7.35	Multiplet
	—CH_2—O	5.68	Triplet
	—CH_2—CH_2	7.80	Triplet
	—CH_2—O	5.09, 5.61	Quartet, quartet
	—CH—CH_2	7.15	Multiplet

relative areas were in harmony with the structures I and II. Also included for comparison is the compound 2-methyl-1-oxabicyclo[2.2.0]hexane, recently reported by Srinivasan.[18b]

Chemical reactivity. In order to place I on a rough reactivity scale a number of its reactions were studied. These reactions, shown in Chart III, indicate that I probably possesses no unusual strain properties relative to simpler oxetanes previously studied.[19]

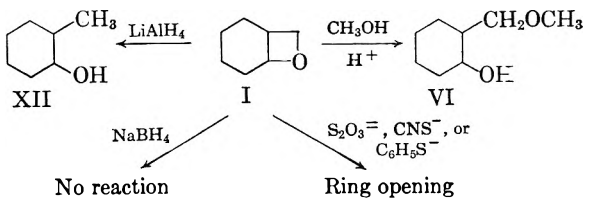


Chart III. Reactions of 7-oxybicyclo[4.20]octane

Methanolysis[19a,c] of I was facile when acid-catalyzed, but more difficult in base, although alkaline cleavage did occur in a sealed tube at 175°. The product could be converted to a six-membered cyclic ketone (1710 $cm.^{-1}$) on oxidation with chromic oxide in pyridine or acetone, which readily indicated the probable position of the hydroxyl group. Furthermore the product was shown, by mixed melting point determination on the *p*-nitrobenzoate, to be indentical with *cis*-2-methoxymethylcyclohexanol (VI) obtained earlier (IV → VI, see Chart I). Methanolysis therefore occurs by rupture of the CH_2—O bond in I. Vapor phase chromatography showed the acid-catalyzed reaction to be at least 90% selective.[30]

(14) See ref. 28 for experimental precautions dictated by these physical properties.

(15) G. M. Barrow and S. Searles, Jr., *J. Am. Chem. Soc.*, 75, 1175 (1953).

(16) L. F. Schmoyer and L. C. Case, *Nature*, 183, 389 (1959).

(17) τ-values are based on an arbitrary assignment of τ = 10.0 for tetramethylsilane. See G. Van Dyke Tiers, *J. Phys. Chem.*, 62, 1151 (1958). The τ-value for trimethylene oxide was computed from the value given in reference 18a, in which chemical shifts are expressed in δ-units relative to water.

(18) (a) H. S. Gutowsky, R. L. Rutledge, M. Tamres, and S. Searles, Jr., *J. Am. Chem. Soc.*, 76, 4242 (1954). (b) R. Srinivasan, *J. Am. Chem. Soc.*, 82, 775 (1959).

(19) See for example (a) S. Searles, Jr., and C. F. Butler, *J. Am. Chem. Soc.*, 76, 56 (1954); (b) S. Searles, Jr., K. A. Pollart, and E. F. Lutz, *J. Am. Chem. Soc.*, 79, 948 (1957); (c) A. W. Adams, *et al.*, *J. Chem. Soc.*, 559 (1959).

Reductive cleavage with lithium aluminum hydride[19b] proceeded smoothly in refluxing ether, but not at 0°. The product was shown by mixed melting point determination on the *p*-nitrobenzoate, to be identical to *cis*-2-methylcyclohexanol (XII) prepared by another route (IV → XII with lithium aluminum hydride, see Chart I). The reaction appeared to be at least 90% selective, according to gas chromatographic analysis.[30] Sodium borohydride in boiling methanol likewise left the oxide ring intact. The reduction of I thus took place in predictable fashion, rupture occurring between oxygen and the least substituted carbon, as already noted by Searles.[19b] That oxetane I was unaffected by sodium borohydride points to the likelihood that I is not an intermediate in the reaction IV → VI (see Chart I). On the other hand, it is not possible at this time to exclude the possibility that I is an intermediate in the reaction IV → XII (see Chart I), since Goering and Serres[20] obtained the isomeric bicyclic ether 6-oxabicyclo [3.2.1] octane (XIV) by treating the monotosylated XIII of *cis*-3-hydroxymethylcyclohexanol with lithium aluminum hydride. If I were initially formed from IV it would of course be further reduced to XII in the presence of excess reagent.

XIII XIV

The attack of several other nucleophilic reagents on the oxide ring of I was examined. Thus, sodium thiosulfate reacts only to a small extent in the color reaction employed by Ross[21] and by Freeman, *et al.*[22] as a qualitative test for cyclic ethers of various sizes. In addition it was found that the more strongly nucleophilic thiophenoxide and isothiocyanate ions caused more extensive ring cleavage, although no detailed product analyses were made.

EXPERIMENTAL[23]

cis-2-Hydroxymethylcyclohexanol (III) was prepared from methyl salicylate by catalytic hydrogenation over Raney nickel at 1800 p.s.i. and 125° in the presence of traces of alkali, followed by reduction with lithium aluminum hydride. Milder hydrogenating conditions gave more satisfactory results in our hands than did those described in the literature.[11,24] Alternately, cyclohexanone could be converted into IV by the route reported by Smissman and Mode.[25] The viscous glycol, b.p. 80–83° (0.12–0.15 mm.), crystallized slowly and yielded a bis-*p*-nitrobenzoate, m.p. 132.5–133° (lit.[25] m.p. 133.5–.34°).

1-(β-Hydroxyethyl)-cyclohexanol (VII).[13] Ketene was bubbled at a moderate rate for 6 hr. through a solution of 100 ml. of cyclohexanone and 1 ml. of boron trifluoride etherate in 200 ml. of dry ether at −10° to 0°. After washing with 5% sodium carbonate and rinsing with water, the ether solution was dried over magnesium sulfate and evaporated, yielding a crude product whose infrared spectrum showed a strong β-lactone peak at 5.52 μ[26] and a moderate peak at 5.86 μ because of unchanged cyclohexanone. The β-lactone was not purified further, but was reduced directly with excess lithium aluminum hydride. After the usual workup and distillation, three fractions were obtained: a) 21.0 g. of cyclohexanol, b.p. 65–75° (0.2–0.3 mm.), n_D^{25} 1.4632, from reduction of unchanged cyclohexanone; b) 5.4 g. of an intermediate fraction, b.p. 75–90° (0.2–0.3 mm.), n_D^{25} 1.4645; and c) 80.1 g. of VII (58% based on initially used cyclohexanone, 74% after correction for recovered cyclohexanol), b.p. 90–105° (0.2–0.3 mm.), n_D^{25} 1.4835 (lit.[27] b.p. 112–114° (2 mm.), n_D^{26} 1.4850). Redistillation gave pure VII, b.p. 82–85° (0.03 mm.), n_D^{24} 1.4838.

cis-2-Hydroxymethylcyclohexanol monobrosylate (IV) was prepared in nearly quantitative yield by the conventional method (see for example Refs. 8–10 and 20). The product was an oil which crystallized slowly on standing in the refrigerator, care being exercised to remove all traces of pyridine. Darkening can be averted by avoiding unnecessary heating in workup. An analytical sample, m.p. 36–40° (softening at 33° was prepared by dissolving a small amount of the crude waxy product in ether, and adding sufficient petroleum ether (b.p. 30–60°) to cause crystallization upon cooling.

Anal. Calcd. for $C_{13}H_{17}O_4Br$: C, 44.70; H, 4.87. Found: C, 44.87; H, 5.05.

1-(β-Hydroxyethyl)cyclohexanol monobrosylate (VIII) was prepared in nearly quantitative yield by the conventional method.[8–10,20] The oily product tended to darken on standing and was utilized as soon as possible. Although some crystals could be formed in the cold they were low melting, and no analytical sample was made.

cis-2-Chloromethycyclohexanol (V) was prepared according to Clarke and Owen[8] by refluxing a solution of IV and lithium chloride in 95% ethanol, evaporating the solvent, and taking up the product in ether. The chlorohydrin was a liquid with a characteristic halogenic odor, and a tendency to darken which made itdesirable to use it quickly in the next step. Characterization was accomplished through the crystalline *p*-nitrobenzoate, m.p. 45–47°.

Anal. Calcd. for $C_{14}H_{16}O_4NCl$: C, 56.38; H, 5.38. Found: C, 56.18; H, 5.70.

1-(β-Chloroethyl)cyclohexanol (IX) was prepared in nearly quantitative yield from VIII with lithium chloride in refluxing 95% ethanol.[8] The chlorohydrin, possessing the typical halogenic odor, was used without distillation.

1-(β-Hydroxyethyl)cyclohexyl chloride (X) was prepared by stirring 10.6 g. (0.0736 mole) of glycol VII with 80 ml. of concd. hydrochloric acid for 8 hr. at room temperature, diluting with water, extracting with petroleum ether, rinsing with saturated sodium bicarbonate solution and water, drying over anhydrous magnesium sulfate, and evaporating, to obtain 10.6 g. of crude product. Distillation resulted in extensive elimination of hydrogen chloride, with recovery of only 6.8 g. of product, which turned yellow on standing. In subsequent runs the chlorohydrin was subjected to the next

(20) H. L. Goering and C. Serres, Jr., *J. Am. Chem. Soc.*, 74, 5908 (1952).

(21) W. C. J. Ross, *J. Chem. Soc.*, 2257 (1950).

(22) G. G. Freeman, *et al.*, *J. Chem. Soc.*, 1105 (1959).

(23) All melting points and boiling points are uncorrected. Elemental microanalyses were performed by T. Montzka of this laboratory, as well as Microtech, W. Manser, and F. Pascher. N. M. R. spectra were taken on a 60 Mc Varian instrument by Y. Kawazoe. Infrared spectra were taken on a Model 21 Perkin-Elmer spectrophotometer.

(24) H. C. Ungnade and F. V. Morriss, *J. Am. Chem. Soc.*, 70, 1898 (1948).

(25) E. S. Smissman and R. A. Mode, *J. Am. Chem. Soc.*, 79, 3447 (1957).

(26) L. J. Bellamy, *Infrared Spectra of Complex Molecules*, Wiley, New York, 1958, page 188.

(27) D. Papa, H. F. Ginsberg, and F. J. Villiani, *J. Am. Chem. Soc.*, 76, 4441 (1954).

reaction without prior purification. A small purified sample of X had n_D^{24} 1.4868.

7-Oxabicyclo[4.2.0]octane (*I*). A. To a solution of 225 g. (0.64 mole) of monobrosylate IV in 500 ml. of dry ether in a three-necked flask equipped with a stirrer and reflux condenser were added in small portions 40 g. (0.83 mole) of 50% sodium hydride-mineral oil dispersion (Metal Hydrides, Inc., Beverly, Mass.). Addition was continued occasionally over a period of about 2 days with gentle refluxing. Further addition caused no visible hydrogen evolution. The dense white precipitate of sodium *p*-bromobenzenesulfonate and unchanged sodium hydride was filtered, and the clear yellow filtrate was extracted once with 100 ml. of water. After drying over anhydrous sodium sulfate and solvent removal through a Vigreux column *without suction* or excessive heat, the dark orange solution remaining was distilled.[28] After a small forerun of solvent the product was collected in a receiver, cooled in a Dry Ice/acetone bath. Redistillation yielded the analytical sample, b.p. 44.5–45.0° (9–10 mm.), n_D^{25} 1.4625 (lit.[5] b.p. 54° (11 mm.)). The yield of crude oxetane I was 35.6 g., or 49%.

Anal. Calcd. for $C_7H_{12}O$: C, 75.00; H, 10.41. Found: C, 74.53; H, 10.53.

B. To a solution of 4 g. of potassium in 100 ml. of *tert*-butyl alcohol was added 12.2 g. (0.0350 mole) of IV. A dense yellow-white precipitate formed rapidly. The mixture was allowed to stand in the refrigerator for 12 hr., then warmed to room temperature and filtered under suction (cooling the suction flask to −10° to minimize evaporative losses.) The solid thus obtained was dissolved in water, and the aqueous solution was extracted with several portions of ether. The combined ether extracts were added to the yellow *tert*-butyl alcohol filtrate, and after filtering off an additional quantity of white solid the solution was distilled at atmospheric pressure until all the ether and alcohol were removed. The semisolid residue was triturated with ether, and the combined ether triturates were dried over anhydrous sodium sulfate and evaporated at atmospheric, pressure, yielding a pale yellow liquid that gave on distillation the desired oxetane I, b.p. 47–49° (15 mm.). The yield of crude product was 1.85 g., or 47%.

C. A mixture of 3.40 g. (0.0231 mole) of IX and 5 g. of powdered (not dried) potassium hydroxide was heated in an apparatus suitable for removing product from the reaction zone and trapping it in a receiver cooled at −70°. The oil bath temperature was gradually increased from 90° to 150° after 1 hr., and the volatile products were collected and examined. Two phases were present, one of which was water, conveniently removed with a little alumina (Woelm, neutral, activity I). Distillation yielded the desired oxetane I, whose infrared spectrum matched those of previously prepared samples. The yield obtained by this procedure, 1.7 g. or 66%, was superior to the others described above.

cis-2-Methoxymethylcyclohexanol (VI). A. To 11.5 g. (0.033 mole) of IV in 100 ml. of absolute methanol were added 3–4 g. of sodium borohydride by inverse addition. After several hours the reaction mixture was cooled and the precipitate of fine white crystals was filtered off. The filtrate was evaporated, and the residue triturated with several portions of ether. The combined ether triturates were dried over anhydrous sodium sulfate and evaporated, leaving a pale yellow liquid with a pleasing odor. Distillation afforded 1.65 g., or 35%, of colorless product, b.p. 92–95° (12 mm.).

Anal. Calcd. for $C_8H_{16}O_2$: C, 66.67; H, 11.11. Found: C, 66.25; H, 10.80.

A *p*-nitrobenzoate, m.p. 110.5–112.5°, was prepared.

Anal. Calcd. for $C_{15}H_{19}O_5N$: C, 61.48; H, 6.49. Found: C, 61.34; H, 6.66.

The 3,5-dinitrobenzoate, m.p. 87–88°, was prepared but not analyzed.

B. A solution of 5.0 g. (0.045 mole) of I in 25 ml. of absolute methanol containing 2 drops of 95% aqueous sulfuric acid was stirred at 35–40° for 30 hr. Most of the methanol was distilled off and a small amount of solid sodium bicarbonate added to neutralize the acid. Distillation through a Vigreux column yielded a small forerun of methanol followed by 3.8 g. of product (VI), b.p. 92–96° (12–13 mm.), and an additional 0.9 g., b.p. 40–44° (0.3–0.4 mm.). The total yield was 4.7 g., or 67%, n_D^{25} 1.4624.

The *p*-nitrobenzoate, m.p. 110–112°, was undepressed when mixed with the authentic sample prepared above.

cis-2-Methylcyclohexanol (XII). A. A solution of 11.7 g. of IV in 50 ml. of dry ether was added dropwise to an ice cold stirred suspension of 1.5 g. of lithium aluminum hydride in 50 ml. of dry ether. After 48 hr. and the usual workup there was obtained a colorless liquid, which on distillation yielded 2.2 g., or 59%, of the desired product (XII), b.p. 67–69° (17 mm.).

That XII is the *cis* isomer was demonstrated by means of its infrared spectrum which contained all the bands characteristic for this isomer,[29] and of a derivative, the *p*-nitrobenzoate, m.p. 56.5–57° (lit.[29] m.p. 55–56°).

B. To a stirred ice cold suspension of 1.15 g. (0.03 mole) of lithium aluminum hydride in 50 ml. of dry ether was added dropwise a solution of 2.24 g. (0.02 mole) of I in 25 ml. of dry ether. After 56 hr. of refluxing, the product was isolated in the usual manner and distilled, yielding 1.2 g., or 53%, of pure XII, b.p. 67–68° (13 mm.).

The *p*-nitrobenzoate, m.p. 56–57° (lit.[29] m.p. 55–56°), was undepressed when mixed with the authentic derivative prepared earlier. The 3,5-dinitrobenzoate, m.p. 101–102° (lit.[29] m.p. 99–100°), was likewise prepared.

Gas chromatographic analysis of the crude reduction product showed the reaction to be at least 90% selective.[30]

1-Oxaspiro[3.5]nonane (II). A mixture of 6.70 g. (0.0411 mole) of crude IX and 2 g. of 50% sodium hydride–mineral oil dispersion were stirred magnetically in just enough ether to maintain fluidity. Gas evolution was noticeable. After 1–2 hr. the reaction mixture was warmed gently to remove the solvent. Distillation into a trap cooled in a Dry Ice/acetone bath yielded 2.60 g. of volatile material, b.p. 60–70° (22 mm.), n_D^{25} 1.4520, the bath temperature being raised gradually to 130° during distillation. The brown residue was triturated with ether, and the ether solution, treated as above, yielded an additional 0.2 g. of product. Redistillation of the combined product fractions yielded the desired oxetane II, b.p. 78–79° (34–35 mm.), n_D^{25} 1.4521. The total yield before redistillation was 2.8 g., or 55%. The analytical sample was prepared by a further distillation from metallic sodium.

Anal. Calcd. for $C_8H_{12}O$: C, 76.19; H, 11.11. Found: C, 76.44; H, 11.35.

When VIII was treated with sodium hydride in refluxing tetrahydrofuran (it was not possible to dissolve VIII in ether) cyclization did not occur, no volatile products aside from solvent being isolable. When an intimate mixture of VIII and sodium hydride–mineral oil dispersion was warmed

(28) The high volatility of the oxetanes, in spite of their relatively high boiling points necessitated cautious workup. Solvent take-off on the rotary evaporator was avoided. During vacuum distillation the receivers were cooled at −70° in order to minimize evaporative losses. Precise boiling point determinations, especially on small samples, were rendered difficult both by the tendency of the oxetanes to distill evaporatively, without visible boiling, and by their tendency to froth at the boiling temperature. Gas chromatography revealed traces of diethyl ether in the product even after redistillation.

(29) E. Eliel and C. A. Lukach, *J. Am. Chem. Soc.*, 79, 5986 (1957).

(30) A portion of this work was done by Miss Joanne Groves in the course of her undergraduate research, University of Rochester, 1960. Gas chromatographic analyses were done on a five foot silicone column at a temperature of about 75°.

gradually with stirring to about 110° in the usual apparatus for simultaneous product take-off, only polymerization took place, a trace of water and unidentified, unpleasant smelling liquid being recovered from the trap.

When chlorohydrin X was treated with potassium hydroxide under the conditions used previously,[6] only an unsaturated alcohol was isolated, b.p. 105–106° (20 mm.), n_D^{24} 1.4807, which could have been either or both of the two possible isomers XIa or b. No further effort was made to clarify this point, however, since no oxetane was obtained.

ROCHESTER 20, N. Y.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

2,2′,4,4′,6,6′-Hexamethyl-4,4′-bi-4H-pyran[1,2]

KENNETH CONROW[2a] AND PHILLIP C. RADLICK

Received October 17, 1960

The title compound results from the action of strong organic reducing agents on the 2,4,6-trimethylpyrylium cation. It is believed that this is the first example of a bipyran in which the rings are linked by a single bond and the first example of an alkyl-substituted, nonfunctional 4H-pyran.

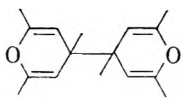
Hafner's elegant preparation of azulene derivatives involves the formation of the seven-membered ring by fusion of a five carbon chain from a pyrylium salt onto the five-membered ring of sodium cyclopentadienide.[3] It was hoped that substitution of the disodium salt of cyclooctatetraene[4] for the cyclopentadienide would not alter the sense of the reaction, so that there would be obtained hydrocarbons with fused seven- and eight-membered rings and extended conjugated double-bond systems.

The reaction between the disodium salt of cyclooctatetraene and 2,4,6-trimethylpyrylium perchlorate was modeled after Hafner's method for the preparation (*ca.* 80%) of the purple 4,6,8-trimethylazulene. The substance isolated (*ca.* 20%) was colorless and proved to have the molecular formula $C_{16}H_{22}O_2$. The possibility that the product arose from the interaction of one dianion of cyclooctatetraene ($C_8H_8=$), one trimethylpyrylium cation ($C_8H_{11}O^+$), and one hydronium ion (H_3O^+) (during work-up) was eliminated by the observation that other strong reducing agents, sodium diphenylketyl or the sodium anthracene complex, also act on the trimethylpyrylium ion to give the product (2 and 22% yield, respectively). Thus it is evident that the product arises from the trimethylpyrylium cation by a reductive dimerization process:

$$2C_8H_{11}O^+ + 2e^- = C_{16}H_{22}O_2$$

The best preparative method yet found for the substance (54% yield) involves the use of the potassium salt of cyclooctatetraene with trimethylpyrylium fluoroborate.

The accumulated evidence shows that the dimer has the structure, 2,2′,4,4′,6,6′-hexamethyl-4,4′-bi-4H-pyran (I).



I

The substance is very nonpolar; it is eluted from alumina before cyclooctatetraene and before anthracene. It exhibits only tail absorption in the quartz ultraviolet region. Thus there are no conjugated double bonds. A perbenzoic acid titration showed the presence of four double bonds. A C-methyl determination showed the presence of at least five methyl groups.

The most instructive single piece of evidence was the NMR spectrum which showed three sharp singlets at τ values of 5.73, 8.25, and 9.10 with areas in the approximate ratio 4:12:6, respectively. The singlet character of these resonance lines requires that no two carbons which bear hydrogen be linked directly to each other. The resonance occurs at the expected[5] shifts for vinyl hydrogens, allylic hydrogens and methyl hydrogens on saturated carbon, except that the vinyl hydrogens absorb at somewhat higher field than usual, probably because they are well shielded by adjacent methyl groups[6] and are vinylogous to the oxygen atom.[7]

During the early stages of the investigation of the structure of this dimer, two misleading results were obtained which considerably impeded our

(1) This research was supported by a Socony Mobil Oil Co. Grant-in-Aid. Grateful acknowledgement of this support is hereby made.

(2) Presented at the A.C.S. Southern California Regional Meeting, Dec. 3, 1960.

(2)(a) New address: Department of Chemistry, Kansas State University, Manhattan, Kansas.

(3) K. Hafner and H. Kaiser, *Ann.*, 618, 140 (1958).

(4) (a) W. Reppe *et al.*, *Ann.*, 560, 15 (1948); (b) See T. J. Katz, *J. Am. Chem. Soc.*, 82, 3784, 3785 (1960); *J. Chem. Phys.*, 32, 1873 (1960) for a description of recent evidence about the structure of this dianion and references to earlier investigations.

(5) G. V. D. Tiers, Minnesota Mining and Manufacturing Co. Handy Pocket Guide to Characteristic Nuclear Resonance Shielding Values, τ, for Hydrogen Bonded to Carbon.

(6) N. F. Chamberlain, *Anal. Chem.*, 31, 56 (1959); esp. Fig. 4 and p. 69.

progress toward elucidation of the correct structure. One was the observation of a strong absorption in the infrared at 1705 cm.$^{-1}$ which we took to be indicative of a ketonic function. Secondly, catalytic hydrogenation in glacial acetic acid with perchloric acid over platinum gave an uptake of about three moles of hydrogen and led to the belief that the dimer had three carbon-carbon double bonds. (The crude hydrogenation product was ketonic, not hydroxylic.)

Closer scrutiny has given evidence that these deductions were erroneous. Attempts to obtain confirmatory evidence for the ketonic function by means of the formation of derivatives (oxime, 2,4-dinitrophenylhydrazone, semicarbazone, α-benzylidene derivative), oxidation (sodium hypoiodite), and reduction (sodium borohydride and lithium aluminum hydride) all failed. The fact that I was recovered unchanged from the basic reaction media (the last four cases) indicates clearly that there is *no* ketone function in the molecule. Thus we are forced to ascribe the absorption at 1705 cm.$^{-1}$ to the enol ether groups of the 4-H-pyran skeleton.

Unfortunately, the literature does not appear to record the infrared spectra of any close models. However, one can make a rough prediction of the enol ether absorption in I if one assumes that the effect of substituents in an enol ether absorption is parallel to the effect of substituents in an ester carbonyl absorption. It is known that formates absorb near 1723 cm.$^{-1}$ and acetates near 1740 cm.$^{-1}$ and that ethyl acetate absorbs at 1740 cm.$^{-1}$ and vinyl acetate at 1776 cm.$^{-1}$[8] Thus substitution of methyl for hydrogen on the carbonyl raises the absorption by 17 cm.$^{-1}$ and introduction of a double bond in the alcohol portion of the ester raises the absorption by 36 cm.$^{-1}$ Under the assumption, and since a number of dihydropyrans with hydrogen on the 2-position absorb near 1650 cm.$^{-1}$,[9] one would predict that a 2-methyl-4-H-pyran would absorb at 1650 + 17 + 36 = 1703 cm.$^{-1}$.[10]

In an effort to obtain a more closely related model compound, 2,4,4,6-tetraphenyl-4H-pyran, the only nonfunctional uncondensed pyran which appears to have been reported,[11] was prepared and found to absorb at 1675 cm.$^{-1}$ While there does not seem to be a convenient way of estimating the amount of lowering of the enol ether absorption frequency by the phenyl substituents on the basis of spectra which appear in the literature, it is clear that an alkyl substituted analog will absorb at higher frequency than this phenyl substituted model.

While these observations cannot be reasonably adduced in direct support of structure I, they do at least indicate that I will absorb at higher frequency than the available model compounds and thus provide permissive evidence for this formulation.

An estimation of the number of double bonds by means of perbenzoic acid indicated, as mentioned above, that there are actually four double bonds in the molecule I. Apparently, the misleading results from catalytic hydrogenation are due to acid catalyzed opening of enol ether functions at least to some extent to give ketonic compounds which resisted further hydrogenation, thus accounting for less than theoretical uptake. The crude hydrogenation product does show strong absorption in the 1700–1710 cm.$^{-1}$ region expected for saturated ketones. Attempts to effect hydrogenation in neutral ethanol or ethyl acetate failed. Attempts at the acid hydrolysis of the enol ether groups gave intractable, easily polymerized oils which gave intractable mixtures of 2,4-dinitrophenylhydrazones. This behavior is not surprising, since the anticipated tetraketone would be capable of a great variety of intra- and intermolecular condensation reactions.

However, when the acid hydrolysis mixtures were treated with base while still fairly dilute, it was possible to isolate various products which appear to have arisen by intramolecular condensation reactions. Four such products were isolated in the pure state and characterized by means of their melting point, analyses, infrared and ultraviolet spectra. Since one can draw over two hundred different compounds (counting stereoisomers) containing only 5-, 6-, and 7-membered rings which could logically arise from the intermediate tetraketone *via* intramolecular aldol reactions, Michael additions, ketalizations and the like, we have made no attempt to pursue the characterization of these substances further.

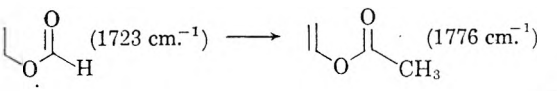
Attempts to produce other examples of 2,4,4,6-tetraalkyl-4H-pyrans by the reaction of trimethylpyrylium perchlorate with organometallic com-

(7) G. V. D. Tiers, Minnesota Mining and Manufacturing Co. N.M.R. Summary, gives the τ value for the corresponding hydrogen in dihydropyran as 5.46, which is to be compared with a value of 4.7 for ordinary disubstituted olefins.[6] The only other possible type of hydrogen which absorbs in this region is that α to an ether oxygen, but all mechanistically reasonable products of this sort would show multiplet absorption bands.

(8) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, 2nd Ed., New York, 1958, pp. 179–180, 182.

(9) C. W. Smith, D. G. Norton, and S. A. Ballard, *J. Am. Chem. Soc.*, **73**, 5270 (1951); Sadtler Standard Spectra No. 381B, Sadtler Res. Labs., Phila., Pa.

(10) Schematically, the hypothetical process



results in an increase in carbonyl frequency of 53 cm.$^{-1}$ The analogous process

should result in a similar increase in absorption of the double bond chromophore: 1650 + 53 = 1703 cm.$^{-1}$

(11) Peres de Carvalho, *Ann. Chim.*, [11] **4**, 449 (1935).

pounds were unavailing. A reaction between 2,4,6-triphenylpyrylium perchlorate and the disodium salt of cyclooctatetraene gave no product analogous to I. Attempts to couple 2,4,6-trimethylpyrylium perchlorate by means of inorganic reducing agents (cuprous chloride, sodium in liquid ammonia or potassium in refluxing tetrahydrofuran) failed.

EXPERIMENTAL[12]

I from trimethylpyrylium perchlorate and disodiocyclooctatetraene. To a well stirred suspension of 3.68 g. of sodium sand (0.16 mole) in 200 ml. of freshly dried tetrahydrofuran in a 1-l. flask equipped with a mercury sealed stirrer, reflux condenser, addition funnel, and a nitrogen inlet, was added 10.0 ml. of cyclooctatetraene (0.08 mole). The mixture was refluxed gently under nitrogen until the sodium had completely dissolved. Two hours usually sufficed; the color of the solution was brown, purple, or orange in different runs. The mixture was cooled to room temperature and 14.72 g. (0.056 mole) of trimethylpyrylium perchlorate[13] added. The color changed to deep red. Most of the tetrahydrofuran was distilled off before the mixture was worked up by the addition of water and extraction with petroleum ether. The orange extracts were dried, concentrated, and chromatographed on alumina. The early pentane fractions were colorless and gave colorless crystals, m.p. 113–118°. Later pentane fractions were yellow and had a strong odor of cyclooctatetraene, but gave rise to additional crystals. Further purification was effected by solution in hot ethanol followed by slow crystallization by removal of the solvent at room temperature, m.p. 120–121.0°. Total yield *ca.* 20%.

Anal. Calcd. for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00; mol. wt., 246.34. Found: C, 78.34, 78.45; H, 8.81, 8.82; mol. wt., 230 (Rast). C-methyl: 4.26.

Spectral data: Ultraviolet: tail absorption only: $\epsilon_{220\ m\mu}^{95\%\ C_2H_5OH}$ 6300. *Infrared:* ν_{max}^{KBr} 3202w, 2930m, 2895m, 2840w, 1705s, 1660w, 1625w, 1450m, 1430m, 1380s, 1360m, 1330w, 1290s, 1225s, 1155s, 1080m, 1050m, 1040w, 1025m, 1000m, 965m, 910m, 895m, 865m, 805s, 675w. In chloroform solution there are four absorptions of about equal intensity in the carbonyl region: 1705, 1685, 1660, 1645 cm.$^{-1}$ Similar loss of strong singlet in the solid state spectrum and appearance of multiple bands in the solution spectrum occurs in the 1225 and 1155 cm.$^{-1}$ regions.

N.M.R.: Two spectra were taken: one in carbon tetrachloride with tetramethylsilane as internal standard and the other with toluene as an external reference. The τ values calculated from the former spectrum were 5.73, 8.25, and 9.10 while the areas determined with a planimeter were in the ratio 3.2:11.9:6.9 and 4.4:11.7:5.8, respectively. The peaks were sharp, symmetrical singlets with widths at their half-height corresponding to 2.5, 3.7, and 2.2 c.p.s., respectively. Any spin-spin coupling, then, must have J values less than about 2.

I from trimethylpyrylium fluoroborate and dipotassiocyclooctatetraene. To 200 ml. of freshly dried and distilled tetrahydrofuran under nitrogen in a 500-ml. flask equipped with mercury sealed stirrer, reflux condenser, addition funnel, and nitrogen inlet, was added 3.91 g. (0.10 mole) of potassium metal followed by 5.75 g. (0.055 mole) of cyclooctatetraene. A spontaneous exotherm occurred as the potassium dissolved and the solution assumed a deep red orange color. After external heating for a few minutes the potassium had completely dissolved. The mixture was cooled to room temperature and 21.0 g. of trimethylpyrylium fluoborate (0.10 mole) in tetrahydrofuran suspension was added from the addition funnel. A slight exotherm accompanied the formation of a white precipitate and lightening of the red color. The bulk of the tetrahydrofuran was removed by distillation at atmospheric pressure and the residue treated with water and petroleum ether (b.p. 60–70°) The aqueous layer was extracted with three additional portions of petroleum ether, the petroleum ether layers combined, dried over magnesium sulfate, and concentrated *in vacuo*. The residue was dissolved in 60 ml. of hot absolute ethanol and allowed to cool. There crystallized 5.45 g. (22 mmoles, 44%) of material, m.p. 112–116°, after collection and washing with cold 95% ethanol. The mother liquor gave additional crystals on dilution with water which were recrystallized from absolute ethanol to give an additional 1.25 g. (10%), m.p. 110–114°, identical with earlier sample by infrared spectrum.

I from trimethylpyrylium perchlorate and sodium diphenylketyl. To 0.92 g. (40 mmoles) of sodium sand in 100 ml. of tetrahydrofuran under nitrogen was added 7.28 g. (40 mmoles) of benzophenone and the mixture stirred until the sodium had dissolved. Then 3.68 g. (14 mmoles) of trimethylpyrylium perchlorate was washed in with more dry tetrahydrofuran. The mixture was stirred and refluxed an hour during which time the color changed to brown. Tetrahydrofuran was distilled off, water was added, the mixture was extracted with petroleum ether and the extracts dried, concentrated, and chromatographed as before. The first pentane eluate yielded a few mg. (*ca.* 2%) of I, m.p. 117–119°, identical with the earlier sample by mixture melting point and infrared spectra.

I from trimethylpyrylium perchlorate and sodioanthracene. To 0.70 g. of sodium sand (30 mmoles) in 150 ml. of dry tetrahydrofuran was added 5.3 g. (30 mmoles) of anthracene. The mixture was stirred and refluxed under nitrogen until the sodium had dissolved and a deep blue solution was obtained. Trimethyl pyrylium perchlorate (5.2 g., 18 mmoles was added in small portions; the color changed to red. After 20 min. at reflux, most of the tetrahydrofuran was removed by distillation and water was added to the residue. The solid was boiled with 65 ml. of absolute ethanol and filtered while hot. The insoluble material, m.p. 215–217°, was anthracene. A crop of less pure anthracene, m.p. 200–215°, was obtained upon cooling the filtrate. The mother liquor was evaporated to dryness *in vacuo*, taken up in petroleum ether and chromatographed on alumina. The first two pentane fractions yielded 0.48 g. (22%) I, m.p. 115–119° and 108–114°, identical with the earlier sample by mixture melting point and infrared spectra.

Perbenzoic acid oxidation of I. A benzene solution of perbenzoic acid was prepared according to Braun[14] using the modifications of Kolthoff.[15] A 5.03-ml. aliquot of the solution was equivalent to 36.70 ml. of 0.1022*N* sodium thiosulfate solution. A solution of 0.1001 g. (0.406 mmole) of I in 10 ml. of benzene was treated with 5.03 ml. of the perbenzoic acid solution and allowed to stand at 25° for 3 days. Then the excess perbenzoic acid was decomposed with a solution of 3 g. of potassium iodide and 5 ml. of glacial acetic acid in 50 ml. of water and the liberated iodine was found to require 4.92 ml. of the standard thiosulfate solution. Thus, 3.98 moles of perbenzoic acid had reacted with each mole of I.

Catalytic hydrogenation of I. A suspension of 35 mg. of platinum oxide in 25 ml. of glacial acetic acid containing 2 drops of 70% perchloric acid was prereduced before 266.1 mg. (108 mmoles) of I was added. A total of 82.6 ml. of hydrogen was absorbed (27.5°, 747 mm.) during about 4.5

(12) Spectral determinations were made by Miss Donna Karasek on a Perkin-Elmer model 21 and on a Cary model 11. The values reported for the infrared absorptions are internally consistent, but have not been corrected for machine errors. The microanalyses were done by Miss Heather King. Melting points are corrected.

(13) O. Diels and K. Alder, *Ber.*, **60**, 716 (1927).

(14) G. Braun, *Org. Syntheses*, Coll. **Vol. I**, 431 (1941).

(15) I. M. Kolthoff *et al.*, *J. Polymer Sci.*, **2**, 199 (1947).

hr.; this corresponds to an uptake of 3.06 moles of hydrogen per mole of I. A similar experiment in which the perchloric acid was omitted, resulted in the uptake of 2.79 moles of hydrogen per mole of I during 2 hr. The products were inhomogeneous oils with strong absorption in the infrared at 1700–1710 cm.$^{-1}$

Hydrolysis of I. Two putatively identical hydrolyses were performed. A solution of 1.25 g. (5.0 mmoles) of I, 5.0 ml. of water, and ten drops of concd. perchloric acid in 25 ml. of dioxane was allowed to stand for 3 days. Then 5 ml. of 10% sodium hydroxide solution was added and the mixture heated to reflux for 1 hr. The resulting mixture was poured into ether and water, the water layer acidified, extracted an additional time with ether, and the combined ether layers washed with saturated saline and dried over magnesium sulfate. The ether was removed *in vacuo*, the residue taken up in petroleum ether (60–80°), concentrated, and chromatographed on activated neutral alumina. From the first of the two hydrolyses (done on one-fifth the above scale) two crystalline substances were obtained in about 11 and 6% yields, respectively: A, from the pentane eluates, m.p. 50–60°, a ketone (ν_{max}^{KBr} 1690 cm.$^{-1}$). Vacuum sublimation gave partial separation; the less volatile material formed needles m.p. 69.0–69.5°. Ultraviolet: tail absorption only, $\epsilon_{220}^{95\%\ C_2H_5OH} \sim 670$. A trace of more volatile material was probably compound C, below.

Anal. Calcd. for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.60; H, 9.32.

B, from the 1:1 pentane:ether eluates, m.p. 70–85° Two recrystallizations from petroleum ether gave platelets, m.p. 121–123°, a hydroxy ketone (ν_{max}^{KBr} 3400, 1697 cm.$^{-1}$). Ultraviolet: weak absorption only, $\epsilon_{220}^{95\%\ C_2H_5OH} \sim 530$; $\epsilon_{280}^{95\%\ C_2H_5OH} \sim 45$.

Anal. Calcd. for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.88; H, 9.05.

From the second hydrolysis two different crystalline substances were obtained in roughly 10% yield each:

C, from the 4:1 pentane:ether eluates, m.p. 81–82°. Vacuum sublimation gave well formed rhombs, m.p. 82.0–83.5°, a hydroxy (?) ketone [ν_{max}^{KBr} 1690 cm.$^{-1}$, 3400 (weak-water in potassium bromide ?)]. Ultraviolet: tail absorption only, $\epsilon_{220}^{95\%\ C_2H_5OH} \sim 690$.

Anal. Calcd. for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.86; H, 9.32.

D, from wet ether eluates, m.p. 80–115°. Sixfold crystallization from petroleum ether gave a very poor recovery of thick needles, m.p. 140–141°, an unsaturated hydroxy ketone (ν_{max}^{KBr} 1638, 3400 cm.$^{-1}$). Ultraviolet: $\lambda_{max}^{95\%\ C_2H_5OH}$ 236 mμ (ϵ 9500). The behavior on crystallization made it evident that the crude material contains at least one other substance more soluble in petroleum ether than D which has not been obtained in a pure state.

Anal. Calcd. for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 77.92; H, 8.95.

LOS ANGELES 24, CALIF.

[CONTRIBUTION FROM RESEARCH LABORATORY, UNION CARBIDE CONSUMER PRODUCTS CO., DIVISION OF UNION CARBIDE CORP.]

Chlorination of Aromatic Hydrocarbons by Cupric Chloride. I. Anthracene

JUDITH C. WARE AND EARL E. BORCHERT

Received July 1, 1960

A study has been made of the reaction of cupric chloride with anthracene to yield 9-chloro- and 9,10-dichloroanthracenes, cuprous chloride and hydrogen chloride. An analogous reaction occurred with cupric bromide. The available evidence is consistent with a polar mechanism. A comparison is made of the reactivity of cupric chloride with that of other metal chlorides, some of which are known to act as chlorinating agents.

Several metal chlorides, among them ferric chloride,[1] antimony pentachloride,[2] and aluminum chloride,[3] can effect chlorination of aromatic hydrocarbons. Considerable evidence has been adduced[1a] to suggest that the reactions proceed by a polar mechanism wherein the metal halide acts as an electrophile. It has been found that cupric chloride also functions as a chlorinating agent, yielding the products to be expected for electrophilic chlorination:

$$Ar—H + 2\ CuCl_2 \longrightarrow Ar—Cl + 2\ CuCl + 2\ HCl$$

The results of a study of the scope and nature of the reaction are presented here.

RESULTS AND DISCUSSION

When a mixture of anthracene and anhydrous cupric chloride was heated at 200°, a yellow solid rapidly sublimed out of the reaction vessel. Hydrogen chloride was evolved as well. Investigation showed the yellow material to consist of a mixture of chloroanthracenes.

The nature of the reaction was explored by further experiments with anthracene (I), which was selected because its chlorination products were relatively well characterized and easily separated. 9-Chloroanthracene (II) and 9,10-dichloroanthracene (III) were isolated. The reaction product was treated by removing the solvent, if any, by steam distillation, dissolving the salts in hydrochloric acid, and extracting the residue with benzene. Where a single product was obtained, it was purified by recrystallization and, occasionally, chromatography. If a mixture was obtained, its infrared

(1) (a) P. Kovacic and N. O. Brace, *J. Am. Chem. Soc.*, **76**, 5491 (1954) and references cited therein; (b) P. Kovacic, R. W. Stewart, and F. J. Donat, Abstracts of Papers, 131st Meeting of the American Chemical Society, Miami, Fla., April, 1957, p. 71-O.

(2) (a) J. W. Mellor, *A Comprehensive Treatise on Inorganic and Theoretical Chemistry*, Vol. IX, Longmans, Green and Co., New York, N. Y. (1929), p. 489; (b) P. Kovacic and A. K. Sparks, Abstracts of Papers, 136th Meeting of the American Chemical Society, Atlantic City, N. J. (September 1959), p. 23-P.

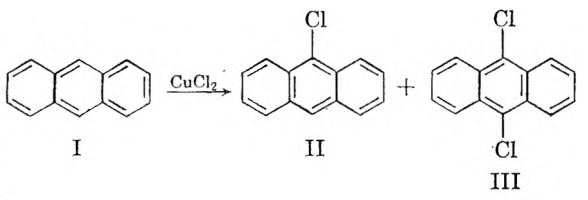
(3) A. Zinke, F. Funke, and N. Lorber, *Ber.*, **60**, 577 (1927).

TABLE I

Moles $CuCl_2$/ Moles (I)	Solvent	Temp.	Time, Hr.	Nature of Product
1.0	None	100	0.17	Mixture containing II and III
1.0	Nitrobenzene	100	1.5	Trace, II
2.0	Nitrobenzene	210	3	Mixture containing 96% II and 4% III
6.4	Nitrobenzene	210	24	III (57% yield)
8.4	Nitrobenzene	210	96	III (69% yield)
8.4	Chlorobenzene	132	72	Mixture containing 18% II and 82% III
8.4	Chlorobenzene	132	96	Mixture containing 13% II and 87% III
8.4	Dimethyl-formamide	153	72	Mixture containing 75% II and 25% III
8.0[a]	Nitrobenzene	210	6	III (57% yield)

[a] 0.004 mole anhydrous aluminum chloride was added to 0.01 mole anthracene.

spectrum was analyzed and results expressed as mole per cent of II and III. The results are presented in Table I.



I II III

It was found that limitation of the amount of cupric chloride did not restrict the reaction to monochlorination; rather, a mixture of products was obtained. Nitrobenzene was the preferred solvent, presumably because of its higher boiling point. It may be noted that a reaction took place in dimethylformamide, the only solvent used in which cupric chloride was soluble. The yield of III in this instance was lower than that observed when chlorobenzene was used as a solvent, which could be attributed to reduced activity of the cupric chloride as a result of its interaction with the solvent. Cupric chloride is known to complex with many oxygen- or nitrogen-containing compounds.[4]

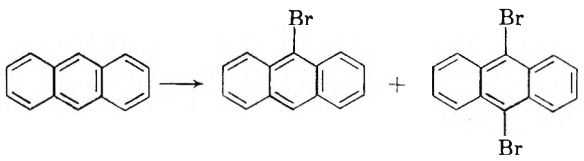
The nature of the products was confirmed by oxidation. When a portion of the chloroanthracene mixture from the solid reaction listed in Table I was treated with chromic oxide in acetic acid, 9,10-anthraquinone was obtained. It would be expected that only I, II, or III could yield this product.

In separate experiments, nitrobenzene was refluxed for several days with both cupric and cuprous chlorides. The nitrobenzene was subsequently distilled unchanged. Its infrared spectrum was also unchanged, suggesting that in neither instance had any reaction occurred between the solvent and copper halide.

The inference that cuprous chloride was formed in the reaction was based upon the fact that when water was added to the crude product of a reaction run without solvent and most of the organic matter extracted with benzene (not all of it would dissolve), a white solid settled out of the aqueous layer. The solid dissolved in concentrated hydrochloric acid. Such behavior is characteristic of cuprous chloride. When a solvent was used, the cuprous chloride, white initially, darkened on standing and gave an analysis too high in copper. It is possible that it suffered photodecomposition in the presence of hydrogen chloride.[5]

The reaction product from a solid reaction was investigated more closely by chromatography in an attempt to discover the nature of any other products. The chloroanthracenes were followed by anthracene when cyclohexane was the eluant. Most of the residual material could then be eluted with increasing proportions of benzene and a small amount of dark-colored, high-melting solid was thus obtained. Its infrared spectrum showed absorption that was in part characteristic of anthraquinone and carbazole, which were known to be trace contaminants in the anthracene used. Nothing else was identified and there was no indication that 9,9′-bianthryl, a possible product of a free radical reaction, had been formed.

It was then demonstrated that under the same conditions, cupric bromide could react with anthracene to yield 9-bromoanthracene (IV) and 9,10-dibromoanthracene (V). The results are found in Table II. Yields were so low that these reactions were not studied further.



IV V

It does not seem likely that the cupric chloride underwent preliminary dissociation and that chlorine was the actual halogenating agent. Equilibrium pressure data, listed in Table III, show that the extent of dissociation should not have been significant under the conditions used.

(4) *Gmelins Handbuch der Anorganischen Chemie*, 60B-I, p. 281 ff. (1958).

(5) See ref. (4), p. 222, for a discussion of the light sensitivity of CuCl.

TABLE II

Moles $CuBr_2$/ Mole (I)	Solvent	Temp.	Time, Hr.	Nature of Product
2.0	None	75	0.5	Trace IV and V
4.0	Nitroben-zene	210	75	V (22% yield)
4.0	Nitroben-zene	210	96	V (26% yield)

TABLE III

$CuCl_2$[a]	Temp.	371	411	421	
	P (mm.)	1.2	4.0	7.2	
$CuBr_2$[b]	Temp.	166.0	180.5	203.5	222.8
	P (mm.)	3.1	6.8	22.0	55.4

[a] W. Biltz and W. Fischer, *Z. anorg. u. allgem. Chem.*, 166, 290 (1927). [b] C. C. Jackson, *J. Chem. Soc.*, 99, 1066 (1911).

The situation with cupric bromide is not so clear-cut, since it dissociates at lower temperatures. Perhaps the significant amount of bromine present at the temperature of refluxing nitrobenzene accounted for the low yield of V (26% at best) and the difficulty of purifying it. Bromine would have been far more reactive than cupric bromide and might have induced the tar formation which was observed.

Kovacic and Brace[1a] found that aluminum chloride catalyzed the reaction between chlorobenzene and ferric chloride. In the present instance, however, aluminum chloride itself can undergo a vigorous reaction with anthracene in the presence of nitrobenzene. It has been reported[6] that when nitrobenzene is added to a 4:1 mixture of aluminum chloride and anthracene, a carbonaceous material is formed. This finding was confirmed and even under far more moderate conditions, no chlorination would be demonstrated. It was surprising, therefore, to find that when aluminum chloride was added to the warm reaction mixture (anthracene, cupric chloride, nitrobenzene), a vigorous reaction ensued and III was formed more rapidly and in good yield. The catalytic effect of aluminum chloride provides additional evidence in support of a polar mechanism for the reaction.

A cursory investigation of the effect of other metal chlorides on anthracene in nitrobenzene was also undertaken for the sake of comparison. Brief contact with antimony pentachloride at 5° was sufficient to cause extensive reaction, the principal product being III, which was separated chromatographically.[7]

Reaction with ferric chloride was extremely vigorous and only by working at 5° was it possible to obtain trace amounts of the simple chloroanthracenes II and III. Phosphorus pentachloride reacted smoothly at room temperature to form pure III in 60% yield. Mikhailov and Promyslov, working in benzene, obtained only a 54% yield of crude III after six days.[8]

Although the formation of chlorination products by stannic chloride at elevated temperatures could be demonstrated, the product was chiefly an intractable tar. With mercuric chloride, no reaction was observed at 100° and 150°, and at 210° apparently only tar formation occurred.

There is no way of evaluating the reduction potentials of these chlorides under the experimental conditions used. It does not seem valid to compare data obtained in aqueous solution where solvation would play a significant role; at the same time, insufficient data are available to calculate the standard free energy changes in most instances. It is likely also that some of these chlorides interact with the nitrobenzene. Black ferric chloride, for example, dissolves to form an orange solution, a color characteristic of hydrated (*i.e.*, complexed) iron (III).

Finally, from a consideration of reduction potentials[9] in aqueous solution and of standard free energies of formation of phosphorus pentachloride and mercuric chloride and the assumption that large relative differences would still carry over to nonaqueous media, a rough grouping in the order of oxidizing ability is possible.

$$\begin{matrix} Cl_2 & & \\ PCl_5 & & HgCl_2 \\ SbCl_5 & > & CuCl_2 > AlCl_3 \\ FeCl_3 & & SnCl_4 \end{matrix}$$

The reactivity of these metal halides (and chlorine) as aromatic chlorinating agents appears, then, to parallel their oxidizing ability. Activity as a Friedel-Crafts catalyst appears to offer no particular advantage in this instance.

EXPERIMENTAL

Melting points were taken in a heated copper block and are uncorrected. Microanalyses were by Huffman Microanalytical Laboratories, Wheatridge, Colo., or Micro-Tech Laboratories, Skokie, Ill. Infrared spectra were taken by J. Schnell and N. Galer.

Materials. Anhydrous cupric chloride was obtained by heating the dihydrate in an oven at 110° overnight. The brown solid thus obtained was kept in the oven until used. The solvents used were Fisher Reagent chemicals. In initial experiments, the nitrobenzene was distilled, but it was later found that there was no difference in products if it was undistilled. Eastman Kodak white label anthracene was used.

Infrared spectra were taken on a Perkin-Elmer Model 21 double beam instrument. Usually only absorption maxima at wave lengths greater than 10.00 μ are given because they proved most useful for purposes of identification.

Inertness of nitrobenzene to cupric and cuprous chloride. In two separate experiments, 50 ml. of nitrobenzene was refluxed for 72 hr. with 2 g. of cupric or cuprous chloride. The mixtures were protected from moisture but not from air.

(6) R. Scholl and C. Seer, *Ber.*, 55, 330 (1922).

(7) J. Kommandeur and J. C. Ware, unpublished work.

(8) B. M. Mikhailov and M. Sh. Promyslov, *J. Gen. Chem. (U.S.S.R.)*, 20, 338 (1950); *Chem. Abstr.*, 44, 6408.

(9) N. A. Lange, *Handbook of Chemistry*, Ninth Edition, pp. 1212–1218, 1576–1630 (1956).

After this time, the solid was filtered off and was unchanged in appearance. The infrared spectrum of the nitrobenzene was unchanged in both instances. The solvent from the cupric chloride experiment was distilled unchanged. That from the cuprous chloride experiment was treated with 6*N* hydrochloric acid, but no organic material was extracted.

General procedure for the reaction of cupric halide with an aromatic hydrocarbon. A. No solvent used. The reactants were ground, mixed, and placed in a round-bottom flask which was heated with a mantle. The flask was equipped with an air condenser, thermometer, and drying tube. Air was not excluded. The mixture was stirred from time to time. When the reaction was over, an excess of 6*N* hydrochloric acid was added and the mixture was extracted with benzene. There was always some dark-colored material formed that would dissolve in neither phase. The benzene extract was treated with Norit activated carbon and then the solvent was removed by evaporation. If the product was to be chromatographed, it was dissolved in cyclohexane; the substrate was silica gel. Usually, cyclohexane was used to develop the chromatogram as well. Toward the end, increasing proportions of benzene were sometimes needed. It was found convenient to equip the chromatographic columns with Teflon stopcocks, which require no lubrication.

B. Solvent used. The equipment was the same as in A; a stirrer was used as well. The hydrocarbon was dissolved in the solvent prior to the addition of copper halide. At the end of the reaction, after addition of a few milliliters of concentrated hydrochloric acid, the solvent was removed by steam distillation and the product treated as before.

Action of cupric chloride on anthracene. A. Initial experiments. One gram of anthracene and 10 g. of cupric chloride was mixed without solvent in a beaker and placed on the hot plate (*ca.* 200°). After a few minutes, a yellow solid began to sublime out of the beaker and hydrogen chloride was evolved. After about 10 min., the mixture was cooled and extracted with benzene; the benzene was removed by evaporation and the residual yellow-brown solid chromatographed. First eluted was a yellow solid, m.p. 150–160°. After recrystallization from cyclohexane and then acetone, it melted from 166–186°. The infrared spectrum showed it to consist, in part, of 9,10-dichloroanthracene. Additional absorption at 12.41, 11.88, 11.58, and 10.46 μ remains unexplained; it could not be attributed to anthracene, 9-chloroanthracene, anthraquinone, or bianthryl and is assumed to be caused by a more highly chlorinated anthracene. Later experiments were carried out at lower temperatures in order to reduce the degree of chlorination.

B. 9-Chloroanthracene (II). A mixture of 1.78 g. (0.01 mole) of anthracene and 1.35 g. (0.01 mole) of cupric chloride was heated in 50 ml. of nitrobenzene at 100° for 1.5 hr. This product was chromatographed and the first fraction, m.p. 92–96°, was recrystallized from cyclohexane and then alcohol to give flat yellow plates, m.p. 104.5–105.5° (lit.,[10] m.p. 103°).

Anal. Calcd. for $C_{14}H_9Cl$: C, 79.06; H, 4.26. Found: C, 79.00; H, 4.32.

A portion of the cyclohexane-soluble portion of a similar reaction was oxidized with chromic anhydride in glacial acetic acid.[11] From 0.3 g. of material, 0.21 g. of a quinone, m.p. 286°, was obtained. The melting point was undepressed by admixture with 9,10-anthraquinone.

C. 9,10-Dichloroanthracene (III). A mixture of 1.78 g. (0.01 mole) of anthracene and 11.4 g. (0.084 mole) cupric chloride was refluxed with nitrobenzene for 96 hr. The product was treated with Norit and recrystallized from cyclohexane and then alcohol to yield 1.7 g. (69%) of yellow needles, m.p. 209.5–211° (lit.,[12] m.p. 209°).

Anal. Calcd. for $C_{14}H_8Cl_2$: Cl, 28.7. Found: Cl, 28.1.

Analysis of mixtures II and III was based upon two infrared absorption maxima at 11.44 and 11.98 μ, which were found to be characteristic of II. II possessed additional maxima at 15.03, 13.85, 12.98, 11.27 and 10.65 μ. Absorption maxima for III occurred at 14.37, 13.42, and 10.58 μ.

Examination of the inorganic product. A mixture of 3.56 g. (0.02 mole) of anthracene and 0.50 g. (0.0037 mole) cupric chloride was placed in *ca.* 100 ml. of nitrobenzene and stirred and refluxed. A white solid appeared rapidly in the reaction mixture which, after a few hours, began to darken. When the solid was filtered out after 3 days, it was gray in color.

Anal. Calcd. for CuCl: Cu, 64.2. Found: Cu, 67.8.

Action of cupric bromide on anthracene. A. 9,10-Dibromoanthracene (V). A mixture of 2.23 g. (0.01 mole) of cupric bromide and 1.78 g. (0.01 mole) of anthracene was heated at 75° for 30 min. When the product was chromatographed, the first fraction consisted of bright yellow needles, m.p. 221–223°. They were rechromatographed and the first few fractions recrystallized from alcohol, m.p. 221–222° (lit.,[13] m.p. 226°).

Anal. Calcd. for $C_{14}H_8Br_2$: Br, 47.6. Found: Br, 47.7.

B. 9-Bromoanthracene (IV). When the reaction (A) was repeated without solvent, the chromatographic separation was not satisfactory and the first fraction had the m.p. 190–210°. This was rechromatographed and the second fraction (0.17 g.) consisted of light yellow needles, m.p. 99–100°. After recrystallization from alcohol and cyclohexane, the material melted at 97–101°. The filtrate from the second recrystallization, however, deposited tiny needles, which were collected and washed with petroleum ether, m.p. 101.5–102° (lit.,[10] m.p. 100°).

Anal. Calcd. for $C_{14}H_9Br$: C, 65.39; H, 3.53. Found: C, 65.26; H, 3.57.

Action of aluminum chloride on anthracene. Two grams of anthracene was mixed with 8 g. of aluminum chloride. When 25 ml. of nitrobenzene was added, a vigorous reaction ensued; the mixture became hot and a black, tarry material was formed. After a few minutes, 6*N* hydrochloric acid was added and the nitrobenzene removed by steam distillation. There remained 3.0 g. of black, powdery residue. It did not melt below 400° and burned slowly, leaving no ash.

Anal. Found: C, 78.87; H, 3.87; O, 2.27; N, 3.22; Cl, 9.50.

Reaction of anthracene with phosphorus pentachloride. A mixture of 1.78 g. (0.01 mole) of anthracene and 17.0 g. (0.082 mole) of phosphorus pentachloride was placed in 50 ml. of nitrobenzene at room temperature. A yellow-orange solution immediately formed. After stirring for 1.5 days, the mixture was hydrolyzed with sodium hydroxide and the solvent removed by steam distillation. A yellow-brown solid remained. After treatment with Norit and recrystallization from cyclohexane, 1.47 g. (60%) of 9,10-dichloroanthracene, m.p. 211°, was obtained.

Anal. Calcd. for $C_{14}H_8Cl_2$: C, 68.04; H, 3.26; Cl, 28.70. Found: C, 68.23; H, 3.25; Cl, 28.67.

Reaction of anthracene with ferric chloride. Only tar was produced when 1.78 g. (0.08 mole) of anthracene was refluxed with 13.04 g. (0.08 mole) of anhydrous ferric chloride in 100 ml. of nitrobenzene for 2 days. The same results were obtained when such a mixture was heated at 100° or when the reaction was run at room temperature. When the components were held at 5° for 45 min., it was possible to extract a small portion of dark brown solid from the product, although it was mostly tar. When the extract was chromatographed, only a small fraction of it could be eluted with cyclohexane. There was insufficient material to be weighed accurately. It was possible to obtain a few infrared spectra, however, and from these, it was evident that initially III was eluted which was followed by mixtures of II and anthracene. The products were not examined further.

(10) A. G. Perkin, *Chem. N.*, **34**, 145 (1876).

(11) C. Marschalk and C. Stumm, *Bull. Soc. chim. France*, **15**, 418 (1948).

(12) C. Graebe and C. Liebermann, *Ann.*, **160**, 137 (1871).

(13) I. M. Heilbron and J. S. Heaton, *Org. Syntheses*, Coll. Vol. I, p. 207 (1941).

The action of stannic chloride on anthracene. A. A solution of 1.78 g. (0.01 mole) of anthracene and 20.8 g. (0.08 mole) of stannic chloride in 100 ml. of nitrobenzene was heated at 90° for 3 hr. The mixture turned red-brown as soon as the stannic chloride was added. It was hydrolyzed with sodium hydroxide solution and organic material was removed as well as possible by extraction with benzene. The solvent was removed by a steam distillation, during which some of the solids distilled also. When the nitrobenzene was removed from the distillate by vacuum distillation, 0.12 g. of pale yellow crystals remained. The infrared spectrum showed it to be anthracene plus traces of II and III. The residue consisted of 1.45 g. of dark brown solid in which the infrared spectrum corresponded to that of anthracene and a small amount of II.

B. The reaction was repeated under reflux for 24 hr. When 6*N* sodium hydroxide was added to the dark brown solution, a black tar formed. The mixture did not separate and about half of it was steam distilled. Again, the products distilled as well. A few milligrams of yellow crystals in the condenser was judged to be III on the basis of the infrared spectrum. The residue was an intractable tar which was not examined further.

Reaction of anthracene with mercuric chloride. A mixture of 1.78 g. (0.01 mole) of mercuric chloride was heated in 100 ml. of nitrobenzene at 100° for 24 hr. The solvent was removed by steam distillation, and the residue was found to be unchanged anthracene on the basis of its melting point and infrared spectrum. When the procedure was repeated, heating at 150° for 5 days, the anthracene, except for some tar formation, was unchanged. When the components were heated at reflux for 5 days, only a "tar," a high-melting black solid, was recovered.

Acknowledgment. The authors wish to thank J. O. Kochler for advice and encouragement during the course of this work.

CLEVELAND 1, OHIO

[CONTRIBUTION FROM RESEARCH LABORATORY, UNION CARBIDE CONSUMER PRODUCTS CO., DIVISION OF UNION CARBIDE CORP.]

Chlorination of Aromatic Hydrocarbons by Cupric Chloride. II. Reactivity of Some Polynuclear Compounds

JUDITH C. WARE AND EARL E. BORCHERT

Received July 1, 1960

A study of the products of the reaction of anhydrous cupric chloride with benzene, naphthalene, phenanthrene, anthracene, tetracene, and pyrene has shown them to be consistent with those expected from an electrophilic substitution reaction. Perylene formed products which have not as yet been characterized.

In the first paper of this series,[1] the halogenation of anthracene by anhydrous cupric chloride was investigated. It was of interest to learn whether the reaction would be of preparative value and its scope has been investigated by extension to other aromatic systems.

RESULTS AND DISCUSSION

The procedures were much the same as those described earlier.[1] Reaction of the solids seldom produced much product and so, usually, the hydrocarbon to be investigated was dissolved in nitrobenzene and treated with an excess of cupric chloride. The products were frequently extremely difficult to separate; chromatography was used often and with varying success. Reaction mixtures wherein either naphthalene or phenanthrene was dissolved in nitrobenzene were analyzed by fractional distillation. The results of these studies are presented in Table I.

It is evident that complex mixtures frequently resulted. Such mixtures are often encountered in aromatic halogenations and often only the simpler halogenated derivatives have been characterized. Separations were further complicated by the fact that the chloroaromatics in most cases were more soluble than the parent hydrocarbons and often differed little among themselves in physical properties.

The sealed-tube reactions were particularly useful for the chlorination of the less reactive aromatics. Addition reactions, which often complicate polychlorinations,[2] apparently did not occur, or if they did, they were followed by dehydrohalogenation. The preparation of hexachlorobenzene by this technique is the only single-step synthesis of this compound that has been found. Considerable pressure developed during the reactions, however, and the tubes often broke. Since no suitable bomb was available, the investigation could not be pursued.

When a 2:1 mixture of cupric chloride–perylene was heated in nitrobenzene at 100° for seventy-two hours, a yellow-orange product was obtained which had the proper analysis for dichloroperylene (with increasing proportions of cupric chloride and higher temperatures, even more complex mixtures were obtained). The melting range was usually about 215–245° and on vapor phase chromatography, two very poorly resolved peaks appeared. All attempts to separate the components by crystalli-

(1) J. C. Ware and E. E. Borchert, *J. Org. Chem.*, to be published (1960).

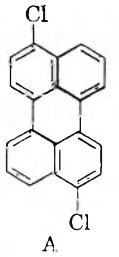
(2) G. S. Badger, *Structures and Reactions of the Aromatic Compounds*, University Press, Cambridge, 1954, p. 257.

TABLE I

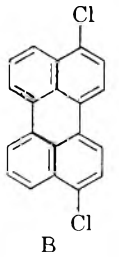
Hydrocarbon	Moles $CuCl_2$ / Moles Hydrocarbon	Solvent	Temp.	Time, Hr.	Nature of Product
Benzene	12.0	None—sealed tube	300	72	Mixture: 1,2,4,5- and 1,2,3,5-tetrachlorobenzenes
Benzene	12.0	None—sealed tube	400	72	Hexachlorobenzene
Naphthalene	7.0	None	100	0.5	None
Naphthalene	6.4	Nitrobenzene	210	72	1-Chloronaphthalene and 1,4-dichloronaphthalene[a]
Naphthalene	12.0	None—sealed tube	300	72	Unidentified yellow crystals, m.p. 118–128°; analysis approximated that for a tetrachloronaphthalene[b]
Anthracene	8.4	Nitrobenzene	210	72	9,10-Dichloroanthracene[c]
Phenanthrene	8.4	Chlorobenzene	132	96	None
Phenanthrene	4.1	Nitrobenzene	210	168	Some 9,10-dichlorophenanthrene[d]
Pyrene	1.0	None	100	0.5	Small amount of 3-chloropyrene
Pyrene	16.5	Nitrobenzene	210	72	Mixture: 3,8- and 3,10-dichloropyrenes, small amount of 3,5,10-trichloropyrene[e]
Tetracene	2.0	None	100	1	Some 5,11-dichlorotetracene[d]
Tetracene	8.4	Chlorobenzene	132	168	Some 5,11-dichlorotetracene[d]
Perylene	2.0	Nitrobenzene	100	72	Dichloroperylene

[a] Separation from solvent was incomplete. [b] The tip of the tube broke and the crystals remaining within the tube were examined. [c] From ref. 1. [d] Part of product was unidentified. [e] The products were not completely separated—the (only) separation (see ref. 13) of these isomers required over 400 melting point determinations.

zation, column chromatography, and sublimation have failed. The usual dichlorination product of perylene is the 3,9-derivative (A), m.p. 291°.[3] A small amount of impure 3,10-dichloroperylene (B), m.p. *ca.* 180°, has also been isolated.[4]



A



B

It is likely that in the present instance, the same products have been obtained although in different proportions. The problem is still under investigation.

With the possible exception of perylene, the hydrocarbons investigated have yielded the same products as those to be expected from an electrophilic chlorination[5] (under controlled conditions, in the case of reactive hydrocarbons). No evidence has been obtained for an addition-elimination reaction path. As well as can be judged, the reactivities of the aromatic hydrocarbons (perylene, pyrene, tetracene > anthracene, phenanthrene > naphthalene, benzene) fell in the order which might have been anticipated for an electrophilic substitution.[6] The action of cupric chloride is less vigorous than that of chlorine or of the other metal chlorides, known to cause nuclear halogenation, which have been studied.[7] Cupric chloride is easy to handle and stoichiometry is easily controlled. For that reason, it might be of utility for the chlorination of sensitive compounds provided that suitable conditions could be found.

EXPERIMENTAL

All melting points were taken in a heated copper block and are uncorrected. Microanalyses were by Micro-Tech Laboratories, Skokie, Ill., and Huffman Microanalytical Laboratories, Denver, Colo. Infrared spectra were determined by J. Schnell and N. E. Galer.

Action of cupric chloride on benzene. A. 1,2,4,5- and 1,2,3,5-Tetrachlorobenzenes. A mixture of 1.56 g. (0.02 mole) of benzene and 32.3 g. (0.24 mole) of cupric chloride was placed in a heavy-walled tube(1/2" I.D. × 11" with wall thickness 3 mm.). The tube was cooled in liquid nitrogen, evacuated, and sealed. An iron pipe with perforated caps screwed on each end was used as a shield. The tube was placed in an oven at 300° for 72 hr. When it was opened, a considerable amount of hydrogen chloride was evolved. The solid, then tan colored, was extracted with benzene in a Soxhlet extractor for 2 days. When the benzene had evaporated from the extract, white crystals remained, some of which were lost by sublimation. These were recrystallized from alcohol-water, m.p. 122–138° (lit., m.p. of 1,2,4,5-tetrachlorobenzene, 138°,[8] and m.p. of 1,2,3,5-tetrachlorobenzene, 51°[9]). The infrared spectrum of the crystals contained maxima at 6.79, 8.16, and 8.95 μ, characteristic of 1,2,4,5-tetrachlorobenzene, and one at 14.43 μ, characteristic of 1,2,3,5-tetrachlorobenzene.[9]

(3) A. Zinke, K. Funke, and N. Lorbes, *Ber.*, **60**, 577 (1927).

(4) A. Zinke, A. Pongratz, and K. Funke, *Ber.*, **58**, 330 (1925).

(5) The Monograph by E. Clar, *Aromatische Kohlenwasserstoffe*, Second Edition, Springer-Verlag, Berlin (1952), contains sections on all of the polynuclear hydrocarbons studied and describes their chlorination products.

(6) See reference (2), p. 242.

(7) *Cf.* P. Kovacic and N. O. Brace, *J. Am. Chem. Soc.*, **76**, 5491 (1954).

(8) A. F. Holleman, *Rec. trav. chim.*, **39**, 736 (1920).

(9) E. K. Plyler, H. C. Allen, Jr., and E. D. Tidwell, *J. Research Natl. Bur. Stds.*, **58**, 255 (1957).

B. Hexachlorobenzene. The same quantities of materials contained in a sealed tube (1/2" I.D. × 22 1/2" and wall thickness 3 mm.) were heated at 400° for 72 hr. White needles had sublimed onto the walls above the grayish mass of cuprous-cupric chloride. The material was extracted as before and on evaporation of the benzene, 4.50 g. of a light yellow solid remained. It was treated with Norit and recrystallized from cyclohexane to yield white needles, m.p. 221–222° (lit.,[10] m.p. of hexachlorobenzene, 226–227°). The yield was 80% and the infrared spectrum agreed with that of hexachlorobenzene.[9]

Anal. Calcd. for C_6Cl_6: C, 25.30; Cl, 74.70. Found: C, 24.88; H, 0.40; Cl, 74.55.

The inorganic product was dried and analyzed. Calcd. for CuCl: Cu, 64.2. Found: Cu, 63.0.

Action of cupric chloride on naphthalene. A. 1-Chloronaphthalene. A mixture of 3.85 g. (0.03 mole) of naphthalene and 32.3 g. (0.24 mole) of cupric chloride was heated in refluxing nitrobenzene for 1 week. The nitrobenzene could not be removed by steam distillation because the products distilled as well and so the former was removed by distillation through a two-foot, helix-packed column. The residue (*ca.* 10 ml.) was then distilled in a spinning band column.

Boiling Range	Pressure, Mm.	Weight, G.
59.2	0.6	1.73
44.2–44.5	0.15	2.14
44.5–66.0	0.15	0.31

All of the fractions contained 1-chloronaphthalene contaminated with nitrobenzene, according to their infrared spectra. The 66° distillate contained, in addition, another component which absorbed at 10.15, 7.40, and 6.54 μ. When 1,4-dichloronaphthalene was added to a portion of the latter and the infrared spectrum retaken, there were no new peaks observed and the heights of the peaks mentioned were enhanced. For the analysis, it was estimated that 1,4-dichloronaphthalene constituted one-third of the fraction by weight. A quantitative estimate of the amount of 1-chloronaphthalene present in the three fractions, based upon infrared peak height ratios at 2.99 and 9.77 μ, was 2.78 g. The minimum yield then was 57%.

B. A mixture of 1.28 g. (0.01 mole) of naphthalene and 10.75 g. (0.08 mole) of cupric chloride was heated in a sealed tube (22 1/2" × 1/2" I.D.) at 300° for 72 hr. The tip broke off the tube sometime during this period, but a quantity of yellow crystalline material as well as tan solid remained in the tube. The whole was extracted as before with benzene and the extract treated with Norit and recrystallized from cyclohexane. Yellow crystals, m.p. 118–128°, were obtained.

Anal. Calcd. for $C_{10}H_4Cl_4$: C, 45.16; H, 1.52; Cl, 53.32. Found: C, 43.99; H, 1.91; Cl, 54.17.

The action of cupric chloride on phenanthrene. A mixture of 5.34 g. (0.03 mole) of phenanthrene and 16.70 g. (0.124 mole) of cupric chloride was refluxed in 100 ml. of nitrobenzene for 1 week. Since previous experiments had shown that steam distillation did not separate the solvent from the products, the copper salts were filtered off and the filtrate distilled. Most of nitrobenzene was removed at 10 mm. through a two-foot, helix-packed column and the residue was distilled at 0.6 mm. in a spinning band column. Initial fractions consisted mostly of nitrobenzene which also contaminated the first product fraction.

No.	Boiling Range	Weight, g.	Nature of Distillate
1	161–164	1.5	Red oil containing some white solid
2	164–186	2.1	Yellow-orange solid
3	186	0.8	Orange solid
4	(Benzene-soluble residue)	0.6	Dark orange solid

When solid from No. 1 was crystallized from alcohol, white crystals, m.p. 135–150°, were obtained. Neither chromatography nor further recrystallization would separate the mixture.

Anal. Calcd. for $C_{14}H_9Cl$: C, 79.06; H, 4.27; Cl, 16.67, $C_{14}H_8Cl_2$: C, 68.04; H, 3.26; Cl, 28.70. Found: Cl, 24.38.

Fractions 2 and 3 were combined and chromatographed after recrystallization failed to achieve separation. First, about 1.5 g. of crystals, m.p. 130–150°, were obtained. They were recrystallized from cyclohexane and then from alcohol, yielding white needles, m.p. 158–160° (lit.,[11] m.p. of 9,10-dichlorophenanthrene, 160–161°). The infrared absorption spectrum had long wave-length maxima at 14.01, 13.42, 11.10 and 10.27 μ.

Anal. Found: C, 67.66; H, 3.51; Cl, 28.92.

Later fractions, again, consisted of oils and solids with broad, low melting ranges. Fraction 4 could not be separated by recrystallization or chromatography either. The infrared spectra of all four fractions contained absorption maxima characteristic of 9,10-dichlorophenanthrene.

Action of cupric chloride on pyrene. A. 3-Chloropyrene. A mixture of 2.02 g. (0.01 mole) of pyrene and 1.35 g. (0.01 mole) of cupric chloride was heated without solvent at 100° for 0.5 hr. When the product was chromatographed, it was found to be principally unchanged pyrene. The leading fractions, however, contained other materials. The first, m.p. 115–120°, was rechromatographed and after some higher melting material had been eluted, a quantity of crystals, m.p. 119–120°, was obtained. The material was assumed to be 3-chloropyrene (lit.,[12] m.p. 119°, m.p. of red picrate, 177–178°). Recrystallization of the material served only to widen its melting range; it gave a red picrate, m.p. 150–178°.

Anal. Calcd. for $C_{16}H_9Cl$: C, 81.19; H, 3.83. Found: C, 80.60; H, 3.98.

B. 3,5,8-Trichloropyrene; 3,8- and 3,10-dichloropyrenes. A mixture of 2.02 g. (0.01 mole) of pyrene and 22.3 g. (0.165 mole) of cupric chloride was refluxed in 50 ml. of nitrobenzene for 3 days. The tarry residue of the steam distillation was extracted with benzene. After treatment with Norit and successive recrystallizations from benzene (m.p. 175–200°), acetic acid (m.p. 197–250°), and toluene, 0.1 g. of buff-colored needles, m.p. 247–251°, remained (lit.,[13] m.p. of 3,5,10-trichloropyrene, 256–257°). No further purification of this material was attempted.

Anal. Calcd. for $C_{16}H_7Cl_3$: C, 62.9; H, 2.3; Cl, 34.8. Found: C, 64.2; H, 2.6; Cl, 33.1.

The rest of the material, about 1.0 g., was recrystallized from acetic acid, m.p. 162–170°, and the remainder then from toluene, m.p. 154–160° (lit.,[13] m.p. of 3,8-dichloropyrene, 194–196°; m.p. of 3,10-dichloropyrene, 154–156°). A separation of isomers was not attempted since it was found to be exceedingly difficult and time-consuming. The crystals obtained from acetic acid were analyzed.

Anal. Calcd. for $C_{16}H_8Cl_2$: C, 70.87; H, 2.98; Cl, 26.15. Found: C, 70.54; H, 3.23; Cl, 25.69.

Action of cupric chloride on tetracene. 5,11-Dichlorotetracene. A mixture of 1.14 g. (0.005 mole) of tetracene and 1.35 g. (0.01 mole) of cupric chloride was heated without solvent at 100° for 1 hr. Good contact with the tetracene could not be achieved because the flaky crystals were not easily broken up. When the product was chromatographed, it moved very

(10) C. Willgerodt and K. Wilcke, *Ber.*, **46**, 2752 (1910).

(11) J. Schmidt and G. Ladner, *Ber.*, **37**, 4492 (1904).

(12) H. Vollman, H. Becker, M. Corell, and H. Streech, *Ann.*, **531**, 1 (1937).

(13) G. Goldschmiedt and R. Wegscheider, *Monat.*, **4**, 666 (1883).

slowly; the first material to be eluted consisted of red-orange crystals, m.p. 217–221°. Recrystallization twice from methyl ethyl ketone afforded brick-red needles, m.p. 218–220° (lit.,[14] m.p. of 5,11-dichlorotetracene, 220°). When the reaction was repeated in refluxing chlorobenzene, an inseparable mixture of chlorinated products was obtained.

Anal. Calcd. for $C_{18}H_{10}Cl_2$: Cl, 23.87. Found: Cl, 24.04.

Action of cupric chloride on perylene. A mixture of 1.26 g. (0.005 mole) of perylene and 1.35 g. (0.01 mole) of cupric chloride was heated in 25 ml. of nitrobenzene at 100° for 3 days. A black precipitate which formed during the course of the reaction was removed by filtration. It disappeared on hydrolysis, yielding a yellow-orange organic product and, presumably, copper salts. A small portion of the product, dissolved in the solvent, had an infrared spectrum essentially the same as that obtained from the black precipitate and so the two were combined. No purification could be achieved by recrystallization from cyclohexane, benzene, acetone, or ethyl alcohol. When purification with Norit was attempted, the product could not be desorbed even by boiling chlorobenzene and the reaction had to be repeated. The melting range was generally about 215–245°. If the material was chromatographed on alumina with cyclohexane, it moved very slowly, but finally yellow-orange crystals could be obtained in which the melting range was about the same as before. Infrared absorption maxima occurred at 10.20, 11.37, 12.15, 12.47, 12.75, 13.15, and 14.53 μ. Later fractions contained perylene contamination as well. There was obtained 1.29 g. of the yellow-orange material. A portion of the latter was recrystallized from cyclohexane, m.p. 218–245°.

Anal. Calcd. for $C_{20}H_{10}Cl_2$: C, 74.78; H, 3.14; Cl, 22.08. Found: C, 74.84; H, 3.26; Cl, 22.21.

If dichloroperylene had been formed, then 1 mole of cupric chloride introduced 1 mole of chlorine instead of 0.5 mole as experienced previously. On this basis, the yield of dichloroperylene was 80%. Oxidation by sulfuric acid yielded no distinct product.

(14) C. Marschalk and C. Stumm, *Bull. Soc. Chem. France*, **15**, 418 (1948).

CLEVELAND 1, OHIO

[CONTRIBUTION FROM THE OHIO STATE UNIVERSITY RESEARCH FOUNDATION]

Conversion of Trichloromethyl Groups into Dichloromethyl Groups[1]

EHRENFRIED KOBER[2]

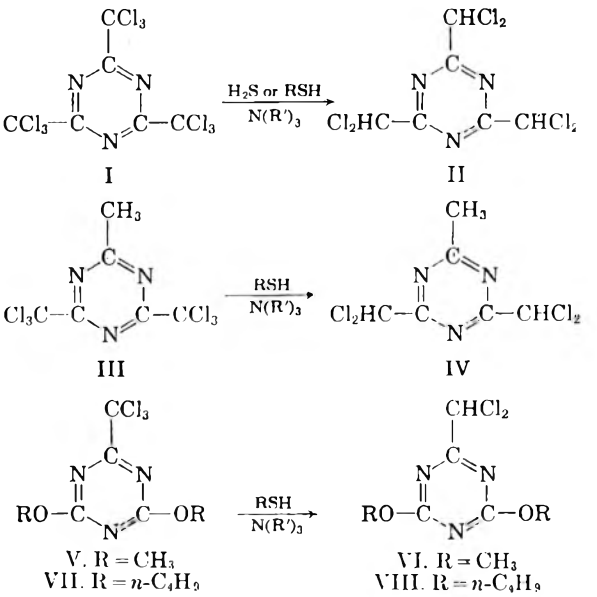
Received October 28, 1960

Trichloromethyl-*s*-triazines and derivatives of trichloroacetic acid can be converted into the corresponding dichloromethyl compounds by means of mercaptans in the presence of tertiary amines; mercaptals are formed as by-products.

In connection with a study on the reactivity of trichloromethyl groups attached to the *s*-triazine nucleus we had found that the reaction of trichloromethyl-*s*-triazines with alcohols in the presence of certain tertiary amines led, depending on the reaction conditions, to the stepwise replacement of trichloromethyl groups by alkoxy groups.[3] Furthermore, we reported that the reaction of 2,4,6-tris(trichloromethyl)-*s*-triazine (I) with water and certain tertiary amines resulted in the formation of tertiary amine salts of 2-hydroxy-4,6-bis(trichloromethyl)-*s*-triazine.[3]

It was of interest to know whether the reaction of trichloromethyl-*s*-triazines with mercaptans instead of alcohols would proceed in the presence of tertiary amines correspondingly and result in the formation of alkylthio-*s*-triazines. It also appeared desirable to determine whether the reaction of I with hydrogen sulfide instead of water would lead in the presence of tertiary amines, in an analogous fashion, to the formation of tertiary amine salts of 2-mercapto-4,6-bis(trichloromethyl)-*s*-triazine.

It was surprisingly found that 2,4,6-tris(trichloromethyl)-*s*-triazine (I) reacted with either ethanethiol or 1-butanethiol in the presence of triethylamine to give 2,4,6-tris(dichloromethyl)-*s*-triazine (II). This result indicated that the reaction of compound I with mercaptans in the presence of triethylamine took an entirely different course as compared with the reaction of compound I with alcohols; instead of being replaced by alkylthio groups, the trichloromethyl groups were converted into dichloromethyl groups.



(1) This article is based on work performed under Project 116-B of The Ohio State University Research Foundation sponsored by the Olin Mathieson Chemical Corporation, New York, N. Y.

(2) Olin Mathieson Chemical Corporation, Organics Division, New Haven, Conn.

(3) E. Kober, *J. Org. Chem.*, 25, 1728 (1960).

The general usefulness of this conversion for the *s*-triazine series was ascertained when other trichloromethyl substituted *s*-triazines were subjected to this type of reaction; the corresponding dichloromethyl-*s*-triazines were obtained in each case. Thus, 2-methyl-4,6-bis(trichloromethyl)-*s*-triazine (III) was converted into 2-methyl-4,6-bis(dichloromethyl)-*s*-triazine (IV), 2,4-bismethoxy-6-trichloromethyl-*s*-triazine (V) gave 2,4-bismethoxy-6-dichloromethyl-*s*-triazine (VI), and 2,4-bis-*n*-butoxy-6-trichloromethyl-*s*-triazine (VII) afforded 2,4-bis-*n*-butoxy-6-dichloromethyl-*s*-triazine (VIII).

The reaction of compound I with hydrogen sulfide in the presence of triethylamine again did not occur as one might have expected from the corresponding reaction of compound I with water and triethylamine. Instead, the principal product proved to be II, indicating that the reaction with hydrogen sulfide proceeded in the same manner as with mercaptans.

Extending our studies, we found that derivatives of trichloroacetic acid also undergo this type of reaction. This was shown by the conversion of trichloroacetamide and ethyl trichloroacetate into the corresponding dichloro derivatives, dichloroacetamide (IX) and ethyl dichloroacetate (X).

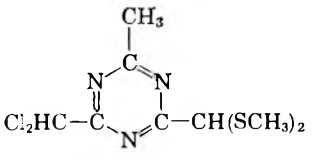
In all cases, including those studies in the *s*-triazine series, the reaction proceeded according to the following equation:

$$R{-}CCl_3 + 2\,RSH + R_3N \longrightarrow R{-}CHCl_2 + RSSR + R_3N{\cdot}HCl$$

If an excess of the tertiary amine was used, part of the dichloromethyl compound reacted further with excess mercaptan to give the corresponding mercaptal:

$$R{-}CHCl_2 + 2\,RSH + 2\,R_3N \longrightarrow RCH(SR)_2 + 2\,R_3N{\cdot}HCl$$

Thus, the methylmercaptal of the 2-methyl-4-dichloromethyl-*s*-triazine-(6) carboxaldehyde (XI) was obtained as a by-product from the reaction of 2-methyl-4,6-bis(trichloromethyl)-*s*-triazine (III) with methanethiol and triethylamine. In addition, 1,1-bis(methylthio)acetamide (XII) and ethyl 1,1-bis(methylthio)acetate (XIII) were isolated along with the desired derivatives of dichloroacetic acid when trichloroacetamide and ethyl trichloroacetate, respectively, reacted with methanethiol in the presence of triethylamine.[4]



XI

$(CH_3S)_2CHCONH_2$ = XII
$(CH_3S)_2CHCOOC_2H_5$ = XIII

(4) Sulfur-containing compounds were also formed in the other experiments reported here; however, no efforts were made to identify these products.

The conversion of trichloromethyl into dichloromethyl groups by means of mercaptans and tertiary amines represents a novel method which, in general, is more widely applicable than procedures reported previously for this transformation. Its limitations are indicated by the observation that —in contrast to trichloromethyl substituted *s*-triazines and derivatives of trichloroacetic acid —the trichloromethyl group was not affected when 2,2,2-trichloroethanol, 1,1,1-trichloro-2-methyl-2-propanol, chloral hydrate, 1,1,1-trichloroethane, or benzotrichloride were treated with mercaptans and triethylamine. Apparently, only compounds having the trichloromethyl group attached to a rather strong electronegative moiety are being converted to the corresponding dichloromethyl compound. However, if the electronegative moiety is too strong a electron-withdrawing group such as the trichloromethyl group, the reaction will not stop after one chlorine atom has been exchanged by hydrogen. Thus, hexachloroethane reacted to give a mixture of partially chlorinated ethanes and ethenes, indicating that pentachloroethane was probably formed as an intermediate but underwent further reaction under the conditions employed.

EXPERIMENTAL[5]

2,4-Bismethoxy-6-trichloromethyl-s-triazine (V). (a) An amount of 39 g. of 2,4-dichloro-6-trichloromethyl-*s*-triazine[6] was dissolved, with stirring, in a solution of 6.7 g. of sodium in 150 ml. of methanol and kept at 0° for 6 hr. The sodium chloride formed was removed by filtration. After removal of the methanol from the filtrate by vacuum distillation at room temperature, an oily residue was obtained from which, upon addition of ether, a solid precipitated. The solid was filtered and the ether removed from the filtrate. The resulting oily residue was fractionated to give 18.5 g. of 2,4-bismethoxy-6-trichloromethyl-*s*-triazine (V), b.p. 100–103° (0.6 mm.), n_D^{29} 1.5228.

Anal. Calcd. for $C_6H_6N_3Cl_3O_2$: C, 27.88; H, 2.34; N, 16.26; Cl, 41.15. Found: C, 27.89; H, 2.39; N, 16.14; Cl, 41.41.

When the same reaction was carried out with triethylamine instead of sodium as hydrogen scavenger, a mixture of products was obtained which could not be separated by fractional distillation.

(b) 2,4-Bismethoxy-6-trichloromethyl-*s*-triazine (V) was also obtained by employing the method recently described for the preparation of other 2,4-bisalkoxy-6-trichloromethyl-*s*-triazines.[3]

An amount of 56 g. of 2,4,6-tris(trichloromethyl)-*s*-triazine (I) reacted with methanol (200 ml.) in the presence of triethylamine (48 g.) at room temperature. The desired compound V was isolated from the reaction mixture by vacuum distillation; b.p. 99–105° (0.6 mm.); n_D^{33} 1.5222; yield: 24.0 g.

Procedures for the conversion of trichloromethyl into dichloromethyl groups. (a) One mole equivalent of a trichloromethyl substituted s-triazine (I, III, V, or VII) or of a derivative of trichloroacetic acid is added, with stirring,

(5) Melting points were determined with the Fisher-Johns apparatus; analyses are by Galbraith Microanalytical Laboratories, Knoxville, Tenn., and by Spang Microanalytical Laboratory, Ann Arbor, Mich.

(6) E. Kober and Ch. Grundmann, *J. Am. Chem. Soc.*, **81**, 3769 (1959).

TABLE I

DICHLOROMETHYL COMPOUNDS

Compound	Hydrogen Source	Yield, %	M.P.	B.P. (mm.)	n^t_D	t	Empirical Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found
II	C_4H_9SH	77.3	68[a]				$C_6H_2N_3Cl_5$	21.82	21.79	0.91	0.92	12.74	12.88	64.56	64.47
II	C_2H_5SH	64.7	66.5–68[a]												
II	H_2S	23.8	65–67[a]												
IV	CH_3SH	90.5	88–90	128–142 (0.2)			$C_6H_5N_3Cl_4$	27.62	27.69	1.91	1.97	16.11	16.28	54.35	54.04
VI	CH_3SH	66.9		90–93 (0.06)[c]	1.5197	26									
VIII	CH_3SH	53.2		153.5–157 (1.4)	1.4968	26.5	$C_{12}H_{19}N_3Cl_2O_2$	46.76	47.19	6.22	6.43	13.64	13.64	23.01	22.72
IX	CH_3SH	87.1	95–96.5[b]												
X	CH_3SH	26.5		70 5–73 5 (30)[d]	1.4397	26	$C_4H_6Cl_2O_2$	30.61	30.91	3.85	3.99			45.17	43.89

[a] Lit.[7] m.p. 68°. [b] Lit.[8] m.p. 98°. [c] Lit.[9] b.p. 86–88° (0.045 mm.); n^{23}_D 1.5200. [d] Lit.[10] b.p. 156° (738 mm.); n^{20}_D 1.4386.

TABLE II

MERCAPTALS

Compound	Yield, %	B.P. (mm.) or M.P.	n^t_D	t	Empirical Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found	Chlorine, % Calcd.	Chlorine, % Found
XI	4.5	120–122 (0.07)	1.5869	20	$C_8H_{11}N_3S_2Cl_2$	33.82	34.11	3.90	4.18	14.79	15.28	22.56	22.58	24.95	24.33
XII	11.7	146–147			$C_4H_9NS_2O$	31.79	31.96	6.01	6.09	9.27	9.37	42.34	41.99		
XIII	41.6	98–102 (8)	1.5069	27	$C_6H_{12}S_2O_2$	39.97	39.86	6.71	6.72			35.57	35.72		

to a mixture of a mercaptan (5–20 mole equivalents) and triethylamine (1.5–5 mole equivalents) at −20° (if methanethiol is employed) or at 0° (if ethanethiol or 1-butanethiol are used). The reaction mixture is allowed to warm to room temperature upon stirring. The precipitated triethylamine hydrochloride is filtered off and washed with ether or petroleum ether (b.p. 30–40°). The wash solvent, excess triethylamine, and the dialkyl disulfide formed are removed from the filtrate by distillation. If the reaction product is volatile, the residue is fractionated *in vacuo* to give the desired dichloromethyl substituted compound (II, IV, VI, VIII, or X) and a higher boiling, sulfur-containing material (XI and XIII were thus obtained in pure form and identified as mercaptals). If the reaction product is a solid, the residue is recrystallized from suitable solvents to isolate the diehloromethyl compound (II was isolated in one experiment by recrystallization of the residue from ligroin; compound IX was purified by dissolving the residue in ether and reprecipitation with ligroin, the mercaptal XII was contained in the triethylamine hydrochloride filter cake and was separated and purified by crystallization from water).

(b) Hydrogen sulfide was passed into a solution of 33 g. of 2,4,6-tris(trichloromethyl)-*s*-triazine (I) and 35.1 g. of triethylamine in 200 ml. of ether at 0° for 7 hr. The reaction mixture was allowed to stand for 12 hr. at room temperature. Then, 250 ml. of ether were added to the reaction mixture, the salts and sulfur formed were removed by filtration, and the ether distilled from the filtrate. The resulting dark residue was recrystallized from 25 ml. of ligroin. Upon cooling to −20°, crystals and an oily product separated from the ligroin. The crystals were collected and freed from adhering oil by pressing on a clay plate. Thus, 5.96 g. of 2,4,6-tris(dichloromethyl)-*s*-triazine (II) was isolated.

Compounds prepared according to these procedures are listed in Tables I and II. Dichloromethyl compounds for which an analysis is not recorded were identified either by a mixed melting point or by comparing the boiling point and refractive index with an authentic sample.

Acknowledgment. The author is indebted to the Olin Mathieson Chemical Corporation for its generous support of this work.

188 SANDQUIST CIRCLE
HAMDEN, CONN.

(7) Ch. Grundmann, G. Weisse, and S. Seide, *Ann.*, **577**, 77 (1952).
(8) A. Pinner and F. Fuchs, *Ber.*, **10**, 1066 (1877).
(9) Ch. Grundmann and E. Kober, *J. Am. Chem. Soc.*, **79**, 944 (1957).
(10) J. W. Brühl, *Ann.*, **203**, 22 (1880).

[CONTRIBUTION FROM THE SCHOOL OF PHARMACY, OSAKA UNIVERSITY]

Reduction of Phthalimides with Sodium Borohydride

ZEN-ICHI HORII, CHUZO IWATA, AND YASUMITSU TAMURA

Received September 26, 1960

Reduction of phthalimide derivatives with sodium borohydride in methanol results in the formation of 3-hydroxyphthalimidines (II), or a mixture of II and *o*-hydroxymethylbenzamides III depending on the amount of reducing agent present. The mechanism of this reduction is proposed.

Although it has been known that the imido group does not undergo reduction by sodium borohydride,[1] we have found that *N*-(6-oxo-5,6,7,8-tetrahydro-1-naphthyl)phthalimide is reduced by sodium borohydride in methanol to *o*-hydroxymethyl-*N*-(6-hydroxy-5,6,7,8-tetrahydro-1-naphthyl)-benzamide. It would be of interest to establish this novel reduction of the phthalimide since sodium borohydride has prominent selectivities toward various groups on reduction and, thus, this reduction may be expected to serve as a useful preparative method. The present paper describes the reduction of the phthalimide derivatives (Ia–i) shown in Fig. 1 with sodium borohydride.

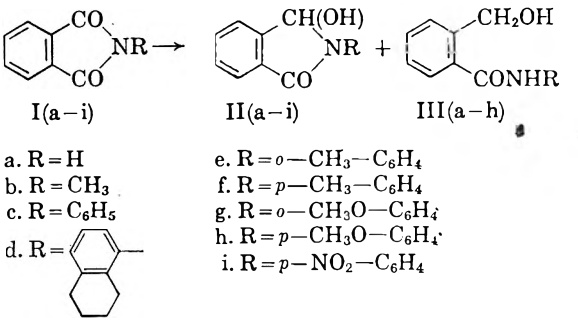


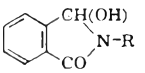
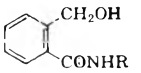
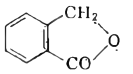
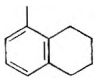
Figure 1

The reduction was carried out by adding a methanolic solution of sodium borohydride to a suspension of the phthalimide in methanol at 25–30°, followed by stirring at this temperature for seven to ten hours. When two molecular equivalents of sodium borohydride was employed, the product was the 3-hydroxyphthalimidine (II) or a mixture of II and the *o*-hydroxymethylbenzamide (III). Thus, phthalimide (Ia) and *N*-methylphthalimide (Ib) were converted to 3-hydroxyphthalimidine (IIa) and 3-hydroxy-2-methylphthalimidine (IIb) in yields of 66% and 56%, respectively. Similarly, *N*-(*p*-nitrophenyl)phthalimide (Ii) was converted to 3-hydroxy-2-(*p*-nitrophenyl)-phthalimidine (IIi) in 81% yield. Compounds IIa and IIb were prepared previously by reduction with zinc in sodium hydroxide solution[2] or with magnesium and ammonium chloride in methanol,[3]

(1) N. G. Gaylord, *Reduction with Complex Metal Hydrides*, Interscience, New York, 1956, p. 629.
(2) A. Reissert, *Ber.*, 46, 1484 (1913).
(3) A. Dunet and A. Willemart, *Bull. soc. chim. France*, 1081 (1948).

TABLE I

REDUCTION PRODUCTS OF THE PHTHALIMIDES WITH $NaBH_4$

R	Reaction Temp.	Reaction[c] Time, Hr.	Yield, % II 	III 		Method of Separation of Products
H[a]	25–30°	7	66	—	3	d
H[b,f]	25–30°	14	—	45	30	d
CH_3[a]	25–30°	7	56.3	—	14.3	d
C_6H_5[a]	25–30°	7	23.5	50	—	e
C_6H_5[a]	50–53°	5	16	45	15	d,e
C_6H_5[a]	Reflux (CH_3OH)	5	—	40	33	d
C_6H_5[b]	25–30°	14	—	92	—	d
	25–30°	7	37	55	—	d
o-$CH_3C_6H_4$[a]	25–30°	7	23	66	—	d,e
p-$CH_3C_6H_4$[a]	25–30°	10	40	37	—	e
o-$CH_3OC_6H_4$[a]	25–30°	8	27	40	—	d,e
p-$CH_3OC_6H_4$[a]	25–30°	8	18	47	—	e
p-$NO_2C_6H_4$[a]	25–30°	8	81	—	—	d

[a] With two molecular equivalents of $NaBH_4$. [b] With four molecular equivalents of $NaBH_4$. [c] After completion of the addition of $NaBH_4$. [d] Products were separated by procedure (i) in the general method. [e] Products were separated by procedure (ii) in the general method. [f] The reduction was carried out using the same procedure as in the reduction of Ic by procedure c.

but this new reduction method with sodium borohydride offers a more convenient and reproducible method for these materials. However, the reductions of the other phthalimides investigated gave mixtures of the 3-hydroxyphthalimidine (II) and the *o*-hydroxymethylbenzamide (III), as indicated in Table I.

On the other hand, employment of four molecular equivalents of sodium borohydride in the reduction resulted in an increase in yield of III, accompanied with a simultaneous decrease in yield of II. Thus, the reduction of Ia with four moles of sodium borohydride gave *o*-hydroxymethylbenzamide (IIIa) in 45% yield, accompanied with the 30% yield of phthalide, instead of IIa. The formation of the phthalide, which was also observed to a lesser extent during the reduction of Ia and Ib using two moles of sodium borohydride, is ascribable to hydrolysis of IIIa. In the reduction of *N*-phenylphthalimide (Ic) with the four moles of sodium borohydride only *o*-hydroxymethyl-*N*-phenylbenzamide (IIIc) was obtained in 92% yield, although the reduction with two moles of sodium borohydride gave a mixture of 3-hydroxy-2-phenylphthalimidine (IIc) (24% yield) and *o*-hydroxymethyl-*N*-phenylbenzamide (IIIc) (50% yield).[4] This reduction provides a new preparative method for phthalide, since IIIc was hydrolyzed with ethanolic sodium hydroxide to yield phthalide in quantitative yield.

In view of the results obtained in the reductions of Ic or Ia, it seems reasonable that the first reaction of sodium borohydride on the phthalimide (Ic) produces the phthalimidine (IIc), which is converted slowly to IIIc with an excess of sodium borohydride. This is also supported by the conversion of IIc into IIIc in 96% yield under exactly the same reduction conditions.[5] It has been observed that the reduction of some compounds containing the —N—C—O— grouping, with lithium aluminum hydride or sodium borohydride, resulted in cleavage of the carbon-nitrogen bond. The reduction of the *N*-acyl heterocyclic compounds,[6] the *N*-acyl-*N*-sulfonyl compounds,[7] the *N*-mono or dialkyl (or aryl) amides (including the lactam),[6,8] the *N*,*N*-diacyl amines,[6,9] etc., with lithium alumi-

(4) On the reduction of Ic with two moles of sodium borohydride, raising a reaction temperature up to 50–67° did not improve the yields of IIc and IIIc, but prompted the formation of phthalide.

(5) The catalytic reduction of IIc over palladium-charcoal in dioxane or dioxane–glacial acetic acid at room temperature did not proceed.

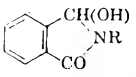
(6) N. G. Gaylord, *Reduction with Complex Metal Hydride*, Interscience, New York, 1956, pp. 575–590, 601, 619–622.

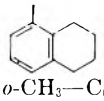
(7) A. Mustafa, *J. Chem. Soc.*, 2435 (1952); Z. Pravda and J. Rudinger, *Chem. listy.*, **48**, 1663 (1954).

(8) F. Galinovsky and R. Weiser, *Experientia*, **6**, 377 (1950); F. Galinovsky, A. Wagner, and R. Weiser, *Mh. Chem.*, **82**, 551 (1951); D. G. M. Diaper, *Can. J. Chem.*, **29**, 964 (1951); F. Weygand, G. Eberhardt, H. Linden, F. Schäfer, and I. Eigen, *Angew. Chem.*, **65**, 525 (1953); M. Davis, *J. Chem. Soc.*, 3981 (1956); H. C. Brown and A. Tsukamoto, *J. Am. Chem. Soc.*, **81**, 502 (1959).

(9) E. Testa, L. Fontanella, G. F. Cristiani, and L. Mariani, *Helv. Chim. Acta*, **42**, 2370 (1959).

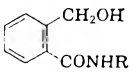
TABLE II

CHARACTERISTICS OF THE 3-HYDROXYPHTHALIMIDINES 

R	M.P.[a]	Recryst. from	Formula	Found, % C	Found, % H	Found, % N	Calcd., % C	Calcd., % H	Calcd., % N	Infrared Spectrum (in Nujol), —CO—N—R Cm.$^{-1}$, Amide I
H	179[b]	H_2O	$C_8H_7NO_2$	64.15	4.72	9.35	64.42	4.73	9.39	1698
CH_3	130[c]	$CH_3COOC_2H_5$	$C_9H_9NO_2$	66.21	5.49	8.66	66.24	5.56	8.58	1672
C_6H_5	171–172[d]	$CH_3COOC_2H_5$	$C_{14}H_{11}NO_2$	74.66	5.07	6.15	74.65	4.92	6.22	1689
	201	$C_2H_5OH—H_2O$	$C_{18}H_{17}NO_2$	77.54	6.09	5.01	77.39	6.13	5.01	1669 1692
o-$CH_3—C_6H_4$	192–193	$C_2H_5OH—H_2O$	$C_{15}H_{13}NO_2$	75.30	5.50	5.85	75.30	5.48	5.85	1672
p-$CH_3—C_6H_4$	167	$C_2H_5OH—H_2O$	$C_{16}H_{13}NO_2$	74.98	5.41	5.93	75.30	5.48	5.85	1664
o-$CH_3O—C_6H_4$	189–190	$CH_3COOC_2H_5$	$C_{15}H_{13}NO_3$	70.67	5.24	5.46	70.58	5.13	5.49	1669
p-$CH_3O—C_6H_4$	156	$CH_3COOC_2H_5$	$C_{15}H_{13}NO_3$	70.64	5.20	5.51	70.58	5.13	5.49	1661 1678
p-$NO_2—C_6H_4$	251–252	CH_3COOH	$C_{14}H_{10}N_2O_4$	62.33	3.89	10.24	62.22	3.73	10.37	1692

[a] Uncorrected. [b] Reported m.p. 178°, A. Dunet and A. Willemart, *Compt. rend.*, **226**, 821 (1948). [c] Reported m.p. 129°, A. Dunet and A. Willemart, *Bull. soc. chim. France*, 1081 (1948). [d] Reported m.p. 170°, *Bull. soc. chim. France*, 1081 (1948).

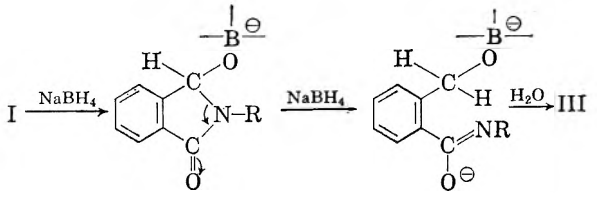
TABLE III

CHARACTERISTICS OF THE *o*-HYDROXYMETHYLBENZAMIDES, 

R	M.P.[a]	Recryst. from	Formula	Found, % C	Found, % H	Found, % N	Calcd., % C	Calcd., % H	Calcd., % N	Infrared Spectrum (in Nujol), Cm.$^{-1}$, —CONHR Amide I	Amide II
H	150–151[b]	$CH_3COOC_2H_5$	$C_8H_9NO_2$	63.55	5.95	9.13	63.56	6.00	9.27	1653	1618
C_6H_5	144	C_2H_5OH	$C_{14}H_{13}NO_2$	74.00	5.50	6.19	73.99	5.77	6.16	1639	1531
	193	C_2H_5OH	$C_{16}H_{19}NO_2$	76.90	6.75	5.06	76.84	6.81	4.98	1637	1527
o-$CH_3C_6H_4$	179	C_2H_5OH	$C_{15}H_{16}NO_2$	74.91	6.45	5.53	74.66	6.27	5.81	1637	1527
p-$CH_3C_6H_4$	173	C_2H_5OH	$C_{15}H_{15}NO_2$	74.82	6.23	5.85	74.66	6.27	5.81	1647	1536
o-$CH_3O—C_6H_4$	133	C_2H_5OH	$C_{15}H_{15}NO_3$	70.24	5.76	5.48	70.02	5.88	5.44	1639	1541
p-$CH_3O—C_6H_4$	161–162	C_2H_5OH	$C_{15}H_{15}NO_3$	69.99	5.91	5.51	70.02	5.88	5.55	1631	1527

[a] Uncorrected. [b] Reported m.p. 149–150°, J. J. Brown, J. Blair, and G. T. Newbold, *J. Chem. Soc.*, 708 (1955).

num hydride, lithium diethoxyaluminohydride, or lithium borohydride would be included in this type of reaction. Gaylord[10] recently reported that the reduction of the benztriazol derivatives with lithium aluminum hydride or sodium borohydride resulted in cleavage of the carbon-nitrogen bond. The transformation of IIc to IIIc would seem to proceed in a similar fashion and, thus the following representation for the reduction is proposed;



The procedure was found to be suitable for the reduction of aliphatic imides, and thus the reduction of *N*-phenylsuccinimide using four molecular equivalents of sodium borohydride yielded γ-butyrolactone in 40% yield, together with a small amount of γ-hydroxy-*N*-phenylbutyramide.

EXPERIMENTAL

Starting materials. The various phthalimide derivatives were prepared by refluxing a mixture of appropriate amines and phthalic anhydride in glacial acetic acid for 7–15 hr., while *N*-methylphthalimide was obtained by reaction of potassium phthalimide with methyl *p*-toluenesulfonate.[11]

General method of the reduction. A solution of 2 moles of sodium borohydride in methanol (20–25 ml. per 1 g.) was added to a suspension of 1 mole of the phthalamide in 90% methanol (6–8 ml. per 1 g.) at 25–30° dropwise while stirring (20–40 min.). The reaction mixture was stirred for an addi-

(10) N. G. Gaylord and D. J. Kay, *J. Org. Chem.*, **23**, 1574 (1958).

(11) E. J. Sakellarious, *Helv. Chim. Acta*, **29**, 1675 (1946).

tional 7–10 hr. at 25–30° then allowed to stand overnight at room temperature. Excess hydride was decomposed with glacial acetic acid. The reaction mixture was concentrated *in vacuo*, then water was added to the residual solid, and filtered. The filter cake was purified by the following two methods. i) In the case of Ia, b, d, e, g, or i, the products IIa, b, d, e, g, or i were separated and purified by recrystallization of the filter cake from an appropriate solvent. ii) In the case of Ic, f, or h,[12] a part of the filter cake was recrystallized once from ethanol to give IIIc, f, or h. The rest of the filter cake was hydrolyzed by boiling with sodium hydroxide-ethanol, yielding IIc, f or h and the phthalide, which were separated by recrystallization.

Reduction of N-phenylphthalimide (Ic). a) A solution of 1.2 g. (0.03 mole) of sodium borohydride in 25 ml. of methanol was added to a suspension of 3.4 g. (0.015 mole) of (Ic) in 25 ml. of 90% methanol at 25–30° dropwise over a period of 25 min. The reaction mixture was stirred for 7 hr. at 25–30°, then allowed to stand overnight at room temperature. Excess hydride was decomposed with glacial acetic acid. The mixture was concentrated *in vacuo*, water was added to the residue and filtered. The filter cake was washed with five 30-ml. portions of ether and the white solid obtained was recrystallized from ethanol to give 1 g. (29%) of IIIc, m.p. 144°. The ether washings were combined and concentrated and the residue was hydrolyzed by refluxing with a solution of 1 g. of sodium hydroxide in 30 ml. of ethanol for 7 hr. After removal of ethanol on a steam bath, 30 ml. of water was added to the cooled residue and the mixture was extracted with ethyl acetate.

The water layer was acidified with concd. hydrochloric acid under ice cooling. The precipitate was collected and recrystallized from water to yield 0.45 g. (21%) of phthalide, m.p. 73–74°, which was identified by comparison with the authentic sample. The ethyl acetate extract was concentrated *in vacuo* to give a semisolid, which was washed with a small amount of ether and recrystallized from ethyl acetate to 0.8 g. (23.5%) of IIc m.p. 171–172°. Concentration of this ether washing yielded aniline, which was proved to be acetanilide.

This experiment would indicate that the crude reduction product before hydrolysis consisted of IIc (23.5% yield) and IIIc (50% yield), because phthalide would be formed by hydrolysis of IIIc.[12]

b) A solution of 0.8 g. (0.022 mole) of sodium borohydride in 20 ml. of methanol was added to a suspension of 2.5 g. (0.011 mole) of Ic in 25 ml. of 90% methanol in the same manner as in the general method. The reaction mixture was kept at room temperature for 30 min. and, then at 50–53° for 5 hr. with stirring. Excess hydride was decomposed with glacial acetic acid. The reaction mixture was concentrated *in vacuo*, water was added to the residue, and the mixture filtered. The filter cake was washed with a small amount of ethyl acetate (*ca.* 5 ml.) and hydrolyzed as described in procedure a), giving 0.6 g. (45%) of phthalide, m.p. 73–74° and 0.4 g. (16%) of IIc m.p. 171–172°. The ethyl acetate wash was concentrated and the residue was recrystallized from water to yield 0.2 g. (15%) of phthalide, m.p. 73–74°.

(12) In this case, complete separation into III and II by recrystallization was difficult to be attained and, further, it was found that III was easily hydrolyzed with sodium hydroxide–ethanol to give phthalide, while II did not undergo hydrolysis.

When this reduction was carried out by stirring at room temperature for 30 min. and at reflux temperature for an additional 5 hr., the following result was obtained. After excess of hydride was decomposed with glacial acetic acid, the reaction mixture was concentrated *in vacuo*. Water was added to the residue and the insoluble material was recrystallized from ethanol to yield 1 g. (40%) of IIIc, m.p. 144°. The mother liquor was concentrated on a steam bath and the residual solid was recrystallized from water to yield 0.5 g. (33%) of phthalide, m.p. 73–74°.

c) A solution of 0.8 g. (0.022 mole) of sodium borohydride in 20 ml. of methanol was added to a suspension of 2.5 g. (0.011 mole) of Ic in 15 ml. of 90% methanol in the same manner as in procedure a). After standing overnight, an additional 0.8 g. (0.22 mole) of sodium borohydride in 20 ml. of methanol was added to the reaction mixture as outlined above. Excess hydride was decomposed with glacial acetic acid and the reaction mixture was concentrated *in vacuo*. Water was added to the residue, filtered, and the filter cake was recrystallized from ethanol to yield 2.3 g. (92%) of IIIc, m.p. 144°.

A mixture of 0.7 g. of IIIc and 0.2 g. of sodium hydroxide in ethanol was refluxed for 5 hr. The reaction mixture was concentrated on a steam bath and water was added to the residue. Extraction with ethyl acetate yielded aniline. The aqueous layer was acidified with concd. hydrochloric acid and the precipitate was recrystallized from water to yield 0.35 g. (98%) of phthalide, m.p. 73–74°.

Reduction of 3-hydroxy-2-phenylphthalimidine (IIC). A solution of 0.8 g. (0.022 mole) of sodium borohydride in 20 ml. of methanol was added to a suspension of 2.5 g. (0.011 mole) of IIc in 15 ml. of 90% methanol and worked up as usual. The product was recrystallized from ethanol to yield 2.4 g. (96%) of IIIc, m.p. 144°.

Reduction of N-phenylsuccinimide. A solution of 2.3 g. (0.06 mole) of sodium borohydride in 45 ml. of methanol was added to a suspension of 5 g. (0.03 mole) of *N*-phenylsuccinimide in 45 ml. of methanol dropwise with stirring. The reaction mixture was kept at 10–15° during the addition (*ca.* 40 min.) and stirred for an additional 7 hr. at 10–15°, then allowed to stand overnight at room temperature. An additional 2.3 g. (0.06 mole) of sodium borohydride in 45 ml. of methanol was added dropwise to the above reaction mixture with stirring at 10–15° (*ca.* 40 min.). After being stirred for 10 hr. at 10–15°, the reaction mixture was allowed to stand overnight at room temperature. Excess hydride was decomposed by addition of 10% hydrochloric acid. The mixture was concentrated on a steam bath and the residual semisolid was extracted with ether. The dried ether extract was distilled to yield 1.1 g. (44%) of γ-butyrolactone b.p.$_{108}$ 134°, which was identified by comparison with the infrared spectrum of the authentic sample. The distillation residue was recrystallized from ether to yield 0.2 g. (4%) of γ-hydroxy-*N*-phenylbutyramide, m.p. 83–84°.

Anal. Calcd. for $C_{10}H_{13}O_2N$; C, 67.02; H, 7.31; N, 7.82. Found: C, 67.12; H, 7.29; N, 7.82. The infrared spectra in chloroform indicated maxima at 3401, 3322, 1669, 1603, 1538 (shoulder), 1524, and 1502 cm.$^{-1}$

When acetic acid was used instead of 10% hydrochloric acid to decompose excess hydride in this reduction, the main product was γ-hydroxy-*N*-phenylbutyramide (34% yield), accompanied with a small amount of γ-butyrolactone.

TONEYAMA, TOYONAKA, OSAKA, JAPAN

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF BUFFALO]

Lithium Aluminum Hydride Reactions in Pyridine Solution. II. The Role of Steric Effects in the Reductive Cleavage of Pinacolones

PETER T. LANSBURY, JOHN R. ROGOZINSKI,[1] AND FAY L. COBLENTZ[2]

Received October 13, 1960

The occurrence of carbon-carbon cleavage during the reduction of benzpinacolone and related ketones by lithium aluminum hydride in pyridine appears to depend, to some degree, on steric compression in the intermediate alkoxyaluminohydrides, as well as on the stability of the leaving group.

It has previously been observed that reduction of certain benzpinacolones with lithium aluminum hydride in pyridine results in surprisingly facile cleavage reactions, leading to triarylmethanes and benzyl alcohol.[3] The need for a highly stabilized carbanion as leaving group in this reaction, where no proton donor is available, is shown by the failure of phenyl benzhydryl ketone to undergo reductive cleavage.[3] Pyridine, by virtue of its excellent coordination properties, liberates the unassociated alkoxide ion from the initially formed alkoxyaluminohydride by nucleophilic displacement on aluminum.[3] The thermal cleavage of metal alkoxides to carbonyl compounds (which, in this instance, may undergo further reduction) and carbanions has been found to proceed most rapidly when the oxygen-metal bond is highly ionic,[4] thus explaining the role of pyridine in the present case. Since those alkoxides which cleave during reduction appear to suffer considerable steric compression, it appeared advisable to investigate the role of steric factors in promoting cleavage, in addition to the stability of the leaving group and the effect of the solvent.

A classical case of steric acceleration in free radical chemistry is the effect of *ortho* substituents on the ease of dissociation of hexaarylethanes into triarylmethyl radicals.[5] For example, hexa-*o*-tolylethane dissociates more readily than hexa-*p*-tolylethane; also, bis(9-phenyl-9-fluorenyl) dissociates less readily than hexaphenylethane, since two phenyl rings on each ethane carbon of the former compound are "tied back" and steric compression is partially relieved.[5] The cleavage of alkali metal salts of the highly branched diisopropylalkylcarbinols is also accelerated by increasing bulk in the primary alkyl group which is cleaved.[4a]

In order to gain information relating to possible steric acceleration of reductive cleavage, we have prepared two ketones which are isomeric with benzpinacolone, namely α-(*p*-biphenylyl)desoxybenzoin (I) and α-(*o*-biphenylyl)desoxybenzoin (II), and studied their behavior toward lithium aluminum hydride in pyridine. The cleaved carbanions would all have comparable resonance stability, and indeed the anions of 4-benzylbiphenyl and 2-benzylbiphenyl can be generated from their conjugate acids under the conditions of reduction (see below). Also, α-(1-naphthyl)desoxybenzoin (III) was reduced, although the cleaved anion would have only nine resonance forms, rather than ten as do the other species under consideration. Finally, methyl trityl ketone was compared with benzpinacolone in order to evaluate the effect of a smaller group in opposition to the neighboring phenyls of the trityl group.

Ketones I and II underwent normal reduction without any evidence of carbanion formation, as shown by the complete absence of characteristic orange to purple colors attributable to the anions. Also, product studies and infrared spectra showed that no cleavage products were present. Furthermore, it was observed that 1,2-diphenyl-2-*p*-biphenylylethanol was not cleaved by hot alcoholic sodium hydroxide, under conditions where benzpinacolyl alcohol was converted to triphenylmethane and benzaldehyde.[6] Reduction of III also gave only normal product. Regardless of which diastereomer would result in the reduction of these ketones, the intermediate alkoxyaluminohydride can achieve a conformation in which no aryl group is flanked by *two* aryl groups on the adjacent carbon.

Such nonbonded interaction of large groups, evident in the alkoxyaluminohydride from benzpinacolone (IV), causes considerable stretching and weakening of the carbon-carbon bond and may facilitate the cleavage reaction. Methyl trityl ketone (V) when subjected to reductive cleavage conditions, gave less than 10% yield of triphenylmethane, whereas IV had given 72% cleavage in a parallel experiment.[3] This difference can most satisfactorily be attributed to steric factors.[7]

(1) Taken in part from the B.S. thesis of J. R. Rogozinski, U. of Buffalo, June 1960.

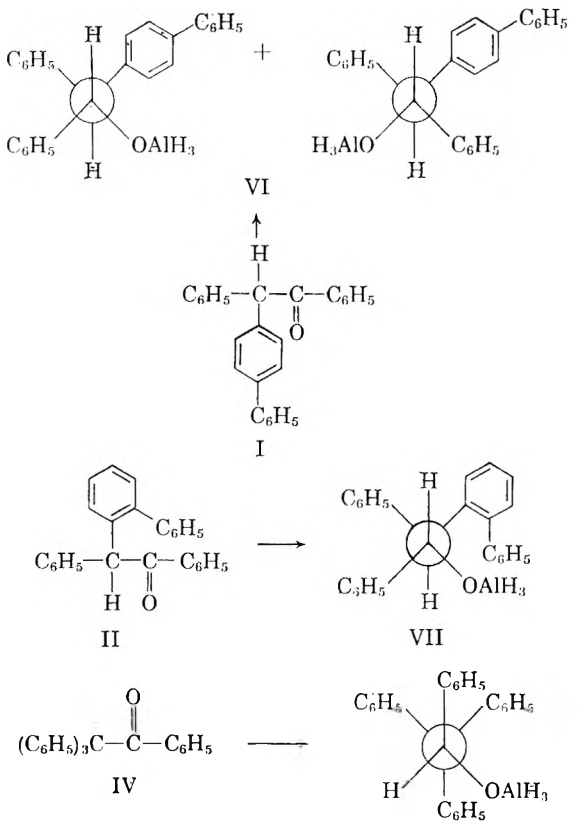
(2) Participant in a summer research program for high school teachers of science in 1960, sponsored by the National Science Foundation (Grant G-10957).

(3) P. T. Lansbury, *J. Am. Chem. Soc.*, **83**, 429 (1961).

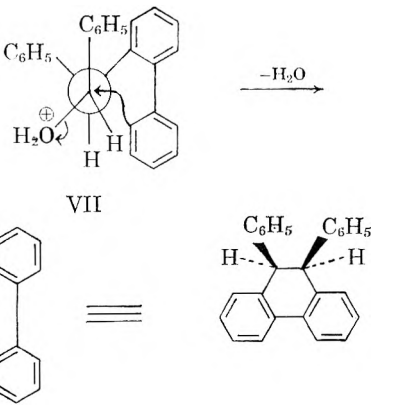
(4) (a) H. D. Zook, J. Marsh, and D. F. Smith, *J. Am. Chem. Soc.*, 81, 1617 (1959); (b) D. J. Cram *et al.*, *J. Am. Chem. Soc.*, **81**, 5740–5790 (1959).

(5) E. S. Gould, *Mechanism and Structure in Organic Chemistry*, Holt, Dryden, and Winston, Inc., New York, N. Y., 1959, p. 676.

(6) L. Ellison and J. Kenyon, *J. Chem. Soc.*, 779 (1954).

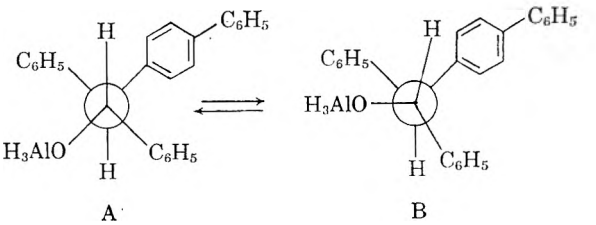


Ketones I, II, and III were prepared by the stereospecific addition of the appropriate organolithium compound to *dl*-benzoin, yielding the *dl-erythro*-triarylethylene glycols,[8] followed by pinacol rearrangement of the diols. The crude oily carbinols, VI and VII, resulting from reduction of I and II were shown to be free of ketone and cleavage products by infrared spectroscopy. Since I could undergo reduction equally well in either of two preferred conformations (assuming equal bulk for phenyl and *p*-biphenylyl),[9] it is not surprising that the crystallized product exhibited a broad melting range, suggesting a mixture of the two diastereomeric racemates. Although the carbinol from II could not be obtained in crystalline form, it was apparently quite pure *dl-threo* racemate, as predicted by Cram's rule.[9] This conclusion is based on the finding that cyclodehydration of the crude carbinol affords pure *cis*-9,10-diphenyl-9,10-dihydrophenanthrene[10] and none of the more stable *trans* isomer. In the dehydration step, the displacement of water from the protonated carbinol by



the ideally situated aryl group occurs with inversion of configuration, as in the pinacol rearrangement.[11] Apparently, no free long-lived carbonium ion is formed, since such an intermediate should lead to at least some *trans* isomer. Moreover, any hydrogen or phenyl migration in the intermediate ion, prior to alkylation, should lead to 9-phenyl-9-benzylfluorene or 9-benzhydrylfluorene, neither of which were found in the reaction mixture. A similar dehydration of 1,2-diphenyl-2-α-naphthylethanol, obtained from reduction of the corresponding ketone (III), and hence presumably rich in *threo* racemate,[9] gave an oily product from which no *cis*-1,2-diphenylacenaphthene could be obtained. The expected presence of both racemates in this alcohol mixture,[12] as well as the anticipated difficulty in forming the acenaphthene ring may well be responsible for the complexity of the dehydration product.

The acidity of triphenylmethane, 2-benzyl- and 4-benzylbiphenyl toward lithium aluminum hydride in pyridine is shown by the formation of typical highly colored carbanion solutions,[13] the first being blood red, the second orange, and the last deep violet. Since the three above carbanions can all be formed under reduction conditions, the cleavage of IV, versus normal reduction of I and II, appears to depend on steric compression due to phenyl-phenyl interaction in the alkoxyalumino-



(7) However, the resonance energy of acetaldehyde, which is obtained from cleavage of V, is not as great as benzaldehyde, from IV, and therefore the carbonyl-forming transition state from V may be less stabilized than that from IV.

(8) D. J. Cram and K. Kopecky, *J. Am. Chem. Soc.*, **81**, 2748 (1959); D. Y. Curtin, E. E. Harris, and E. K. Meislich, *J. Am. Chem. Soc.*, **74**, 2901 (1952).

(9) D. J. Cram and F. A. Elhafez, *J. Am. Chem. Soc.*, **74**, 5828 (1952).

(10) E. D. Bergmann and Z. Pelchowicz, *J. Org. Chem.*, **19**, 1387 (1954).

(11) P. D. Bartlett and R. F. Brown, *J. Am. Chem. Soc.*, **62**, 2927 (1940).

(12) A. McKenzie and W. S. Dennler, *J. Chem. Soc.*, **125**, 2105 (1924). These workers observed a moderate degree of stereospecificity in the sodium-alcohol reduction of α-naphthylbenzoin oxime, the ratio of diastereomeric products being about 4:1.

(13) J. E. Leffler, *The Reactive Intermediates of Organic Chemistry*, Interscience Publishers, Inc., New York, N. Y., 1956, p. 177.

hydride ion from IV. When a neighboring phenyl is flanked on one side by a hydrogen atom, a small rotational adjustment toward the small group appears to relieve interference with the large group flanking the other side, as shown in conformation B for alkoxide VI.

The small amount of cleavage from methyl trityl ketone is due to the absence of severe phenyl-phenyl interactions in the alkoxide from V, and their replacement by the less effective phenyl-methyl interactions.

EXPERIMENTAL[14]

Preparation of α-(p-biphenylyl)hydrobenzoin. A solution of *p*-biphenylyllithium was prepared, according to the procedure of Gilman and Dunn,[15] from 1.34 g. (0.19 g.-atom) of lithium, 20.9 g. (0.089 mole) of *p*-bromobiphenyl, and 400 ml. of anhydrous ether. The gradual addition of 5.30 g. (0.025 mole) of benzoin led to the appearance of an olive-green color. After setting overnight, the reaction mixture was hydrolyzed with saturated ammonium chloride solution and the resulting ether layer washed with sodium bicarbonate solution, dried over sodium sulfate, and subsequently evaporated nearly to dryness. The remaining paste was stirred with ligroin and the resulting solid filtered and dried. This crude material showed no carbonyl absorption in the infrared (Nujol mull). Recrystallization from ethanol gave three crops of the desired carbinol, totaling 6.55 g. (72%) and melting at 205–218°. The analytical sample of the alcohol had m.p. 220.5–221.5° (from ethanol).

Anal. Calcd. for $C_{26}H_{22}O_2$: C, 85.2; H, 6.1. Found: C, 84.4; H, 6.0.

Preparation of α-(p-biphenylyl)desoxybenzoin. Five grams of the above glycol was dissolved in 25 ml. of hot acetic acid, which contained a few drops of sulfuric acid, and refluxed for 5 min. The solution was then cooled, poured into ice water, and the white precipitate removed by filtration, washed with water, dilute bicarbonate, and dried. This crude material was free of glycol, as judged by infrared. Recrystallization from ethanol (Norit) gave 2.2 g. of the ketone (I), m.p. 146–149°, from which an analytical sample was obtained, m.p. 147–149°. The yield of I was 46%, although more impure ketone could be isolated from the filtrates.

Anal. Calcd. for $C_{26}H_{20}O$: C, 89.6; H, 5.9. Found: C, 89.4; H, 5.8.

The ketone showed a strong carbonyl band at 1685 cm.$^{-1}$ in its infrared spectrum (Nujol mull).

Reduction of α-(p-biphenylyl)desoxybenzoin (I) with lithium aluminum hydride in pyridine. A half gram of I (1.4 mmoles) was dissolved in 10 ml. of dry pyridine and 0.11 g. of lithium aluminum hydride (2.9 mmoles) added, whereupon an exothermic reaction ensued and a pale green color appeared. The reaction mixture was allowed to stand for 3 hr. in a stoppered Erlenmeyer flask, then poured into excess 5% hydrochloric acid. The acidic slurry was extracted two times with ether and the extracts were washed with sodium bicarbonate solution, salt solution, and finally dried over magnesium sulfate. Removal of the ether left an oil whose infrared spectrum showed strong hydroxyl absorption at 3600–3300 cm.$^{-1}$, no absorption in the carbonyl region, and no band at 855 cm.$^{-1}$, where 4-benzylbiphenyl, the product which would result from reductive cleavage, displays a medium intensity band. The crude product was taken up in ethanol, from which several crops of alcohol (VI) melting in the range 111–130° were obtained, yield: 0.39 g. (78%). For analysis, a sample of VI, containing both diastereomeric racemates, was obtained as fluffy crystals, m.p. 125–130° (from ethanol).

Anal. Calcd. for $C_{26}H_{22}O$: C, 89.1; H, 6.3. Found: C, 89.2; H, 6.3.

Reduction of α-(1-naphthyl)desoxybenzoin (III) with lithium aluminum hydride in pyridine. The ketone (III) was prepared according to the procedure of McKenzie and Roger,[16] by rearrangement of the pinacol prepared from 1-naphthylmagnesium bromide and benzoin. In our hands, the glycol had m.p. 181–183° (from ethanol or benzene) whereas McKenzie reported m.p. 205°, and claimed the isolation of a 180–181° epoxide from acid-catalyzed rearrangement of the glycol, in addition to III. Our glycol showed strong hydroxyl absorption at 3600–3400 cm.$^{-1}$ and therefore could not be an epoxide.

One half gram of III, m.p. 107–108°, was reduced with excess lithium aluminum hydride in pyridine as described above for ketone I. The crude oily product showed strong hydroxyl absorption (3650–3400 cm.$^{-1}$) and only a trace of ketone at 1685 cm.$^{-1}$ Trituration with cold ethanol afforded 0.15 g. (30%) of crystals melting at 108–124° and showing an infrared spectrum essentially identical with that of the above oil, except that carbonyl absorption was completely absent. From this diastereomeric mixture, an analytical sample was obtained, m.p. 126–132 (ethanol).

Anal. Calcd. for $C_{24}H_{20}O$: C, 88.9; H, 6.3. Found: C, 88.9; H, 6.2.

A portion of the oily carbinol from III was refluxed for 15 min. with glacial acetic acid, containing a small amount of *p*-toluenesulfonic acid. Cooling and dilution did not give any crystalline product.

Preparation of α-(o-biphenylyl)hydrobenzoin. *o*-Biphenylyllithium was prepared according to the procedure of Gilman and Dunn,[15] using 1.34 g. (0.19 g.-atom) of lithium wire, 20.9 g. (0.088 mole) of 2-bromobiphenyl, and 300 ml. of anhydrous ether. Benzoin (5.3 g., 0.025 mole) was added in portions to the lithium reagent and the mixture then allowed to stand overnight. Work-up of the product followed the procedure used for the *p*-biphenylyl analog (above), yielding 6.41 g. of crude glycol, m.p. 145–173°, yield: 57%. The first crop of material, m.p. 166–173°, was examined by infrared and found to be free of carbonyl absorption. Recrystallization of this material from ethanol-benzene provided an analytical sample, m.p. 173–174°.

Anal. Calcd. for $C_{26}H_{22}O_2$: C, 85.2; H, 6.1. Found: C, 85.1; H, 6.0.

The known α-(*o*-biphenylyl)desoxybenzoin (II) was prepared from the above glycol by treatment with iodine–acetic acid in the usual manner. Fractional recrystallization from ethanol separated the crude product into 9,10-diphenylphenanthrene, m.p. 234–235° and mixed m.p. 234–235°, which results from the slow cyclodehydration of II[17] and the desired ketone, m.p. 94–98° (reported[17] m.p. 98–99°).

Reduction of α-(o-biphenylyl)desoxybenzoin (II) with lithium aluminum hydride. One half gram of II (1.4 moles) was dissolved in 10 ml. of pyridine and treated with 0.11 g. (2.9 mmoles) of lithium aluminum hydride. As in the reduction of ketones I and III, no bright colors attributable

(14) Melting points were taken in a "Mel-temp" capillary melting point apparatus which was checked with known compounds, and are uncorrected. Infrared spectra were obtained with a Perkin-Elmer model 21 spectrometer equipped with sodium chloride optics. Solids were examined as Nujol mulls and oils were smeared between salt plates. Elemental analyses were performed by Dr. Alfred Bernhardt, Max Planck Institute, Mulheim, Germany. The technique employed for running lithium aluminum hydride reductions in pyridine is essentially the same as that reported previously.[3]

(15) H. Gilman and G. E. Dunn, *J. Am. Chem. Soc.*, **73**, 5078 (1951).

(16) A. McKenzie and B. Roger, *J. Chem Soc.*, **125**, 853 (1924).

(17) C. K. Bradsher and L. J. Wissow, *J. Am. Chem. Soc.*, **68**, 1094 (1946).

to carbanions were noted. Work-up in the usual manner gave an oil whose infrared spectrum indicated complete reduction of the ketone (no absorption at 1685 cm.$^{-1}$) but which resisted crystallization. Stirring with cold ethanol allowed the separation of a few milligrams of 9,10-diphenylphenanthrene, m.p. 233–235°, which apparently was a minor contaminant in II. When further attempts to crystallize the oil failed, it was treated with hot acetic acid, which contained a small amount of *p*-toluenesulfonic acid. After 15 min. of reflux, the solution on cooling yielded pure *cis*-9,10-diphenyl-9,10-dihydrophenanthrene, m.p. 169–171°, in 70% yield. The reported[10] m.p. is 168–169°. The ultraviolet spectrum of this product, taken in ether solution, was identical with the reported curve,[10] showing λ_{max} 269 mμ and log ϵ = 4.05.

Further proof of the structure of the dehydration product was gained by dehydrogenation to 9,10-diphenylphenanthrene. This was accomplished by refluxing the dihydro compound (0.2 g.) with an equimolar quantity of *N*-bromosuccinimide (0.11 g.) in carbon tetrachloride for 2 hr., under conditions where the monobromo derivative readily loses hydrogen bromide.[18] The expected amount of succinimide was recovered by filtration of the cooled solution, which was then evaporated down on a steam bath. Recrystallization of the crude product, m.p. 197–213°, from acetic acid, containing a little potassium acetate afforded pure 9,10-diphenylphenanthrene, m.p. 234–236°, weight 0.13 g. The possibility that the dihydro compound was the *trans* isomer was precluded by the lower reported melting point of 130–131°.[19]

Repetition of the reduction of II, followed by dehydration of the crude carbinol, gave *cis*-9,10-diphenyl-9,10-dihydrophenanthrene as the only isolable product.

Reductive cleavage of methyl trityl ketone. One gram (3.5 mmoles) of methyl trityl ketone[20] in 20 ml. of pyridine was treated with 0.20 g. of lithium aluminum hydride, whereupon an exothermic reaction ensued and a blood red coloration soon developed. After 3 hr., the reaction mixture was hydrolyzed and worked up in the usual manner, yielding a pale yellow oil whose infrared spectrum showed strong hydroxyl absorption in the 3600–3400 cm.$^{-1}$ region and generally resembled that of pure methyltritylcarbinol. Chromatography of the oil over alumina yielded an initial fraction of crude triphenylmethane (0.10 g.; 12% yield) having m.p. 65–79°, which was eluted with benzene. Recrystallization from methanol afforded 0.06 g. of triphenylmethane which had m.p. 85–90°. Further elution with benzene and then 1:1 benzene-ethanol, gave 0.82 g. (82%) of methyltritylcarbinol, m.p. 94–97° (reported[21] m.p. 93–95°) after combination of the several fractions which had fairly sharp melting points in the range 86–98°. A mixed melting point of the alcohol with triphenylmethane was strongly depressed and the spectra of the two compounds were wholly different.

Attempted cleavage of 1,2-diphenyl-2-biphenylylethanol with ethanolic sodium hydroxide. The alcohol (0.15 g.; m.p. 125–130°) was dissolved in 10 ml. of 95% ethanol and a pellet of sodium hydroxide added. The resulting solution was refluxed for 15 min., then diluted with water and allowed to cool. Two crops of crystals (0.15 g.) were obtained, m.p. 113–116° and 109–112°, which amounted to an essentially quantitative recovery of the alcohol. The infrared spectrum of the combined crystals was identical with that of the starting diastereomeric alcohol mixture. A portion of the filtrates was made acidic and tested with 2,4-dinitrophenylhydrazine, resulting in a negative test for benzaldehyde.

Metalation of triphenylmethane, 2-benzylbiphenyl, and 4-benzylbiphenyl by means of lithium aluminum hydride in pyridine.[22] When small quantities of triphenylmethane (1.0 to 2.0 g.) were dissolved in pyridine and *ca.* two molar equivalents of lithium aluminum hydride added, the evolution of gas was evident, as well as the appearance of the blood red color of triphenylmethide ion.[3,13] The resulting carbanion solutions were allowed to stand for 1–2 hr. in stoppered flasks, then poured onto a crushed Dry-Ice–ether slurry. After evaporation of excess Dry Ice, the mixture was hydrolyzed with 5% hydrochloric acid and the ether layer separated and extracted with 5% sodium hydroxide. Acidification of the alkaline extract afforded triphenylacetic acid, m.p. 255–265° (with prior softening). Yields of the acid were as high as 19% using this method of carbonation; bubbling carbon dioxide gas into stirred carbanion solutions gave decidedly inferior yields.

Several exploratory reactions of 4-benzylbiphenyl, carried out as above, yielded deep purple colored solutions of the carbanion. Difficulty was experienced in preparing the carboxylic acid, however. The anion of 2-benzylbiphenyl was also similarly obtained as a deep orange solution. It should be noted that these intense colors constitute convincing evidence for the presence of resonance-stabilized carbanions,[13] and their appearance is not confusable with the pale orange-green coloration noted when lithium aluminum hydride interacts with pyridine.

BUFFALO 14, N. Y.

(18) R. A. Barnes, *J. Am. Chem. Soc.*, **70**, 145 (1948).
(19) W. Schlenk and E. Bergmann, *Ann.*, **463**, 89 (1928).
(20) Kindly furnished by Professor H. D. Zook.
(21) V. Prelog, E. Philbin, E. Watanabe, and M. Wilhelm, *Helv. Chim. Acta*, **39**, 1086 (1956).
(22) Several of these experiments were performed by Dr. N. Simmons.

[CONTRIBUTION FROM THE CHEMICAL RESEARCH DEPARTMENT, AGRICULTURAL DIVISION, AMERICAN CYANAMID CO.]

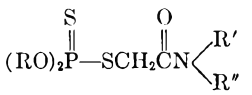
O,O-Dialkyl S-(carbamoylalkyl) phosphorodithioates

GERALD BERKELHAMMER, SHIRLEY DuBREUIL, AND RICHARD W. YOUNG

Received October 13, 1960

The preparation of thirty-six O,O-dialkyl S-(carbamoylalkyl) phosphorodithioates is described. Several new or improved synthetic routes are employed, most importantly one utilizing S-carboxymethyl O,O-dimethyl phosphorodithioate. The product of displacement of a phosphorothioate salt on an α-haloamide is shown to have the phosphorothiolate structure.

It has been reported[1] that a number of O,O-dialkyl S-(alkylcarbamoylmethyl) phosphorodithioates (I) exhibit activity as animal systemic insecticides.

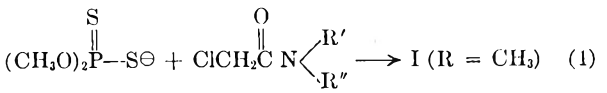


I

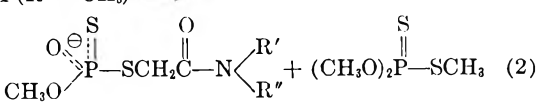
Work in these laboratories and elsewhere[2] has also established their utility as contact and systemic agents for use against insects and mites infesting plants. Many of the O,O-dimethyl esters I (R = CH_3) combine high activity with relatively low mammalian toxicity. The purpose of this paper is to record the synthesis of these and certain other members of the carbamoylalkyl phosphorodithioate series.

Thirty-six phosphorodithioates were prepared and are listed in Tables I and II. Amide nitrogen substituents include, among others: alkyl, dialkyl, aryl, heterocyclic, acyl, and sulfonyl. In addition, some variation was introduced into the phosphorus-bound alkoxyls and the alkylene group joining the phosphorodithioate and carbamoyl moieties.

Hoegberg and Cassaday[3] first prepared compounds of this class by the reaction of O,O-dialkyl phosphorodithioate salts with α-haloamides in ketonic solvents. Much of the work reported here employed variations on this technique. It was soon discovered, however, that in the syntheses of the O,O-dimethyl compounds, the method was not very satisfactory, owing to the excellent methylating ability of the products, which could successfully compete with the haloamides for the phosphorodithioate anion:



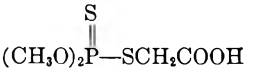
II



(1) R. Hewitt, A. Brebbia, and E. Waletzky, *J. Econ. Entomol.*, **51**, 126 (1958).

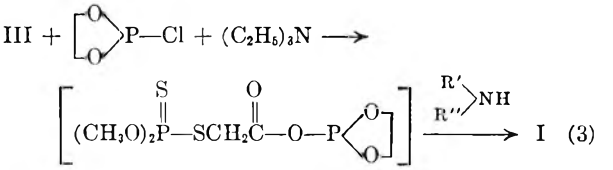
The formation of large amounts of O,O,S-trimethyl phosphorodithioate was characteristic of those reactions conducted by the conventional procedures.[3]

An effective means of shortening the synthetic route and at the same time avoiding the difficulty outlined above was discovered in the preparation and subsequent utilization of S-carboxymethyl O,O-dimethylphosphorodithioate (III). This compound, which was prepared from the reaction of II



III

(potassium salt) with chloroacetic acid, yielded only unidentifiable products when attempts were made to convert it to amides through the acid chloride. A search for milder conditions led to the discovery of the following successful route:



R = Methyl

A simple procedure which has proved valuable in the field of peptide synthesis,[4] this sequence could be carried out under mild conditions in benzene solution. It generally gave yields comparable to those obtainable from direct displacement on the chloroamides and often afforded products of superior purity.

Several other peptide-forming agents were tried in the preparation of the carbamoylalkyl phosphorodithioates, but with generally less success. In a variation of the phosphorochloridite method above, S-(*t*-butylcarbamoylmethyl) O,O-dimethyl phosphorodithioate (XVIII) was obtained impure and in low yield by treating III with IV.[4,5]

(2) W. J. Magee and J. C. Gaines, *J. Econ. Entomol.*, **43**, 281 (1950); E. E. Ivy, *Agr. Chem.*, **8**, 47 (1953); P. DePietri-Tonelli, *Ital. Agr.*, **1956**, No. 1.

(3) E. I. Hoegberg and J. T. Cassaday, *J. Am. Chem. Soc.*, **73**, 557 (1951).

(4) R. W. Young, K. H. Wood, R. J. Joyce, and G. W. Anderson, *J. Am. Chem. Soc.*, **78**, 2126 (1956).

(5) G. W. Anderson, J. Blodinger, R. W. Young, and A. D. Welcher, *J. Am. Chem. Soc.*, **74**, 5304 (1952).

TABLE I

O,O-DIMETHYL *S*-CARBAMOYLMETHYL PHOSPHORODITHIOATES

$(CH_3O)_2P(=S)-S-CH_2-C(=O)-Y$

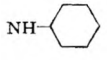
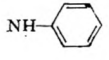
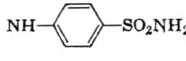
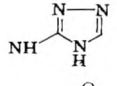
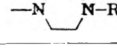
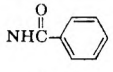
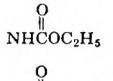
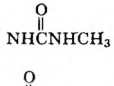
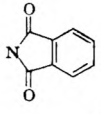
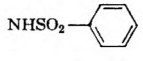
Compound	Y	Method	Recrystallization Solvent	Yield, %[a]	M.P. or n_D^{25}[b]	Calcd. C	Calcd. H	Calcd. N	Calcd. P	Found C	Found H	Found N	Found P
XII	$NHCH_3$	C	Toluene-heptane	53	50–51	26.2	5.28	6.11	13.5	26.4	5.38	6.40	13.6
XIII	NHC_2H_5	C	Toluene-heptane	67	67–68	29.6	5.80	5.76	12.7	30.0	6.19	5.85	12.6
XIV	NHC_3H_7-*n*	A	Methanol	19	63.5–64	32.7	6.27	5.44	12.0	32.8	6.29	5.73	12.1
XV	NHC_3H_7-*i*	A	Methanol-ether	28	76–77	32.7	6.27	5.44	12.0	33.0	6.18	5.16	12.4
XVI	NHC_4H_9-*n*	A	Ether (−70°)	<5	31–31.5	35.4	6.68	5.16	11.4	35.5	6.64	4.87	11.4
XVII	NHC_4H_9-*i*	A	Methanol-water	31	68.5–69	35.4	6.68	5.16	11.4	35.7	6.86	4.99	11.6
XVIII	NHC_4H_9-*t*	C[c]	Ethanol-water	53	64.5–65	35.4	6.68	5.16	11.4	35.2	6.59	4.96	11.6
XIX	NHC_8H_{17}-*n*	D	Chromatographed[d]	20	1.5136	44.0	8.01	4.28	9.46	44.1	7.82	4.23	9.45
XX	$NH-CH_2-CH=CH_2$	A	Methanol	33	57.5–58	32.9	5.53	5.49	12.1	32.8	5.73	5.64	12.3
XXI		A	Ethanol-water	37	102–103	40.4	6.78	4.71	10.4	40.4	6.86	4.56	10.7
XXII		B[e]	Methanol-water	16	83.5–84	41.2	4.84	4.81	10.6	41.2	5.03	4.79	10.6
XXIII		B[e]	Ethanol-water	19	136.5–137.5	32.4	4.08	7.56	8.36	32.5	4.31	7.43	8.07
XXIV		C	Isopropanol	<5	151–153	25.5	3.93	19.9	11.0	26.0	4.08	19.8	10.9
XXV	$NHCH_2C(=O)OCH_3$	C	Ether	25	41–42	29.3	4.91	4.88	10.8	29.6	5.09	4.78	10.7
XXVI	$NHCH_2C(=O)NH_2$	B	Ethanol	31	97–97.5	26.5	4.81	10.3	11.4	26.7	5.00	10.2	11.4
XXVII	$NHOCH_3$	D	Ether	23	42.5–43.5	24.5	4.93	5.71	12.6	24.7	5.09	5.78	12.5
XXVIII	$N(CH_3)_2$	C	B.p. 106°/0.005 mm.[f]	9	1.5400	29.6	5.80	5.76	12.7	30.0	6.09	5.49	12.5
XXIX	$N(C_2H_5)_2$	C	Chromatographed[g]	<5	1.5275	35.4	6.68	5.16	11.4	35.7	6.91	5.14	11.0
XXX		D	Benzene	46	70.5–71.5	35.7	5.99	5.20	11.5	35.7	6.42	4.95	11.8
XXXI		D	Chromatographed[h]	52	1.5523	38.1	6.40	4.94	10.9	37.8	6.94	5.09	10.8
XXXII		C	Ethanol-water	61	63.5–64	33.4	6.31	4.87	10.8	33.5	6.18	4.87	10.7
XXXIII		D	Methanol	5	137.5–138.5	29.9	5.01	5.81	12.8	29.6	5.14	5.44	12.6

TABLE I (*Continued*)

Compound	Y	Method	Recrystallization Solvent	Yield, %[a]	M.P. or n_D^{25}[b]	Calcd. C	Calcd. H	Calcd. N	Calcd. P	Found C	Found H	Found N	Found P
XXXIV		B	Isopropanol	49	115–116	41.4	4.42	4.39	9.70	41.4	4.47	4.30	9.75
XXXV		B	Ether-hexane	55	57.5–58[f]	29.3	4.91	4.88	10.8	29.2	4.95	4.94	10.8
XXXVI		B[e]	CCl_4	56	106.5–107.5	26.5	4.81	10.3	11.4	26.7	4.85	10.1	11.4
XXXVII		B	$CHCl_3$—CCl_4	15	108–109	41.7	3.50	4.06	8.97	41.7	3.56	3.98	8.93
XXXVIII		B[j]	CCl_4	53	86–87	33.8	3.97		8.72	34.1	4.27		8.84

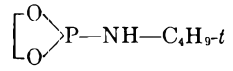
[a] Yields quoted are of analytically pure material or of material very close in melting point or refractive index to the pure compound. Losses in work-up were often high, especially in Methods A and B; and only in a few cases were efforts made to maximize yields. [b] Melting points are uncorrected. [c] A three-solvent system was used: 90 g. of water, 110 g. of toluene, and 49 g. of methanol for a 0.3 mole reaction. [d] Acid-washed unactivated alumina. Compound placed on column in benzene, eluted with benzene followed by ether and finally chloroform. [e] Acetone instead of methyl isobutyl ketone was used as solvent. The reactants were heated under reflux for from 35 min. to 3 hr., the solvent removed under vacuum, and the residue taken up in benzene, chloroform, or methyl isobutyl ketone for washing. The rest of the work-up was performed as detailed under Method B in the Experimental. [f] Molecular distillations. The boiling points listed represent the temperature of the heating jacket of the still. [g] Acid-washed unactivated alumina. Compound placed on column in benzene, eluted with chloroform followed by chloroform-ether mixtures. A fraction eluted with 60:40 chloroform:ether was rechromatographed and eluted with benzene-hexane to give the pure material. [h] Acid-washed activated alumina. Compound placed on column in benzene. Elution with benzene gave several impure fractions, but later benzene fractions, followed by fractions eluted with ether and chloroform, all had identical infrared spectra and n_D^{25} 1.5520–1.5524. [i] G. Schrader, Ger. **963,872**, reported m.p. 46°. [j] The crude product was taken up in 10% sodium bicarbonate, the solution extracted with chloroform, and the product reprecipitated with hydrochloric acid. The reprecipitated oil was dissolved in chloroform and dried over magnesium sulfate before recrystallization. [k] R = $(CH_3O)_2P(S)CH_2C(O)$—.

TABLE II

O,O-DIALKYL *S*-CARBAMOYLALKYL PHOSPHORODITHIOATES, $(RO)_2P(S)-SR'C(O)NHR''$

Compound	R	R′	R″	Method	Recrystallization Solvent	Yield,[a] %	M.P. or n_D^{25}[b]	Calcd. C	Calcd. H	Calcd. N	Calcd. P	Found C	Found H	Found N	Found P
XXXIX	CH_3	$-CH(CH_3)-$	CH_3	B	Ether (−20°)	30	52.5–53	29.6	5.80	5.76	12.7	29.4	5.78	5.48	12.9
XL	CH_3	$-CH(C_2H_5)-$	CH_3	B	Heptane	5	72–73	32.7	6.27	5.44	12.0	32.8	6.29	5.39	12.2
XLI	CH_3	$-CH_2CH_2-$	CH_3	C	Ether	43	56.5–57	29.6	5.80	5.76	12.7	29.4	5.78	5.59	12.6
XLII	C_2H_5	CH_2	CH_3	B[c]	Ether-pet. ether (−70°)	83	27–28[d]	32.7	6.27	5.44	12.0	32.8	6.23	5.36	12.1
XLIII	C_2H_5	CH_2	C_2H_5	B[c]	[e]	83	1.5231			5.16	11.4			5.33	11.5
XLIV	C_2H_5	CH_2	i-C_3H_7	B[c]	[e]	93	1.5147			4.91	10.9			4.52	11.1
XLV	C_2H_5	CH_2	t-C_4H_9	A	Ether (−70°)	24	31–31.5	40.1	7.41	4.68	10.4	40.1	7.75	4.67	9.83
XLVI	C_2H_5	CH_2	$CH_3C(O)-$	B	B.p. 90–92°/0.001 mm.[f]	51	1.5300	33.7	5.65	4.91	10.9	33.9	5.88	4.84	10.8
XLVII	C_2H_5	$-CH(CH_3)-$	CH_3	B	Methanol-water	59	62–63	35.4	6.68	5.16	11.4	35.3	6.62	5.26	11.4

[a] See footnote a, Table I. [b] Melting points are uncorrected. [c] See footnote *e*, Table I. [d] Reported by Hoegberg and Cassaday[3] as an oil. [e] The crude oils proved to be analytically pure. [f] See footnote *f*, Table I.

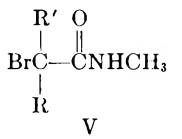


IV

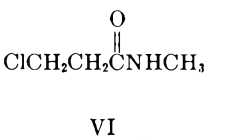
The use of dicyclohexylcarbodiimide[6] with III and either propylamine or *t*-butylamine failed to give the amides. In a single trial, the carbonic-carboxylic anhydride method using ethyl chlorocarbonate[7] did not yield any XII. Though the synthesis of peptides *via* some of the phosphite procedures is catalyzed by an equivalent of imidazole,[8] no such catalysis was detected in the preparation of the *n*-octyl compound (XIX) by the phosphorochloridite method.

A second means of reducing the consequences of reaction (2) was found in the use of a two-phase solvent system. In a toluene-water or a chloroform-water system, for example, reaction (1) occurs in the aqueous phase, while the product is immediately extracted into the organic layer as it is produced. This method was limited to those haloamides with some degree of water solubility, although in some cases, *e.g.*, compound XVIII, an unfavorable distribution of haloamide between the two phases could be overcome by the addition of a third solvent, such as methanol or ethanol.

Among those reactions carried out by direct displacement of potassium *O,O*-dimethyl phosphorodithioate on a haloamide, the effect on yields of variation in haloamide reactivity was studied.



V



VI

In the series of monoalkyl-substituted α-bromoamides, V (R′ = H), yields decreased with increasing bulk of R. Thus V (R = CH_3) gave a 30% yield of phosphorylated product after four hours at 50° in methyl isobutyl ketone whereas V (R = C_2H_5) gave a 2% yield under the same conditions, and reaction of V (R = $i-C_3H_7$) at 80° for fifteen hours resulted only in a 75% recovery of bromoamide. The tertiary bromide, V (R = R′ = CH_3), yielded no identifiable products when treated for eight hours with triethylammonium *O,O*-dimethyl phosphorodithioate in refluxing benzene. Compound VI and potassium *O,O*-dimethyl phosphorodithioate in refluxing acetone for 7.5 hours resulted in a 53% recovery of chloroamide, a 21% recovery of phosphorodithioate salt, and no desired product. On the other hand, the corresponding β-bromoamide yielded 43% of product after a considerably shorter time in refluxing toluene-water.

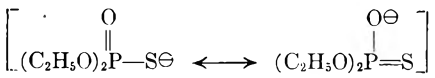
(6) J. C. Sheehan and G. P. Hess, *J. Am. Chem. Soc.*, **77**, 1067 (1955).

(7) J. R. Vaughan, Jr., and R. L. Osato, *J. Am. Chem. Soc.*, **74**, 676 (1952).

(8) G. W. Anderson, A. C. McGregor, and R. W. Young, *J. Org. Chem.*, **23**, 1236 (1958).

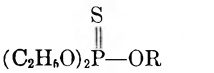
The procedures discussed above were applied to the synthesis of phosphorothioates by the reaction of potassium *O,O*-dimethyl phosphorothioate with α-haloamides.

Recently, Mandel'baum, *et al.*[9] have claimed that reaction of *O,O*-diethyl phosphorothioate salts (VII) with α-haloamides and esters have given the

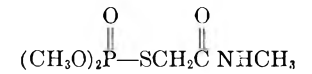


VII

phosphorothionate form of the product (VIII). In one case which we have carefully examined, the preparation of IX, spectral data conclusively



VIII



IX

show that the product has the thiol structure. Thus, the infrared spectrum shows a strong band at 1250 cm.$^{-1}$, which is characteristic of the P = O group.[10] The assignment of the thiol structure was supported by the proton magnetic resonance spectrum,[11,12,13] taken in deuterochloroform, which showed resonance peaks of 2.62 and 2.88 p.p.m., which have been assigned[11] to the CH_3OP and $PSCH_2C{=}O$ moieties respectively from observations of a number of model compounds. They have the appropriate intensity ration and appear as doublets[14] due to spin-coupling with the phosphorus nucleus. The splittings correspond to those commonly observed[11] for CH protons linked to phosphorus through oxygen or sulfur and in this compound have the values 16 c.p.s. for the CH_3OP group and 11 c.p.s. for the CH_2SP group. The formation of the phosphorothiolate isomer in this reaction is consistent with most of the work which has been reported on displacements of phosphoromonothioate salts on alkyl halides.[3,15]

A novel reaction occurred during an attempt at preparation of X. The low-melting solid, presumably X, that was initially obtained, changed on standing to a compound that melted at 170° and was water soluble. On the basis of infrared and NMR spectral data, it has been assigned the

(9) Ya A. Mandel'baum, N. N. Mel'nikov, and P. G. Zaks, *Zhur. Obsch. Khim.*, 29, 283 (1959).

(10) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley & Sons, Inc., New York, 1954, p. 258.

(11) J. E. Lancaster, These Laboratories, Personal Communication.

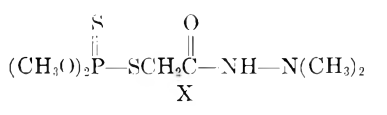
(12) S. DuBreuil and R. W. Young, 136th Meeting of the American Chemical Society, Atlantic City, N.J., Sept. 18, 1959.

(13) NMR spectra were taken with a Varian Associates V4300B high resolution spectrometer operating at 40 mc. Benzene was used as an external standard. All shifts given in this paper occur to the high field side of the benzene position.

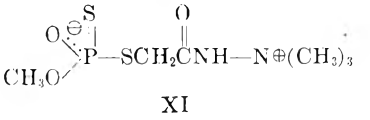
(14) T. Yamasaki, *J. Chem. Soc. Japan, Pure Chem. Sect.*, **79**, 832 (1958).

(15) M. I. Kabachnik and T. A. Mastryukova, *Zhur. Obsch. Khim.*, **25**, 1924 (1955) and references cited therein.

structure of the zwitterion XI, a product of the "internal" demethylation of X (see Experimental).



X



XI

EXPERIMENTAL[16,17]

O,O-Dialkyl carbamoylalkyl phosphorodithioates—Method A. S-(Isobutylcarbamoylmethyl) O,O-dimethyl phosphorodithioate (XVII). Triethylamine (36 g., 0.24 mole) in 20 ml. of reagent-grade benzene was added portionwise to a stirred solution of *O,O*-dimethyl hydrogen phosphorodithioate (43 g., 0.24 mole of 89% acid) in 50 ml. of benzene while maintaining the temperature between 15 and 25°. To this was added a solution of 2-chloro-*N*-isobutylacetamide (36 g., 0.24 mole) in 30 ml. of benzene, after which the reaction mixture was stirred at room temperature for 23 hr. The triethylamine hydrochloride (25 g., 75%) was removed by filtration and the filtrate was washed with 5% sodium bicarbonate until the washings were neutral or slightly basic. After washing with saturated sodium chloride solution and drying over magnesium sulfate, the solvent was removed under vacuum to give 48 g. of crude solid. Several recrystallizations from methanol-water and ethanol-water gave 20.5 g. (31%) of white crystals, m.p. 68–68.5°. The analytical sample (from methanol-water) melted at 68.5–69°.

Method B. S-(Carbamoylmethylcarbamoylmethyl) O,O-dimethyl phosphorodithioate (XXVI). To a suspension of potassium *O,O*-dimethyl phosphorodithioate[3] (20 g., 0.10 mole of salt 98.2% pure by alkaline iodine[18] titration) in 50 ml. of methyl isobutyl ketone was added *N*-carbamoylmethyl-2-chloroacetamide (15 g., 0.10 mole) in 50 ml. of methyl isobutyl ketone, followed by sodium bicarbonate[19] (8.4 g., 0.10 mole). The stirred suspension was heated at 50–60° for 5 hr. After the insoluble solids were allowed to settle, the solution was decanted or filtered and the filtrate washed with 5% sodium bicarbonate and saturated brine. Some material settled out on cooling[20] and was combined with the residue remaining after removal of the solvent under vacuum and with additional material from acetone extraction of the inorganic salts. Several recrystallizations from ethanol gave 8.5 g. (31%) of white crystalline solid, m.p. 96.5–97°. The analytical sample (from ethanol) melted at 97–97.5°.

Method C. O,O-Dimethyl S-(morpholinocarbonylmethyl) phosphorodithioate (XXXII). A solution of potassium *O,O*-dimethyl phosphorodithioate[3] (20 g. 0.10 mole of 98.2%[18] material) in 20 ml. of water was added dropwise over a 20-min. period to a rapidly stirred refluxing mixture of 4-chloroacetylmorpholine (20 g., 0.12 mole) in 20 ml. of water and 40 ml. of toluene. After an additional 5 min. stirring under reflux, the layers were separated and the aqueous layer extracted with two 10-ml. portions of fresh toluene. The combined toluene fractions were washed with 5% sodium bicarbonate and saturated sodium chloride solutions and dried over magnesium sulfate. Removal of the solvent *in vacuo* left a viscous oil, which solidified upon trituration and cooling in absolute ether; yield 20.6 g., m.p. 58–61°. Recrystallization from 20 ml. ethanol–35 ml. water gave 17.6 g. (61%) of a white crystalline solid, m.p. 63–64°.

Method D. O,O-Dimethyl S-(1-pyrrolidinylcarbonylmethyl) phosphorodithioate (XXX). Ethylene phosphorochloridite[21] (9.6 g., 0.075 mole) in about 15 ml. of reagent-grade benzene was added dropwise to a stirred, cooled solution of *S*-carboxymethyl *O,O*-dimethyl phosphorodithioate (16.2 g. 0.075 mole, see below) and triethylamine (7.6 g., 0.075 mole) in about 50 ml. of benzene in a flask protected by a drying tube. The temperature of the reaction mixture was kept below 20° during the addition. After 10 min. stirring at room temperature, the triethylamine hydrochloride (86%) was removed by filtration. Pyrrolidine (5.3 g., 0.075 mole) in about 10 ml. of benzene was added to the filtrate and the solution was heated under reflux for 30 min. The cooled solution was filtered to remove a small amount of white gum which had formed and the opalescent filtrate washed with 30 ml. of water followed by two 30-ml. portions of 20% potassium bicarbonate. After being dried over magnesium sulfate, the solvent was removed under vacuum. The residual yellow oil (12 g.) crystallized on cooling to a solid melting at 55–65°. Recrystallization from 25 ml. of benzene gave 9.4 g., (46%) of white crystals, m.p. 68.5–71.5°. The analytical sample (from benzene) melted at 70.5–71.5°.

S-(t-Butylcarbamoylmethyl) O,O-dimethyl phosphorodithioate (XVIII) *via the phosphite amide procedure.* Ethylene phosphorochloridite[21] (12.7 g., 0.1 mole) in 10 ml. of benzene was added dropwise to a stirred, cooled solution of *t*-butylamine (7.3 g., 0.1 mole) and triethylamine (10.1 g., 0.1 mole) in 20 ml. of benzene, the temperature being kept below 20°. The reaction mixture was stirred at ice temperature for 10 min. following the addition and at room temperature for an additional 5 min. The precipitated triethylamine hydrochloride (13.5 g., 99%) was filtered off and washed with fresh benzene. The filtrate was divided in half, and to each half was added 10.8 g. (0.05 mole) of *S*-carboxymethyl *O,O*-dimethyl phosphorodithioate in 20 ml. of benzene. One portion was heated under reflex for 30 min., the other for 1 hr. Each was worked up as in Method D, yielding 4.1 g. (30%) and 4.9 g. (36%), respectively, of oily solids. The 30 min. product was slurried in 50 ml. of hexane, cooled in a Dry Ice–acetone bath, filtered, and dried. The resultant oily solid (3.9 g.) exhibited an infrared spectrum virtually identical with that of analytically pure material prepared as shown in Table I.

S-Carboxymethyl O,O-dimethyl phosphorodithioate (III). A solution of 117.6 g. (0.6 mole) of potassium *O,O*-dimethyl phosphorodithioate[3] (as 124 g. of material analyzing 95% pure by Foss[18] titration) in 118 ml. of water was added over a 45-min. period, with efficient stirring, to a refluxing solution of 56.7 g. (0.6 mole) of chloroacetic acid in a mixture of 600 ml. of chloroform and 82 ml. of water. Heating under reflux and rapid stirring were continued for an additional 30 min. The reaction mixture was cooled to room temperature and the layers separated. The water layer was extracted with three 75-ml. portions of chloroform and the combined extracts and original chloroform layer washed with 40 ml. of water and dried over magnesium sulfate. Removal of the solvent under vacuum left 105 g. (81%) of an orange-brown oil, which crystallized on cooling. Three recrystallizations from 60 ml. mixtures of approximately equal volumes of carbon tetrachloride and hexane gave 71.1 g. (55%) of white crys-

(16) Because of the potential toxicity of phosphate esters, caution should be exercised when handling them.

(17) Melting points and boiling points are uncorrected. Melting points were taken on a Fisher-Johns block.

(18) The iodometric titration described by O. Foss, *Acta Chem. Scand.*, 1, 8 (1947), for phosphorothioate salts was used. Dr. D. E. Ailman of these laboratories has found it to be applicable to salts of dimethyl and diethyl phosphorodithioic acids. In the case of the dithio salts, both sulfur atoms are oxidized to sulfate.

(19) The bicarbonate was added to counteract the tendency of these reaction mixtures to become acidic.

(20) In most other preparations using this method, the product did not precipitate, and the methyl isobutyl ketone solution was dried at this point over magnesium sulfate.

(21) H. J. Lucas, F. W. Mitchell, Jr., and C. N. Scully, *J. Am. Chem. Soc.*, 72, 5491 (1950).

talline solid, m.p. 41–43.5° (98.3% pure by potentiometric titration with alkali). The analytical sample, m.p. 42–43°, was obtained by chromatography of the crude material on unactivated acid-washed alumina (ether elution).

Anal. Calcd. for $C_4H_9O_4PS_2$: C, 22.2; H, 4.20; P, 14.3; S, 29.7. Found: C, 22.3; H, 4.35; P, 14.0; S, 29.6.

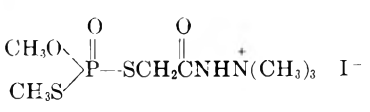
O,O-Dimethyl S-(methylcarbamoylmethyl) phosphorothioate (IX). A solution of potassium *O,O*-dimethyl phosphorothioate (111 g., 0.6 mole, 97.5% purity) and 2-chloro-*N*-methylacetamide in a chloroform-water system (200 ml. of each solvent) was rapidly stirred and heated under reflux for 2 hr. The layers were cooled and separated and the water layer extracted with two 75-ml. portions of chloroform. The combined chloroform fractions were washed with 20 ml. of 20% potassium bicarbonate solution and dried over magnesium sulfate. Removal of the solvent under vacuum left 75.4 g. of a yellow oil. Unchanged chloroamide and *O,O,S*-trimethyl phosphorothioate by-product were removed on a rotary film evaporator at a pressure of 0.4 mm. and bath temperature of 80–85°. There remained 36.9 g. of a yellow oil, which was molecularly distilled at 1 micron pressure and a jacket temperature of 100–110°. After a fore-run of liquids with low refractive index, the product (25.9 g., 20%), a straw-colored viscous oil, was collected as three fractions with n_D^{25} 1.4984, Eisenlohr-Denbigh molar refraction[22] 319.5 (Calcd. 314.3).

Anal. Calcd. for $C_5H_{16}NO_4PS$: C, 28.2; H, 5.68; N, 6.57; P, 14.5; S, 15.0. Found: C, 28.2; H, 5.65; N, 6.28; P, 14.3; S, 15.3.

2-(Mercaptomethoxyphosphinylthioacetyl)-1,1,1-trimethylhydrazonium hydroxide, inner salt (XI). *S*-Carboxymethyl *O,O*-dimethyl phosphorodithioate (38 g., 0.18 mole), ethylene phosphorochloridite (22.2 g., 0.18 mole), triethylamine (17.7 g., 0.18 mole), and anhydrous unsymdimethylhydrazine in a total of 350 ml. of benzene were allowed to react according to Method D, with the exception that following the addition of the hydrazine to the mixed anhydride the reaction mixture was stirred at room temperature for 2.5 hr. instead of being heated under reflux. A viscous oil (26 g., 59%) was obtained which had an infrared spectrum compatible with the expected hydrazide. Trituration of half the product under ether gave a white solid, m.p. 46–48°. On standing for several days this material changed to a gummy substance. Two recrystallizations from absolute ethanol gave 5 g. (23%) of a white solid, m.p. 170° dec.

Anal. Calcd. for $C_6H_{15}N_2O_3PS_2$: C, 27.9; H, 5.85; N, 10.9; P, 12.0; S, 24.8. Found: C, 27.3, 27.7, 27.6; H, 5.72, 5.98, 5.95; N, 11.0, 11.2; P, 12.3, 12.3; S, 24.9.

The zwitterionic structure was assigned on the basis of elemental analysis, the high melting point, solubility properties (soluble in water, insoluble in chloroform and benzene), and spectral evidence. The carbonyl frequency in the infrared was shifted to 1695 cm.$^{-1}$, which is about 45–50 cm.$^{-1}$ higher in frequency than the carbonyl bands of the compounds listed in Tables I and II and is in the direction to be expected for a shift caused by a proximate electron withdrawing group such as quaternary ammonium. The NMR proton spectrum[11,12,13] showed a ratio of 3 nitrogen-bound methyl groups to 1 CH_3OP group. Methylation of the product with methyl iodide gave a solid which, though it melted over a wide range and was undoubtedly impure, showed the characteristic doublet[11] of the CH_3SP group at 4.20 p.p.m. (splitting: 16 cps) in the NMR spectrum and was presumably mainly the expected methylation product of XI,



Known haloamides. The majority of the 2-chloroacetamides were prepared from chloroacetyl chloride according to the two-phase procedure of Speziale and Hamm[23] with the use of methyl isobutyl ketone instead of ethylene chloride as the nonaqueous solvent. The *N*-substituents and appropriate literature references for the known compounds prepared in this manner are as follows: ethyl,[24,25] propyl,[26] *i*-propyl,[23] butyl,[23] *i*-butyl,[26] *t*-butyl,[23] allyl,[27] phenyl,[28] and cyclohexyl.[23] *N*-(Chloroacetyl)morpholine[29] and 2-bromo-*N*-methylbutyramide[30] were similarly prepared.

The following haloamides were prepared from the corresponding haloacyl chlorides by the method described below for 3-chloro-*N*-methylpropionamide: 2-chloro-*N,N*-dimethylacetamide,[21] 2-bromo-*N*-methylpropionamide,[31,32] 2-bromo-*N*-methylisobutyramide,[30,33] and 2-bromo-*N*-methylisovaleramide.[34] The following were made by literature methods: *N*-carbamoylmethyl-2-chloroacetamide,[35] *N-p*-sulfamoylphenyl-2-chloroacetamide,[36] *N*-acetyl-2-chloroacetamide,[37] *N*-benzoyl-2-chloroacetamide,[37] *N*-chloroacetyl-*N'*-methylurea,[38] ethyl chloroacetylcarbamate,[38] and *N*-chloroacetylbenzenesulfonamide.[39] 2-Chloro-*N*-methylacetamide and 2-chloro-*N,N*-diethylacetamide were obtained commercially.

New haloamides. 2-Chloro-N-(3-triazolyl)acetamide. 3-Aminotriazole (33.6 g., 0.4 mole) and chloroacetyl chloride (56.3 g., 0.5 mole) were allowed to react according to the procedure of Speziale and Hamm[23] using methyl isobutyl ketone instead of ethylene chloride as the nonaqueous solvent. An 89% yield of solid material separated directly from the reaction mixture. Recrystallization from acetonitrile gave the analytical sample, m.p. 272° dec.

Anal. Calcd. for $C_4H_5ClN_4O$: C, 29.9; H, 3.13; N, 34.9. Found: C, 30.1 H, 3.17; N, 35.1.

N-Carbomethoxymethyl-2-chloroacetamide. A stirred, cooled (10°) slurry of methyl glycinate hydrochloride (25 g., 0.20 mole) in 300 ml. of anhydrous ether was converted to the free base by bubbling in anhydrous ammonia. The precipitated ammonium chloride (11 g., 100%) was removed by filtration and the filtrate stirred and cooled in an ice methanol bath while triethylamine (20.2 g., 0.20 mole) was added, followed by the addition of chloroacetyl chloride (22.6 g., 0.20 mole) at such a rate as to keep the temperature between −8° and −4°. The triethylamine hydrochloride was filtered off and washed with ether and chloroform. Evaporation of the combined filtrated and wash solutions gave a semi-solid mass, which was extracted with 100 ml. of hot

(22) R. Sayre, *J. Am. Chem. Soc.*, **80**, 5438 (1958).

(23) A. J. Speziale and P. C. Hamm, *J. Am. Chem. Soc.*, **78**, 2556 (1956).

(24) W. A. Jacobs and M. Heidelberger, *J. Biol. Chem.*, **21**, 145 (1915).

(25) Ethylene chloride-water system was used.

(26) M. Backes, *Compt. rend.*, **233**, 66 (1951).

(27) C. Harries and I. Peterson, *Ber.*, **43**, 635, 1758 (1910).

(28) H. K. Iwamoto and de C. Farson, *J. Am. Pharm Assoc.*, **35**, 50 (1946).

(29) P. Malatesta and G. Migliaccio, *Farmaco (Pavia), Ed. Sci.*, **11**, 113 (1956).

(30) S. R. Safir, H. Dalalion, W. Fanshawe, K. Cyr, R. Lopresti, R. Williams, S. Upham, L. Goldman, and S. Kushner, *J. Am. Chem. Soc.*, **77**, 4840 (1955).

(31) W. E. Weaver and W. M. Whaley, *J. Am. Chem. Soc.*, **69**, 1144 (1947).

(32) M.p. 43.5–44.5°. Ref. 31 gives m.p. 40°.

(33) M.p. 59–60°. Ref. 30 gives m.p. 53–55°.

(34) A. Liebrecht, Ger. **261,877**; *Chem. Zentr.*, **84**, 395 (1913).

(35) P. Bergell, *Z. Physiol. Chem.*, Hoppe-Seyler's, **97**, 298 (1916).

(36) W. A. Jacobs and M. Heidelberger, *J. Am. Chem. Soc.*, **39**, 2418 (1917).

(37) J. B. Polya and T. M. Spotswood, *Rec. trav. chim.*, **67**, 927 (1948).

(38) G. Frerichs, *Arch. Pharm.*, **237**, 288 (1899).

(39) J. von Braun and W. Rudolph, *Ber.*, **67**, 1762 (1934).

ethyl acetate. Removal of the ethyl acetate under vacuum and distillation of the residual brown oil gave 52% of material boiling at 121–127°/0.1 mm., n_D^{25} 1.4755.

Anal. Calcd. for $C_5H_8ClNO_3$: C, 36.3; H, 4.87; N, 8.46. Found: C, 36.3; H, 5.08; N, 8.21.

3-Chloro-N-methylpropionamide. Gaseous methylamine (49.0 g., 1.57 moles) was bubbled into a stirred solution of 3-chloropropionyl chloride (100 g., 0.787 mole) in 300 ml. of ethylene chloride at −15 to −10° for 1.5 hr. The thick white slurry was stirred an additional 2 hr. as it warmed to room temperature. The methylamine hydrochloride (52.2 g., 98%) was filtered off and the filtrate evaporated under vacuum to yield 100 g. of a yellow solid, m.p. 59–62°. Recrystallization from ether gave 86.4 g. (90%) of pale yellow crystals, m.p. 62–64°. The analytical sample (from ether-hexane) had m.p. 65–65.5°.

Anal. Calcd. for C_4H_8ClNO: C, 39.5; H, 6.63; Cl, 29.2; N, 11.5. Found: C, 39.6; H, 6.68; Cl, 28.9; N, 11.4.

3-Bromo-N-methylpropionamide. The same procedure utilized for 3-chloro-*N*-methylpropionamide, with the exception that liquid rather than gaseous methylamine was used, gave the 3-bromoamide from 3-bromopropionyl bromide in 52% yield as a white solid, m.p. 74–75.5°, following two recrystallizations from ethyl acetate-hexane. The analytical sample (from chloroform-hexane) melted at 78.5–79°.

Anal. Calcd. for C_4H_8BrNO: C, 28.9; H, 4.86; N, 8.44. Found: C, 29.8, 29.9; H, 5.03, 5.08; N, 8.52.

N-Chloroacetylphthalimide. The procedure of Evans and Dehn,[40] using phthaloyl chloride (101.5 g., 0.5 mole) and chloroacetamide (46.8 g., 0.5 mole) in 500 ml. of toluene, gave 30 g. (27%) of product, m.p. 170–175°, that settled out on cooling. Recrystallization from toluene, followed by chloroform, gave 10.2 g. of colorless crystals, m.p. 180–182°.

Anal. Calcd. for $C_{10}H_6ClNO_3$: C, 53.71; H, 2.71; Cl, 15.86; N, 6.26. Found: C, 53.38; H, 2.93; Cl, 15.68; N, 6.38.

Acknowledgment. We are indebted to Mrs. Melinda Kozma, who performed much of the synthetic work reported here, as well as to Dr. David Ailman, Mr. Frank Wagner, and Mrs. Ella Swartz Zonas for their contributions. We are also grateful to Dr. John Lancaster for NMR data and interpretation and to Dr. Julius Kuck and Mrs. Lee Grim for microanalyses.

STAMFORD, CONN.

(40) T. W. Evans and W. M. Dehn, *J. Am. Chem. Soc.*, 51, 3651 (1929).

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE ROHM AND HAAS CO.]

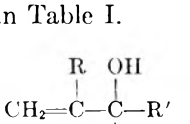
The Reaction of Acrylates and Methacrylates with Organomagnesium Compounds[1]

F. H. OWENS, W. L. MYERS, AND F. E. ZIMMERMAN

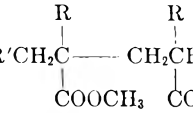
Received July 18, 1960

A study of the products of the reaction of methyl methacrylate, isopropyl acrylate, and methyl acrylate with various organomagnesium compounds has shown that these reactions follow a consistent pattern. The products were separated by distillation and chromatography on alumina and were identified by analysis, by infrared, ultraviolet and NMR spectroscopy and gas chromatography. In addition to the expected product (V), produced by 1,4- addition of the organomagnesium compounds to the unsaturated esters, there were products (VI and XI) produced by a combination of a 1,4- followed by a 1,2- addition of the organomagnesium compound to the unsaturated ester. There were, in addition, two unexpected products, the cyclic ketone VIII, resulting from a Dieckmann condensation, and the ketone XII, probably resulting from a combination of 1,4- and 1,2- additions followed by a reversal of the 1,2- addition.

Earlier investigators have studied the reaction of Grignard reagents with acrylic and methacrylic esters.[2-4] Various products were reported, but rarely was an attempt made to isolate and identify all the products. Lebedeva and co-workers[3] reported that the reaction of methyl methacrylate with ethylmagnesium bromide gave Ic and IIc and with isopropylmagnesium bromide gave IId. With methyl acrylate and ethylmagnesium bromide, the products were Ia, IIa, and IIIa, while with isopropyl magnesium bromide and methyl acrylate, IIb and IIIb were the products. These data are presented in Table I.



Ia. R = H; R′ = C_2H_5
b. R = H; R′ = $CH(CH_3)_2$
c. R = CH_3; R′ = C_2H_5
d. R = CH_3; R′ = $CH(CH_3)_2$



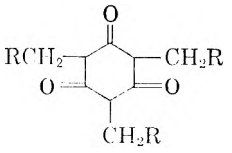
IIa. R = H; R′ = C_2H_5
b. R = H; R′ = $CH(CH_3)_2$
c. R = CH_3; R′ = C_2H_5
d. R = CH_3; R′ = $CH(CH_3)_2$,

(1) Presented in part before the Division of Organic Chemistry at the 137th Meeting of the American Chemical Society, Cleveland, Ohio, April 1960.

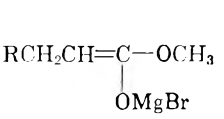
(2) (a) E. E. Blaise and C. Courtot, *Compt. rend.*, 140, 370 (1905); (b) K. A. Ogloblin, *Zhur. Obschei Khim.*, 18, 2153 (1948).

(3) (a) A. I. Lebedeva and E. D. Vainrub, *Zhur. Obschei Khim.*, 22, 1974 (1952); (b) A. I. Lebedeva and E. D. Vainrub, *Zhur. Obschei Khim.*, 24, 1207 (1954); (c) A. I. Lebedeva, L. A. Gavrilova, and T. B. Serdobintseva, *Zhur. Obschei Khim.*, 26, 2436 (1956).

(4) (a) I. N. Nazarov and A. I. Kakhniashvili, *Sbornik Statei Obschei Khim.*, 2, 919 (1954) [*Chem. Abstr.*, 49, 6848 (1955)]; (b) H. Normant and P. Maitte, *Bull. soc. chim. France*, 951 (1956); (c) J. Munch-Petersen, *J. Org. Chem.*, 22, 170 (1957); (d) M. B. Green and W. J. Hickinbottom, *J. Chem. Soc.*, 3262 (1957).



IIIa. R = C_2H_5
b. R = $CH(CH_3)_2$



IV

TABLE I

THE REACTION OF ACRYLIC ESTERS WITH GRIGNARD REAGENTS; DATA OF LEBEDEVA AND CO-WORKERS[3]

Reactants		Products		
Acrylic Ester	Alkylmagnesium Bromide	Carbinol I, %	Ester II, %	Ketone III, %
Methyl methacrylate	Ethyl	34	12	0
Methyl methacrylate	Isopropyl	0	59	0
Methyl acrylate	Ethyl	11	27	61
Methyl acrylate	Isopropyl	0	80[a]	16

[a] Plus 4.7 g. unidentified material.

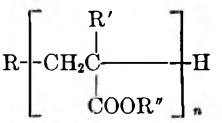
Lebedeva[3b] postulated that compound III resulted from a trimerization of the enolate IV. However, compound III is the keto form of a trisubstituted phloroglucinol, and although the microanalyses and titration data are in accord with the formulation, the ultraviolet absorption at 294 mμ, which Lebedeva attributed to a di-α-substituted ketone, is not in agreement with this structural assignment. Trimethylphloroglucinol absorbs at 271 and 274 mμ,[5] and further substitution on the alkyl group would not be expected to raise the absorption to 294 mμ. Also, in the reaction of methyl acrylate with isopropylmagnesium bromide, a calculation of the yield of all of the products shows that a greater than 100% yield was obtained; therefore, some doubt is cast on the assignment of structure.

The primary objectives of this work were to establish the nature of the products formed by the reaction of methyl methacrylate with dibutylmagnesium, diphenylmagnesium, butylmagnesium bromide, and phenylmagnesium bromide as well as to determine the relative amounts of these products.

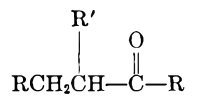
DISCUSSION

The reactions were conducted under an atmosphere of nitrogen by adding the monomer in diethyl ether dropwise over a period of three hours to the organomagnesium compound in ether so that the temperature did not rise above 5°. The ether-insoluble material was removed by filtration, and the soluble portion was dissolved in petroleum ether. Any petroleum ether-insoluble material was removed by decantation.

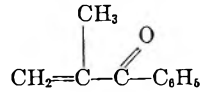
The infrared spectra of the petroleum ether-soluble residues were very complex showing carbonyl maxima attributable to ketone, ester, and in some cases, anhydride and lactone. The residues were distilled through a 24"-spinning band column at reduced pressure. The results are shown in the experimental section. Most of the fractions were still mixtures, but several facts could be ascertained from the spectra of these mixtures. In the case of the reaction of methyl methacrylate with dibutylmagnesium or butylmagnesium bromide, in addition to the maximum at 1740 cm.$^{-1}$ attributable to esters of the type Va, there were maxima at 1715 and 1712 cm.$^{-1}$ attributable to saturated ketone, at 908 and 1640 cm.$^{-1}$ attributable to an unsaturated hydrocarbon, at 1810 and 1770 cm.$^{-1}$ attributable to anhydride, and at 1760 cm.$^{-1}$ attributable to lactone. The spectra of the fractions from the reaction of methyl methacrylate with diphenylmagnesium and phenylmagnesium bromide displayed maxima at 1740 cm.$^{-1}$ (Vb), 1665 cm.$^{-1}$ (benzophenone), 1690 cm.$^{-1}$ (conjugated ketone, either VIb or VII), and at 1712 cm.$^{-1}$ (saturated ketone). Since it was felt that the presence of the phenyl group might be a definite aid in determining the nature of the products, most of the identification work was done on the products of the reaction of methyl methacrylate with diphenylmagnesium and phenylmagnesium bromide.



Va. R = n-C_4H_9; R′ = R″ = CH_3
b. R = C_6H_5; R′ = R″ = CH_3
c. R = $CH(CH_3)_2$; R′ = R″ = CH_3
d. R = C_6H_5; R′ = H; R″ = $CH(CH_3)_2$
e. R = $CH(CH_3)_2$; R′ = H; R″ = CH_3



VIa. R = n-C_4H_9; R′ = CH_3
b. R = C_6H_5; R′ = CH_3
c. R = $CH(CH_3)_2$; R′ = CH_3
d. R = C_6H_5; R′ = H
e. R = $CH(CH_3)_2$; R′ = H



VII

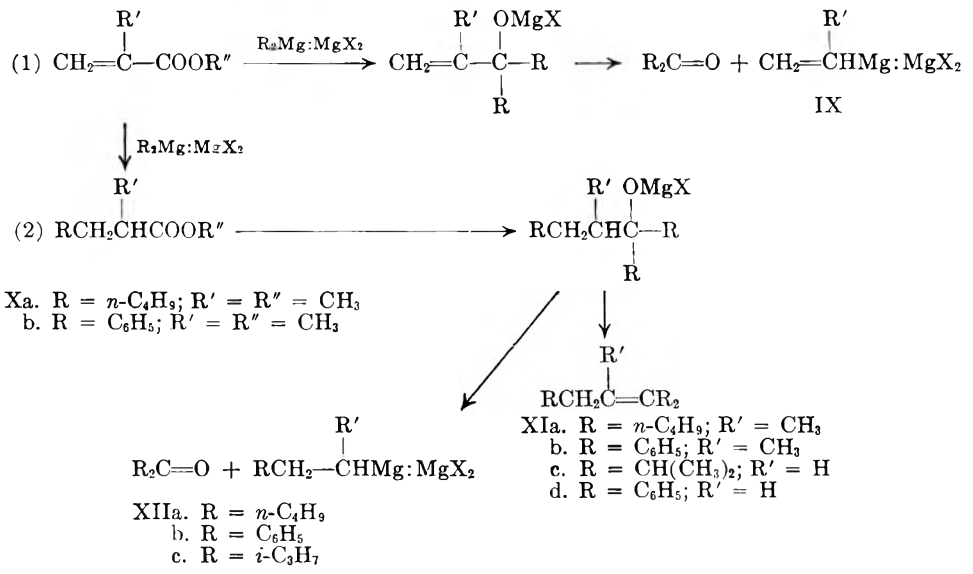
The saturated ketone, absorbing at 1712 cm.$^{-1}$, could only arise by a Claisen-type condensation, since any ketone formed by reaction of diphenylmagnesium or phenylmagnesium bromide with the ester carbonyl would produce a phenyl-substituted ketone which should have a carbonyl absorption lower than 1712 cm.$^{-1}$ Claisen-type condensations induced by Grignard reagents have been reported by several investigators.[6] In this case, the ketone

(5) T. W. Compbell and G. M. Coppinger, *J. Am. Chem. Soc.*, **73**, 2708 (1951).

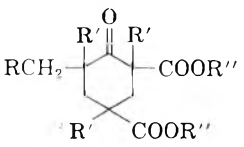
(6) M. S. Kharasch and O. Reinmuth, *Grignard Reactions of Non-Metallic Substances*, Prentice-Hall, Inc., New York, 1954, p. 565.

could be formed by an intermolecular condensation giving rise to an acyclic β-keto ester, but an acyclic ketone with five substituents on the adjacent carbon atoms[7] would be expected to absorb nearer 1700 cm.$^{-1}$ Intramolecular condensation would give rise to a substituted cyclic β-keto ester[8] which would be expected to absorb near 1712 cm.$^{-1}$. A fraction rich in the ketone adsorbing at 1712 cm.$^{-1}$ was chromatographed on alumina. The

The benzophenone could arise by reaction of the organomagnesium compound with adventitious carbon dioxide[9]; however, the organomagnesium compounds were prepared under nitrogen, and the reactions were conducted under nitrogen, so this reason was ruled out. There existed the possibility that the benzophenone might arise as a result of the reversal of the addition of a Grignard reagent to a ketone.



infrared spectrum of the fraction eluted by benzene exhibited carbonyl maxima of equal intensity at 1740 and 1712 cm.$^{-1}$ The microanalysis was consistent with the formula $C_{20}H_{26}O_5$, and the NMR spectrum had one peak at 0.65 (5 protons on benzene), two methyl ester peaks at 2.94 and 3.10, two 2-proton quartets centered at 3.72 and 4.55, a 2-proton doublet at 4.14, and two methyl peaks at 5.23 (intensity, 6) and 5.45 (intensity, 3) p.p.m. from external benzene. Consequently, the ketone having maxima at 1740 and 1712 cm.$^{-1}$ is assigned the structure methyl 5-benzyl-1,3,5-trimethyl-4-oxocyclohexane - 1,3 - dicarboxylate (VIIIb). It was not possible to prepare a 2,4-dinitrophenylhydrazone of this material, probably because of the hindrance of the four substituents *alpha* to the carbonyl group.



VIIIa. R = n-C_4H_9; R' = R'' = CH_3
b. R = C_6H_5; R' = R'' = CH_3
c. R = $CH(CH_3)_2$; R' = R'' = CH_3
d. R = C_6H_5; R' = H; R'' = $CH(CH_3)_2$
e. R = $CH(CH_3)_2$; R' = H; R'' = CH_3

In order to check this possibility, methyl methacrylate-1-C^{14} was treated with phenylmagnesium bromide. The reaction was conducted and worked up as before, and the fraction containing the benzophenone was chromatographed on alumina. The fraction eluted by 10 and 25% benzene in petroleum ether was shown to be an unsaturated hydrocarbon. The fraction eluted by 50% benzene was the ketone absorbing at 1690 cm.$^{-1}$, and the fraction eluted by 75% benzene in petroleum ether and by benzene contained the benzophenone. The latter was recrystallized from petroleum ether and twice sublimed, whereupon it melted at 49° both alone and on admixture with pure benzophenone. It gave a 2,4-dinitrophenylhydrazone melting at 242° alone and at 240° on admixture with authentic benzophenone-2,4-dinitrophenylhydrazone. The specific activities of the methyl methacrylate and the benzophenone were identical within experimental error, showing that the carbonyl group of the benzophenone does come from the carboxyl group of the methyl methacrylate.

If the benzophenone arises as shown in equation 1, it should be possible to isolate propylene or the product of the reaction IX with a carbonyl group. In an experiment in which the effluent gas from the

(7) P. D. Bartlett and M. Stiles, *J. Am. Chem. Soc.*, **77**, 2806 (1955).

(8) L. J. Bellamy and L. Beecher, *J. Chem. Soc.*, 4487 (1954).

(9) H. Gilman and N. B. St. John, *Rec. trav. chim.*, **49**, 1172 (1930); M. Mousseron and R. Granger, *Bull. soc. chim.*, [5], **13**, 251 (1946); G. Schroeter, *Ber.*, **40**, 1584 (1907).

reaction was collected, no propylene was found by mass spectroscopy, and no evidence for the formation of a vinyl ketone was found; therefore, it is believed that the benzophenone arises as shown in equation 2. Although there is no direct evidence for the presence of XII in the reaction mixture, it was possible to identify X in the product mixture by direct comparison of infrared maxima, and evidence is presented later for the presence of XI in addition to the ketone VIb resulting from the addition of one phenylmagnesium bromide to X.

The ketone eluted by 50% benzene in petroleum ether had a carbonyl maximum at 1690 cm.$^{-1}$, melted below 0°, and as pointed out above, could have structure VIb or VII. The empirical formula of the ketone was $C_{16}H_{16}O$ and of its 2,4-dinitrophenylhydrazone was $C_{22}H_{24}N_4O_4$. This ketone is assigned the structure 2-methyl-1,3-diphenylpropan-1-one (VIb). Treatment of methyl 2-methyl-3-phenylpropionate (Xb) with an equivalent of phenylmagnesium bromide yielded a hydrocarbon, 1,1,3-triphenylprop-1-ene (XIb) rather than the expected ketone (VIb). The material eluted by 10 and 25% benzene in petroleum ether had a spectrum identical with this hydrocarbon and an identical melting point, 65–66°, both alone and on admixture. From the infrared spectra of the distillation fractions, it was shown that the remaining material was of the type Vb, with n ranging from one to 4800.

On the basis of the above evidence, the products from the reaction of methyl methacrylate with dibutylmagnesium and butylmagnesium bromide were reexamined. The spectra indicated that there were maxima at 1740 and 1712 cm.$^{-1}$ attributable to Va and VIIIa, at 1715 cm.$^{-1}$ attributable to VIa or dibutyl ketone or both, and at 908 and 1635 cm.$^{-1}$ attributable to hydrocarbon XIa. There were also carbonyl maxima at 1810 and 1770 (anhydride) and 1760 (lactone). Unfortunately, chromatography of these materials on alumina did not yield pure fractions, and the material recovered from the columns did not display the maxima attributed to anhydride and lactone. Since the latter could not be identified and since they were there in rather small amounts, the nature of the lactone and anhydride is still in question. Treatment of methyl n-valerate with the Grignard reagent from 2-bromoheptane yielded 5-methylundecan-6-one (VIa). By comparison of the positions and intensities of the gas chromatographic peaks for VIa, di-n-butyl ketone, and the ketone mixture from the reaction products, it was possible to establish the identity of the two ketones and their relative amounts.

On the basis of the infrared spectra of all these distillation fractions, supported by the structural identifications from alumina and gas chromatography, the semiquantitative data on the reactions of methyl methacrylate with organomagnesium compounds shown in Table II were obtained; however, it must be pointed out that these data are only meant to give an order of magnitude and are subject to the limitations of the infrared method of estimation by comparison of absorbance ratios.[10] A series of reactions in which the organomagnesium compound was added to the methyl methacrylate revealed that much larger amounts of ether-insoluble and petroleum ether-insoluble polymers were obtained. The spectra of the petroleum ether-soluble materials were similar to the spectra of the products where the methyl methacrylate was added to the organomagnesium compound, but because of separation difficulties, quantitative data on these materials were not obtained.

Because the results obtained with methyl methacrylate were at variance with the results reported in the literature, a study of the reaction of isopropyl acrylate with phenylmagnesium bromide was made to determine if the reaction would follow a similar course. Distillation of a portion of the product resulted in extensive decomposition and was abandoned. Chromatography of a portion on alumina achieved little separation, and only 42% of the material was recovered. Although chromatography of a portion of the residue on alumina deactivated with ethyl acetate[12] did not yield pure components, sufficient separation was achieved to enable us to identify the components of the mixtures by comparison with pure materials. In addition to the infrared maximum at 1735 cm.$^{-1}$ (Vd), there were maxima at 1690 cm.$^{-1}$, presumed to be VId by analogy with the results obtained with methyl methacrylate and phenylmagnesium bromide, and at 1712, 1650, and 1615 cm.$^{-1}$ (enolizable β-keto ester) presumed to be VIIId by comparison with the data of Leonard and co-workers[13] and by analogy with the product from the reaction of methyl methacrylate and phenylmagnesium bromide.

In order to furnish unequivocal proof of the structure of these two ketones, they were synthesized and their infrared and ultraviolet spectra were compared. The reduction of benzalacetophenone with zinc in acetic acid[14] gave 1,3-diphenylpropan-1-one (VId). The material was purified by chromatography on alumina followed by sublimation. The infrared spectrum of this material was identical with the spectrum of the ketone absorbing at 1690 cm.$^{-1}$ which was in the reaction mixture from isopropyl acrylate and phenylmagnesium bromide,

(10) R. N. Jones and C. Sandorfy, Chap. IV in *Technique of Organic Chemistry*, Vol. IX, Interscience Publishers, Inc., New York, 1956, p. 469.

(11) R. E. Dessy and G. S. Handler, *J. Am. Chem. Soc.*, **80**, 5824 (1958).

(12) A. C. Cope, H. L. Dryden, Jr., and C. F. Howell, *Org. Syntheses*, **37**, 73 (1957).

(13) N. J. Leonard, H. S. Gutowsky, N. J. Middleton, and E. M. Petersen, *J. Am. Chem. Soc.*, **74**, 4070 (1952).

(14) W. Schneidewind, *Ber.*, **21**, 1323 (1888).

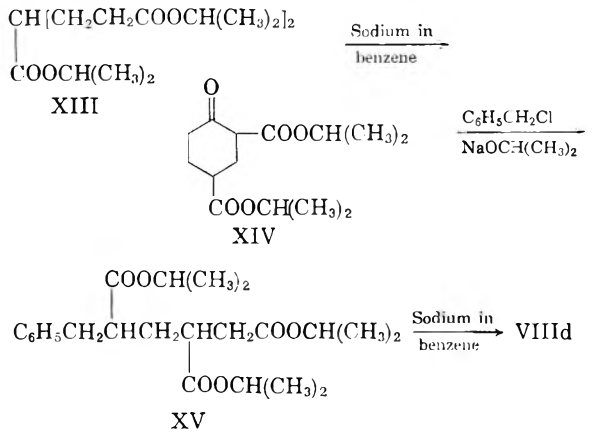
TABLE II

THE REACTION OF ACRYLIC ESTERS WITH ORGANOMAGNESIUM COMPOUNDS

Reactants			Products							
Acrylic[a] ester	Organomagnesium[b] compound	Molar ratio of organomagnesium compound[b] to acrylic ester	Ester V n = 1,2,3, %	Ketone XII, %	Ketone VI, %	Ketone VIII, %	Hydrocarbon XI, %	Lactone, %	Anhydride, %	Polymer[c] V $n > 3$, %
MMA	$(n\text{-}C_4H_9)_2Mg$	0.57	5	1	18	22	2	4	6	42
MMA	$(n\text{-}C_4H_9)_2Mg:MgBr_2$	0.57	36	1	19	10	5	5	1	23
MMA	$(C_6H_5)_2Mg$	0.57	44	8	14	7	1	Trace	Trace	26
MMA	$(C_6H_5)_2Mg$	1.05	43	7	16	15	8	Trace	Trace	11
MMA	$(C_6H_5)_2Mg:MgBr_2$	0.57	70	6	5	6	0	Trace	Trace	13
IPA	$(C_6H_5)_2Mg:MgBr_2$	0.50	50	Trace	3	6	0	0	0	40
MMA	$(i\text{-}C_3H_7)_2Mg:MgBr_2$	1.0	42	Trace	20	13	0	7	0	18
MA	$(i\text{-}C_3H_7)_2Mg:MgBr_2$	1.0	52	1	22	9	0	0	0	16

[a] MMA = Methyl methacrylate; IPA = Isopropyl acrylate; MA = Methyl acrylate. [b] In accordance with the evidence presented by Dessy and Handler,[11] we have adopted the procedure of designating Grignard reagents as $R_2Mg:MgX_2$; thus, 1 mole of $R_2Mg:MgX_2$ is equivalent to 2RMgX. [c] Includes the ether-insoluble and petroleum-ether-insoluble polymer.

allowing for the maxima of the contaminant Vd. The ultraviolet spectrum of VId was identical with that of the material in the reaction mixture. Isopropyl 5 - benzyl - 4 - oxocyclohexane - 1,3-dicarboxylate (VIIId) was synthesized by the sequence of reactions shown below. Malonic ester was quantitatively cyanoethylated to give ethyl 1,1-di(2-cyanoethyl)-methane-1,1-dicarboxylate by



the method of Bruson and Riener.[15] The latter was simultaneously hydrolyzed and decarboxylated and was then converted to the triisopropyl ester (XIII) without isolation of the acid. The triester was cyclized by the method of Sengupta[16] with sodium in benzene.

Openshaw and Robinson[17] observed that the addition of an excess of sodium in methanol to a solution of methyl 4-oxocyclohexane-1,3-dicarboxylate and methyl 3-chloropropionate in methanol containing a small amount of sodium iodide gave an 80% yield of methyl heptane-1,3,5,7-tetracarboxylate which, on cyclization with sodium in methanol, gave methyl 5-(2-carbomethoxyethyl)-4-oxocyclohexane-1,3-dicarboxylate in 80% yield. Treatment of a solution of isopropyl 4-oxocyclohexane-1,3-dicarboxylate (XIV), benzyl chloride, and sodium iodide in isopropyl alcohol with sodium in isopropyl alcohol yielded 67% of isopropyl 5-benzylpentane - 1,2,4 - tricarboxylate (XV) whose infrared spectrum was virtually identical with that of low molecular weight poly(isopropyl acrylate) initiated by phenylmagnesium bromide. Cyclization of triester XV with sodium in benzene gave a 45% yield of isopropyl 5-benzyl-4-oxocyclohexane-1,3-dicarboxylate (VIIId), whose infrared spectrum was identical with that of the ketone having absorption maxima at 1712, 1650, and 1615 cm.$^{-1}$ found in the product of the reaction of isopropyl acrylate with phenylmagnesium bromide. The cyclic ketone VIIId exhibited an ultraviolet maximum at 253 mμ (enolizable β-keto ester) and a shoulder at 208 mμ (phenyl group) but did not obey Beer's law. Bellamy and Beecher[9] have observed that the intensity of the infrared absorption maximum at 1642 cm.$^{-1}$ of ethyl 2-oxocyclohexane-1-carboxylate which they attributed to the chelate form, is independent of concentration, and we find that the intensities of this absorption in both the ultraviolet and infrared spectra do not obey Beer's law.

From the above data and the data obtained from the chromatographic fractions, we were able to determine the amounts of the various products shown in Table II; however, it must be emphasized that these are semiquantitative data because of the reasons given previously and also because not all of the material was recovered from the alumina. Rechromatography of fractions resulted in quantitative recovery, but chromatography of a polymer-containing sample results in a considerable loss of material; therefore, it has been assumed that the difference between the amount of material charged and the amount recovered from the column can be

(15) H. A. Bruson and T. W. Riener, *J. Am. Chem. Soc.*, 65, 23 (1943).

(16) P. Sengupta, *J. Org. Chem.*, 18, 249 (1953).

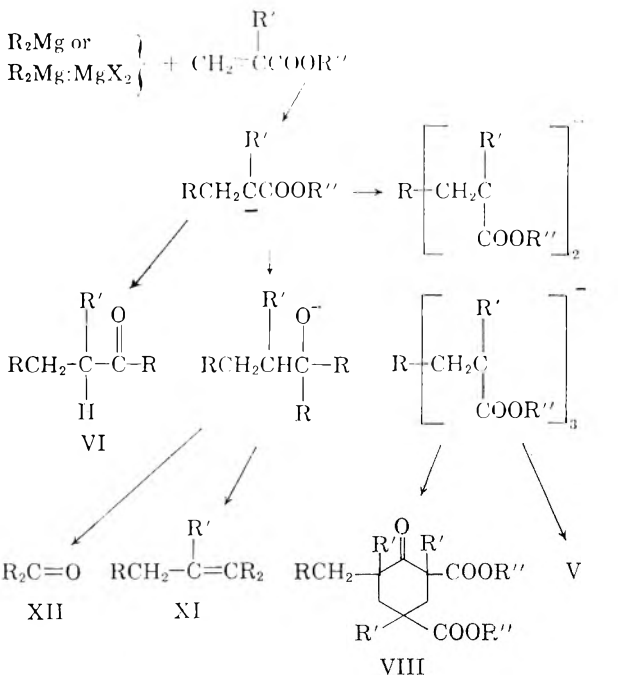
(17) H. T. Openshaw and R. Robinson, *J. Chem. Soc.*, 912 (1946).

considered to be polymer. For these reasons, these data are given only to denote an order of magnitude and are not to be considered quantitative.

The above results seem to indicate that the reactions of isopropyl acrylate and methyl methacrylate with phenylmagnesium bromide follow the same course and that only the amounts of the products differ. However, because of the variance between these data and the data of Lebedeva and collaborators,[3] we have repeated two of their experiments, the reaction of methyl acrylate and of methyl methacrylate with isopropylmagnesium bromide, and analyzed the products by infrared and ultraviolet spectroscopy and by alumina and gas chromatography. The material obtained from the reaction of methyl methacrylate with isopropylmagnesium bromide was distilled. Infrared analysis showed that in addition to the infrared maximum at 1740 cm.$^{-1}$ (Vc), there were maxima at 1715 cm.$^{-1}$ (VIc or diisopropyl ketone or both), at 1712 cm.$^{-1}$ (VIIIc), and at 1760 cm.$^{-1}$ (lactone). As before, the amounts of the different products were determined by infrared analysis of the distillation fractions. Analysis by gas chromatography revealed that there was no diisopropyl ketone, and this result was confirmed by the absence of an infrared maximum at 1025 cm.$^{-1}$ present in the spectrum of diisopropyl ketone. The material obtained from the reaction of methyl acrylate with isopropylmagnesium bromide was chromatographed on deactivated alumina. As was the case with isopropyl acrylate, the separation was incomplete but was sufficient to determine the nature and amounts of the products. There were maxima at 1740 cm.$^{-1}$, attributable to Ve, at 1718 cm.$^{-1}$ attributable to VIe or diisopropyl ketone or both, and at 1712, 1665, and 1612 cm.$^{-1}$ attributable to VIIIe. The ultraviolet spectra of the fractions containing VIIIe had a maximum at 252 mμ but lacked the shoulder at 208 mμ. Gas chromatographic analysis showed the presence of both XVIb and diisopropyl ketone, and this fact was confirmed by the presence of maxima in the infrared spectra of the fractions which were also present in the spectrum of diisopropyl ketone. No evidence could be found for the presence of a trisubstituted phloroglucinol (IIIb). The data on the products of these reactions are shown in Table II.

CONCLUSIONS

From the above data, there emerges a definite, consistent pattern as shown schematically below. In all of these reactions, the predominant product is ester of the type V resulting from successive 1,4-additions to the unsaturated ester, and this result is not surprising in view of the tendency of α,β-unsaturated esters to undergo conjugate addition with Grignard reagents.[18] The ketone VI and the hydrocarbon XI were not unexpected, and the amount of these products are reasonable in view of the data in the literature. It is interesting to note that no products resulting from 1,2- addition of the organomagnesium compound to the *monomer* were found. It is surprising that so much polymer was produced, especially when these results are compared with those of Lebedeva[3] and with those of Munch-Peterson,[4c] but these data do agree with our observations on the ease of polymerization of these monomers with Grignard reagents.



The unexpected products were the ketones VIII and XII. To our knowledge, this is the first example of a Dieckmann cyclization involving a Grignard reagent, although Claisen condensations have been reported,[7] and it is the first example of the reversal of the addition a Grignard to a ketone. It is possible that this reversal occurs on hydrolysis, and it may be a concerted process yielding ketone and hydrocarbon directly.[19] Reversal of the addition of a carbanion to a ketone during hydrolysis has been shown by Hamrick and Hauser.[20]

EXPERIMENTAL[21]

Organomagnesium compounds. The di-*n*-butylmagnesium and diphenylmagnesium were prepared from high purity, sublimed magnesium and the corresponding organomercury compound in ether at reflux under nitrogen by the method of Schlenk.[22] The Grignard reagents were prepared in ether under nitrogen by known techniques.[23]

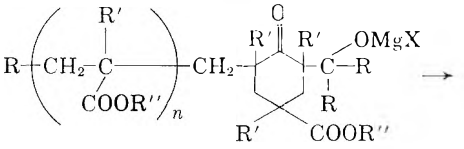
Methyl methacrylate-1-C^{14}. Sodium bisulfite (26 g., 0.25 mole) in 50 ml. water was stirred and cooled to 10°. To this solution was added acetone (14.5 g., 0.25 mole) during about 1 min., with cooling by an ice water bath. The temperature rose to 35°, and the mixture became a thick slush of crystals of the acetone-bisulfite addition product. A solution of C^{14}-labeled potassium cyanide (0.30 mc./mole) (16.3 g., 0.25 mole) in 25 ml. of water was added during about 5 min. with continued external cooling. The crystals dissolved and the

(18) M. S. Kharasch and O. Reinmuth, *op. cit.*, pp. 563–564.

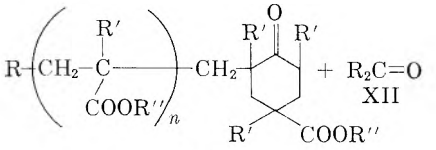
temperature fell to 25° during the addition. The mixture was cooled to 5° and held at this temperature for 30 min. The upper oily layer of acetone cyanhydrin was separated from the aqueous layer, which was extracted with three 20-ml. portions of ether. The original organic layer and ether extracts were combined and extracted with two 20-ml. portions of saturated sodium bisulfite solution to remove unchanged acetone, then with four 20-ml. portions of saturated sodium chloride solution to remove traces of bisulfite. The ether solution was concentrated by distillation at reduced pressure; water was removed azeotropically with benzene, and the residue was distilled collecting the product at 72–73°/10.5 mm. The yield was 15.51 g. (73.2%). The activity was 3.5 μc./g.

Concentrated sulfuric acid (27.6 g., 0.27 mole) and 0.1 g. di-β-naphthol were heated to 70° with stirring in a 100-ml. flask having a thermometer, dropping funnel and reflux condenser. The above acetone cyanhydrin (15.35 g., 0.18 mole) was added from the dropping funnel during about 10 min., holding the temperature at 75–85° by external cooling. Following the addition the temperature was raised to 140° for 30 min. The mixture was cooled to 70° and a mixture of water and 17.5 g. of methanol was added from the dropping funnel. The mixture was heated to reflux and held at reflux for 4.5 hr., the temperature falling from 85° to 78.5° during this time. Changing to a downward condenser, distillate consisting of water, methanol and methyl methacrylate was taken off over a range of 70.5–97°, the pot temperature rising from 79 to 140°. The crude distillate (33 g.) was washed with an equal weight of 40% calcium chloride solution to remove water and methanol. The organic layer (16 g.) was treated again with 40% calcium chloride solution, and the combined calcium chloride washes were extracted with ether (3 × 10 ml.). The combined organic layer and ether extracts were dried over anhydrous calcium chloride. The dried ethereal solution was concentrated, and the residue was distilled at 125 mm. pressure through a small column (1 cm. × 16 cm.) with copper packing. The product was collected at 51–52°. The yield was 6.82 g. (39%), activity 3.3 μc./g. This material was diluted with unlabeled methyl methacrylate so that the final activity was 6.7×10^{-3} μc./millimole.

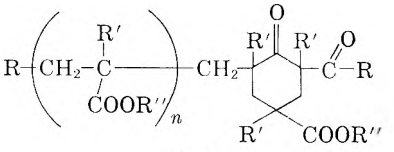
(19) The referee has suggested that ketone XII could arise by a retroaldol reaction of compound XVI to give XVII. There was, however, no evidence for the presence of XVII, XVIII, or XIX in the reaction mixtures. Since



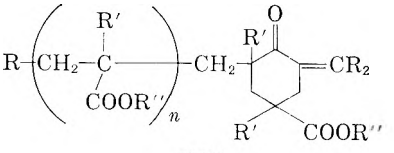
XVI



XVII



XVIII



XIX

it was shown that VI and XI are present, we are inclined toward the reverse Grignard reaction postulated above as an explanation for the origin of the ketone XII.

(20) P. J. Hamrick, Jr. and C. R. Hauser, *J. Am. Chem. Soc.*, **81**, 3144 (1959).

(21) All melting points are corrected. All boiling points are uncorrected. The authors are indebted to Miss J. Cronin for technical assistance and to Mr. C. W. Nash for the microanalyses.

(22) W. Schlenk, *Ber.*, **64**, 734 (1931).

(23) M. S. Kharasch and O. Reinmuth, *op. cit.*, Chapter II.

Spectra. The infrared spectra were obtained on a Perkin-Elmer model 21 double beam recording spectrometer equipped with rock salt optics. The slit program was set at 927, and the 2.0 to 15.0 μ scanning time was 15 min. Capillary films between rock salt plates were used except where noted. Identification of the pure products was accomplished by comparison with spectra of samples prepared by alternate routes.

The relative amount of each product in a fraction was determined from the ratio of the absorption of the carbonyl peaks, assuming that the molar absorption coefficients of the various carbonyl maxima were the same. While this assumption is not strictly valid, this method should serve to determine the order of magnitude of the products and should be more accurate for comparison purposes than integrated absorption intensities.[11] In all cases, selected absorption maxima are reported and the letters in parentheses refer to strong, medium, and weak intensities.

The ultraviolet spectra were obtained on a Beckman model DK-2 recording instrument. The samples were examined as solutions in absolute ethanol.

The reaction of methyl methacrylate with organomagnesium compounds. The general procedure for the reaction of methyl methacrylate with organomagnesium compounds is illustrated below in the specific directions for the reaction of methyl methacrylate with diphenylmagnesium.

The reaction of methyl methacrylate with diphenylmagnesium (Expt. 3). To 300 ml. of an ethereal solution containing 0.17 mole of diphenylmagnesium in a 1-l., three-necked flask equipped with a stirrer, addition funnel, reflux condenser, and thermometer was added dropwise with stirring a solution of 32 ml. (30 g., 0.3 mole) of methyl methacrylate over a period of 3 hr. while the temperature was maintained between 0 and 5° by means of an ice bath. On completion of the addition, the mixture was allowed to stir overnight, whereupon it was hydrolyzed with a solution of 150 ml. of concd. hydrochloric acid in 150 ml. of water, the temperature being maintained between 0 and 10°. The solid polymer was removed by filtration and was washed by stirring in a large volume of water for several hours, whereupon it was collected by filtration and dried in a vacuum oven for 48 hr. There was obtained 3.23 g.

The ether layer was separated, and the aqueous layer was extracted with three 150-ml. portions of ether. The combined ether layer was washed with three 150-ml. portions of a saturated salt solution. The ether was dried and was removed at the water pump. Petroleum ether (b.p. 30–78°) (100 ml.) was added to the residue; most of the material dissolved leaving a semisolid residue. The petroleum ether solution was decanted. After drying in a vacuum oven for 24 hr., the petroleum ether-insoluble material amounted to 1.54 g.

The petroleum ether was removed *in vacuo*, and the residue was distilled through a 24″ vacuum-jacketed spinning band column.

Seven fractions were obtained:

Fraction Number	B.P.	Mm.	Fraction Weight, G.	Infrared Maxima, Cm.$^{-1}$
1	51–68	92	0.50	1740 (s), 1690 (m), 1635 (m)
2	84–86	2.7	3.32	1740 (s), 1665 (w)
3	83–99	0.05	6.69	1740 (s), 1690 (s), 1665 (m)
4	99–103	0.05	7.74	1740 (s), 1690 (s)
5	100–104	0.05	4.08	1740 (s), 1712 (m), 1690 (w)
6	110–118	0.05	2.38	1810 (w), 1770 (m), 1740 (s), 1712 (s)
Residue			6.90	1810 (w), 1770 (m), 1740 (s), 1712 (s), 1690 (w)

The reaction of methyl methacrylate with dibutylmagnesium (Expt. 1). The ether-insoluble polymer amounted to 2.12 g., and 2.34 g. of the petroleum ether-insoluble polymer was obtained. From the distillation there were obtained nine fractions:

The reaction of methyl methacrylate with diphenylmagnesium (Expt. 4). Three hundred milliliters of an ethereal solution containing 0.315 mole of diphenylmagnesium was used. No insoluble polymer was obtained. Distillation gave eleven fractions.

Fraction Number	B.P.	Mm.	Fraction Weight, G.	Infrared Maxima, Cm.$^{-1}$
1	52–63	97	1.36	1740 (s), 1715 (s)
2	76–93	4.95	1.52	1740 (w), 1715 (s)
3	46–50	0.10	2.58	1715 (s), 1640 (w)
4	61–66	0.10	1.50	1740 (s), 1715 (s)
5	68–72	0.025	1.79	1740 (s), 1712 (s)
6	102–116	0.075	8.88	1810 (m), 1770 (s), 1740 (s), 1712 (s)
7	117–120	0.10	3.51	1760 (s), 1740 (s), 1712 (s)
8	120–124	0.10	0.92	1810 (w), 1770 (s), 1740 (s), 1712 (s)
Residue			3.47	1810 (m), 1770 (s), 1740 (s), 1712 (s)

The reaction of methyl methacrylate with butylmagnesium bromide (Expt. 2). The ether-insoluble polymer amounted to 2.39 g., and the petroleum ether-insoluble fraction weighed 0.53 g.

Nine fractions were obtained on distillation:

Four grams of fraction 9 was chromatographed on a 33-mm. bore column packed with three 100-g. portions of alumina separated by 1″ glass wool plugs. There was eluted with 75% benzene in petroleum ether and with pure benzene 0.89 g. of material having infrared maxima at 1740 (s) and 1712

Fraction Number	B.P.	Mm.	Fraction Weight, G.	Infrared Maxima, Cm.$^{-1}$
1	42–46	100	0.58	1740 (s), 1640 (w)
2	65–66	4.55–4.85	0.67	1740 (s), 1715 (s), 1640 (w)
3	82–98	5.00	3.66	1740 (w), 1715 (s)
4	106–108	4.70	2.55	1715 (s)
5	70–73	0.1–0.05	3.49	1740 (s), 1715 (s)
6	74.5–77	0.05	7.16	1740 (s)
7	84–103	0.05	4.28	1740 (s), 1712 (s)
8	116–127	0.10	4.13	1760 (s), 1740 (s), 1712 (s)
Residue			4.14	1760 (s), 1740 (s), 1712 (s)

The reaction of methyl methacrylate with phenylmagnesium bromide (Expt. 5). There was obtained 1.00 g. of ether-insoluble polymer and 0.87 g. of petroleum ether-insoluble polymer. Distillation gave eight fractions:

(s) cm.$^{-1}$ This material did not crystallize, and it was not possible to prepare a 2,4-dinitrophenylhydrazone.

Anal. Calcd. for $C_{20}H_{26}O_5$: C, 69.34; H, 7.57. Found: C, 69.34; H, 7.47.

Fraction Number	B.P.	Mm.	Fraction Weight, G.	Infrared Maxima, Cm.$^{-1}$
1	100–106	3.90	1.01	1740 (s)
2	53–59	0.10	0.81	1740 (s)
3	83–91	0.10	2.49	1740 (s), 1665 (s), 1635 (w)
4	94–101	0.025	3.56	1740 (s), 1690 (w), 1665 (m)
5	102–104	0.025	12.40	1740 (s), 1690 (w)
6	104–108	0.025	3.69	1740 (s)
7	112–124	0.10	3.79	1740 (s), 1712 (s)
Residue			3.90	1810 (w), 1770 (m), 1740 (s), 1712 (m)

Fraction Number	B.P.	Mm.	Fraction Weight, G.	Infrared Maxima, Cm.$^{-1}$
1	47–57	99	0.75	1690 (m), 1665 (m), 1635 (w)
2	75–78	98	4.29	1740 (s), 1690 (m), 1665 (m), 1635 (w)
3	87–110	98	1.54	1740 (s), 1665 (m), 1635 (w)
4	107–111	3.50	1.06	1740 (s), 1665 (w)
5	126–136	4.00	0.34	1740 (s), 1712 (m), 1665 (s)
6	70–79	0.05	0.93	1750 (w), 1712 (w), 1655 (s), 1635 (w)
7	88–94	0.05	4.03	1740 (s), 1712 (m), 1690 (m), 1665 (s), 1635 (w)
8	98–104	0.10	20.68	1740 (s), 1690 (m)
9	114–118	0.10	6.64	1810 (m), 1770 (m), 1740 (m), 1712 (s)
10	121–136	0.10	3.22	1810 (m), 1770 (s), 1740 (s), 1712 (s)
Residue			4.10	1810 (s), 1770 (m), 1740 (s), 1712 (s)

The NMR data, determined by Varian Associates, are given in the discussion section. This material was assigned the structure methyl 5-benzyl-4-oxo-1,3,5-trimethylcyclohexane-1,3-dicarboxylate (VIIIb).

The reaction of methyl methacrylate-1-C^{14} with phenylmagnesium bromide. No polymer was obtained. Distillation gave three fractions and a residue of 24.47 g.: 1. b.p. 48–69° (0.5–0.3 mm.), 0.60 g.; 2. 69–72° (0.3–0.25), 1.50 g.; 3. 80–122° (0.15 mm.), 7.43 g. Fractions 2 and 3 were combined and dissolved in 15 ml. of petroleum ether. The petroleum ether solution was placed on a 30-mm. bore column packed with five 100-g. portions of alumina separated by 1″ plugs of glass wool. The material from fractions 7–14 was sublimed

Fraction Number	Eluent	Fraction Weight, G.	Infrared Maxima, Cm.$^{-1}$
7–14	10 and 25% benzene in petroleum ether	2.18	1740 (w), 1635 (w), 910 (m)
17–20	50% benzene in petroleum ether	1.62	1740 (w), 1690 (s)
22–28	75% benzene in pet. ether and benzene	2.22	1665 (s), 1690 (w)

in vacuo and was shown to have a spectrum identical with that of the material obtained from the reaction of phenylmagnesium bromide with methyl 2-methyl-3-phenylpropionate (*vide infra*) and the melting point was 65–66° both alone and on admixture; therefore it was assigned the structure 2-methyl-1,1,3-triphenylprop-1-ene (XIb).

The material from fractions 17–20 melted below 0° and could not be recrystallized. It was dried in a desiccator at 0.1 mm.

Anal. Calcd. for $C_{16}H_{16}O$: C, 85.68; H, 7.19. Found: C, 85.45; H, 7.07.

A *2,4-dinitrophenylhydrazone* was prepared, m.p. 136°, after three recrystallizations from ethanol–ethyl acetate.

Anal. Calcd. for $C_{22}H_{20}N_4O_4$: C, 65.34; H, 4.99; N, 13.85. Found: C, 65.73; N, 4.80; N, 13.89.

This material was assigned the structure 2-methyl-1,3-diphenylpropan-1-one (VIb).

The material from fractions 22–28 was recrystallized once from petroleum ether, m.p. 48°. Two subliminations *in vacuo* gave material melting at 49° both alone and on admixture with pure benzophenone. The activity was 6.6×10^{-3} μc./mmole. The 2,4-dinitrophenylhydrazone after three recrystallizations from ethanol melted at 242° alone and at 240° on admixture with the 2,4-dinitrophenylhydrazone of benzophenone.

2-Bromoheptane. Hydrogen bromide gas was passed into 232 g. (2 moles) of heptanol-2, prepared by the reduction of heptanone-2, until the alcohol was saturated. The mixture was heated at 83° for 6.5 hr. while a slow stream of hydrogen bromide was passed through it. On cooling, the reaction mixture was diluted with an equal volume of ether, was washed with two 250-ml. portions of a 10% aqueous solution of sodium carbonate and three 250-ml. portions of a saturated aqueous solution of sodium chloride. The ether solution was dried with anhydrous magnesium sulfate, and the ether was removed *in vacuo*. The residue was distilled through a 30 cm. helices-packed column. Two fractions were obtained: 1. b.p. 75–77° (36 mm.), 13.5 g.; 2. b.p. 77° (37 mm.), 248.8 g., n_D 1.4478 (25°) [reported[24] b.p. 85 (50 mm.), n_D 1.4450 (25°)], 70% yield.

Methyl 2-methylheptanoate (Xa). To 200 ml. of ether and 15 g. of magnesium metal in a 500 ml., three-necked, steam-jacketed flask, equipped with a stirrer, Dry Ice condenser, addition funnel, and a stopcock in the bottom attached to a 2-l., 3-necked flask equipped with a stirrer and a Dry Ice condenser, was added dropwise a solution of 80 g. (0.45 mole) of 2-bromoheptane in 80 ml. of ether. On completion of the addition, the solution was heated at reflux by means of steam for 3 hr., whereupon it was allowed to stand overnight. The ether solution of the Grignard reagent was then added during 45 min. through the stopcock in the bottom of the flask to a mixture of 100 g. of powdered Dry Ice and 250 ml. of ether in the lower flask. The mixture was stirred for 1 hr.; the mixture was hydrolyzed with 75 ml. of concd. hydrochloric acid in 75 ml. of water. The layers were separated, and the aqueous portion was extracted with three 150-ml. portions of ether. The combined ether layer was washed with three 150-ml. portions of a saturated aqueous salt solution, was dried with anhydrous magnesium sulfate, and the ether was removed *in vacuo*. Distillation through a 24″, vacuum-jacketed, spinning band column gave two fractions: 1. 73–101° (0.7 mm.), 7.46 g.; 2. 101–103° (0.7 mm.), 25.8 g., n_D 1.4239 (25°), 40% yield.

A solution of 25 g. (0.17 mole) of the above acid, 100 ml. of methanol, 600 ml. of benzene, and 1 g. of *p*-toluenesulfonic acid was heated at reflux for 65 hr. The solvent was removed *in vacuo* at room temperature; ether (150 ml.) was added to the residue, and the ether solution was washed with two 100-ml. portions of a 5% aqueous solution of sodium carbonate and three 100-ml. portions of saturated aqueous salt solution. The ether was dried and was removed on a water pump. The residue was distilled through the spinning band column. After a 0.35-g. forerun, the methyl 2-methylheptanoate distilled at 78–80° (21–24 mm.). There was obtained 15.8 g. (56%) of material having an infrared maximum at 1740 cm.$^{-1}$ This material was shown to be pure by gas chromatography.

6-Methylundecan-5-one (VIa). To 200 ml. of ether and 15 g. of magnesium metal in a 500 ml., three-necked, steam-jacketed flask, equipped with a stirrer, Dry Ice condenser, addition funnel, and a stopcock in the bottom attached to a 1-l., three-necked flask equipped with a stirrer and a Dry Ice condenser, was added dropwise a solution of 80 g. (0.45 mole) of 2-bromoheptane in 80 ml. of ether. On completion of the

(24) L. M. Ellis, Jr., and E. E. Reid, *J. Am. Chem. Soc.*, **54**, 1863 (1932).

addition, the solution was heated at reflux by means of steam for 3 hr., whereupon it was allowed to stand overnight. The ether solution of the Grignard reagent was then added during 90 min. through the stopcock to a solution of 39 g. (0.3 mole) of ethyl *n*-valerate in 100 ml. of ether. The solution was allowed to stir for 1 hr. and was then hydrolyzed with 75 ml. of concd. hydrochloric acid in 75 ml. of water. The ether layer was separated; the aqueous portion was extracted with three 150-ml. portions of ether; the combined ether layer was washed with three 150-ml. portions of saturated sodium chloride solution, was dried with anhydrous magnesium sulfate, and the ether was removed at the water pump. The residue was distilled through the spinning band column. Three fractions were obtained: 1. b.p. 69–73° (0.75 mm.), 1.52 g.; 2, 73–76° (0.75–0.80 mm.), 2.05 g.; 3. 76–78° (0.8 mm.) 4.25 g. Fraction 3 had an infrared maximum at 1715 cm.$^{-1}$

Fractions 6–25 had a maximum in the ultraviolet at 240 mμ, with a shoulder at 280 mμ. Fractions 31–72 had a minimum in the ultraviolet at 253 mμ with a shoulder at 208 mμ.

1,3-Diphenylpropan-1-one (VId). Benzalacetophenone was reduced with zinc in acetic acid by the procedure of Schneidewind.[14] The ether-soluble material was dissolved in 100 ml. of petroleum ether and placed on a 30-mm. bore column packed with five 100-g. portions of alumina separated by 1″ plugs of glass wool. The fractions eluted by 10% benzene in petroleum ether amounted to 6.33 g. and had an infrared maximum at 1690 cm.$^{-1}$ After one sublimation *in vacuo* the melting point was 71–72° (reported[14] m.p. 72°).

Anal. Calcd. for $C_{15}H_{14}O$: C, 85.68; H, 6.71. Found: C, 85.44; H, 6.73.

Ethyl 1,1-di(2-cyanoethyl)methane-1,1-dicarboxylate was prepared according to the procedure of Bruson and Riener,[15] m.p. 61.5–62° (reported[15] m.p. 62°) after one recrystallization from ethanol.

Isopropyl pentane-1,3,5-tricarboxylate (XIII). Pentane-1,3,5-tricarboxylic acid was prepared from the above nitrile by the method of Sengupta.[16] The crude acid was esterified without purification. To the crude acid in a 3-l., two-necked flask, connected to a 30-cm. column packed with Cannon packing, was added 800 ml. of isopropyl alcohol, 1-l. of benzene, and 30 ml. of concd. sulfuric acid. A Barrett-type water separator was connected to the top of the column, and the mixture was heated at reflux for 30 hr. at which time no more water separated. A total of 180 ml. of aqueous phase was collected. The solvent was removed *in vacuo* at room temperature. Ether (1.5 l.) was added, and the ether solution was washed with three 750-ml. portions of a 10% aqueous solution of sodium carbonate which was saturated with sodium chloride. The ether solution was then washed with three 750-ml. portions of saturated salt solution, was dried, and the ether was removed *in vacuo*. The residue was distilled through the spinning band column. The fraction boiling at 124° (0.2 mm.) was shown to be pure by infrared absorption and by gas chromatography. There was obtained 223 g., 70% yield based on the nitrile.

Isopropyl 4-oxocyclohexane-1,3-dicarboxylate (XIV). To 500 ml. of benzene in a 1-l., three-necked, Morton flask

rated solution of sodium chloride and was dried. The ether was removed *in vacuo*. Attempted distillation of a 10-g. portion of the residue resulted in extensive decomposition in the pot and was discontinued. A portion of the residue (10 g.) was dissolved in 75 ml. of petroleum ether and this solution was placed on a 37-mm. bore column packed with five 150-g. portions of alumina separated by 1″ plugs of glass wool. There was eluted by 50% benzene 0.52 g. of material having an infrared maximum at 1735 cm.$^{-1}$; by 10% ether in benzene 1.37 g. of the same material; and by 10, 25, 50, and 75% methanol in chloroform 2.54 g. of material having infrared maxima at 1735 (s) and 1650 (m) cm.$^{-1}$

A 10-g. portion of the residue was dissolved in a mixture of 40 ml. of benzene and 60 ml. of petroleum ether, and this solution was placed on a 37-mm. bore column packed with five 150-g. portions of deactivated[12] alumina separated by 1″ plugs of glass wool. The following fractions were obtained:

Fraction Number	Eluent	Fraction Weight, G.	Infrared Maxima, Cm.$^{-1}$
6–10	25% benzene in pet. ether	2.12	1735 (s), 1690 (w)
11–15	50% benzene in pet. ether	2.24	1735 (s), 1690 (w)
16–21	75% benzene in pet. ether	1.33	1735 (s), 1690 (w)
22–25	Benzene	0.25	1735 (s), 1690 (m)
26–30	10% ether in benzene	0.31	1735 (s), 1712 (w), 1690 (m), 1650 (m), 1615 (m)
31–35	25% ether in benzene	0.17	1735 (s), 1712 (w), 1650 (m), 1615 (m)
36–39	75% ether in benzene	0.08	
71–72	Chloroform	1.04	
80–95	10% Methanol in chloroform	0.40	1735 (s)

Attempted preparation of 2-methyl-1,3-diphenylpropen-1-one (VIb). To 28.2 g. (0.16 mole) of methyl 2-methyl-3-phenylpropionate (Xb) in 250 ml. of ether at 0° was added dropwise 0.08 mole of phenylmagnesium bromide in 100 ml. of ether solution. The mixture was stirred for 4 hr. and was allowed to stand overnight. The mixture was hydrolyzed with 75 ml. of concd. hydrochloric acid in 75 ml. of water. The ether was separated, and the aqueous portion was extracted with three 150-ml. portions of ether. The combined ether layer was washed with three 150-ml. portions of aqueous saturated salt solution. The ether solution was dried, and the ether was removed *in vacuo*. The residue was distilled through the spinning band column. Four fractions were obtained: 1. b.p. 30–72° (0.1 mm.), 1.6 g.; 2.72° (0.1 mm.), 10.1 g.; 3. 55° (0.05 mm.), 1.8 g.; 4. 120–138° (0.1–0.15 mm.) 15.2 g. Fraction 2 was starting material; fraction 3 was a mixture of fractions 2 and 4; and fraction 4 solidified on standing, m.p. 63.5–65°, and exhibited infrared maxima at 1635 and 910 cm.$^{-1}$ indicative of an olefinic, aromatic hydrocarbon. Four grams of fraction 4 was dissolved in 15 ml. of petroleum ether and placed on a 19 mm.-bore column containing four 20 g. portions of alumina separated by glass wool plugs. Five and ten per cent (by volume) benzene in petroleum ether solution eluted 3.9 g. of material, m.p. 65–66°, having infrared maxima at 1635 and 910 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{20}$: C, 92.91; H, 7.09. Found: C, 92.76; H, 7.09. The material was assigned the structure 2-methyl-1,1,3-triphenylprop-1-ene (XIb).

The reaction of isopropyl acrylate with phenylmagnesium bromide. To 50 ml. of an ether solution containing 0.144 mole of phenylmagnesium bromide in a 1-l., three-necked flask equipped with a stirrer, addition funnel, reflux condenser, and thermometer was added dropwise with stirring a solution of 42.5 ml. (38 g., 0.33 mole) of isopropyl acrylate in 100 ml. of ether over a period of 90 min. while the temperature was maintained between 0 and 4°. Stirring was continued for 3 hr., and the mixture was hydrolyzed with 150 ml. of concd. hydrochloric acid in 150 ml. of water. The ether was separated, and the aqueous layer was extracted with three 100-ml. portions of ether. The combined ether solution was washed with three 100-ml. portions of a satu-

equipped with a Labline high speed stirrer, a condenser, and an addition funnel was added 9 g. (0.39- g.-atom) of sodium metal. The benzene was heated at reflux, and the sodium was pulverized with the high speed stirrer. With continued heating and stirring, 0.5 ml. of isopropyl alcohol was added, and 82.5 (0.25 mole) of isopropyl pentane-1,3,5-tricarboxylate was added dropwise during 90 min. Heating and stirring were continued for 6.5 hr., and the mixture was allowed to cool to room temperature. A solution of 50 ml. of acetic acid in 50 ml. of benzene was added followed by 500 ml. of water. The benzene was separated, and the aqueous layer was washed with three 50-ml. portions of benzene. The combined benzene layer was washed with three 200-ml. portions of water saturated with sodium chloride. The benzene solution was dried with magnesium sulfate, and the benzene was removed *in vacuo*. The residue was distilled through the spinning band column. The fraction boiling at 118–121° (0.45 mm.) amounted to 50.6 g., 75% yield, and had infrared maxima at 1735, 1712, 1655, and 1615 cm.$^{-1}$ and an ultraviolet maximum at 250 mμ (ϵ = 9300).

Anal. Calcd. for $C_{14}H_{22}O_5$: C, 62.20; H, 8.20. Found: C, 62.05; H, 8.22.

Isopropyl 5-benzyl-4-oxocyclohexane-1,3-dicarboxylate (VIIId). To a stirred solution of 27 g. (0.1 mole) of isopropyl 4-oxocyclohexane-1,3-dicarboxylate, 11.5 ml. of benzyl chloride, and 0.25 g. of sodium iodide in 100 ml. of isopropyl alcohol was added a solution of 2.5 g. of sodium metal in 250 ml. of isopropyl alcohol dropwise over a period of 2 hr. The solution was allowed to stand at room temperature for 48 hr., whereupon the solvent was removed on a water pump and finally at 0.5 mm. at room temperature. Ether (250 ml.) was added, and the solution was washed with three 150-ml. portions of water and was dried. On removal of the ether, there remained 28 g. of residue having infrared maxima at 1735, 745, and 705 cm.$^{-1}$ but lacking the maxima at 1712, 1655, and 1615 cm.$^{-1}$ found in the cyclohexanonedicarboxylate.

To 500 ml. of toluene in a 1-l., three-necked, Morton flask equipped with a high speed stirrer, reflux condenser, and dropping funnel was added 4 g. (0.17 g.-atom) of sodium metal. The toluene was heated at reflux, and the sodium was dispersed with the high speed stirrer. Isopropyl alcohol (0.5 ml.) was added followed by 25 g. of the above residue dropwise during 90 min. Heating and stirring were continued for 6 hr. The flask was cooled in an ice bath and a solution of 11 ml. of acetic acid in 10 ml. of benzene was added, followed by 100 ml. of water. The toluene was separated; the aqueous layer was extracted with two 50-ml. portions of toluene; the combined toluene layer was washed with two 100-ml. portions of water, and the toluene was dried with anhydrous magnesium sulfate. Removal of the toluene *in vacuo* left 21 g. of residue, 20 g. of which was dissolved in a mixture of 40 ml. of benzene and 40 ml. of petroleum ether. The benzene-ether solution was placed on the top of a 19-mm. bore column packed with four 20-g. portions of deactivated[12] alumina separated by glass wool plugs. There was eluted with 50:50 (v:v) benzene-petroleum ether 10.6 g. (34% based on isopropyl 4-oxocyclohexane-1,3-dicarboxylate) of material having infrared maxima at 1735, 1712, 1650, 1615, 745, and 705 cm.$^{-1}$

Anal. Calcd. for $C_{21}H_{28}O_5$: C, 69.98; H, 7.83. Found: C, 70.08; H, 7.83. This material had an ultraviolet maximum at 253 mμ (ϵ = 8160) and a shoulder at 208 mμ.

The reaction of methyl methacrylate with isopropylmagnesium bromide. The procedure of Lebedeva and Vainrub[3a] was repeated exactly. Distillation through the spinning band column gave six fractions:

Fraction Number	B.P.	Mm.	Fraction Weight, G.	Infrared Maxima, Cm.$^{-1}$
1	92–100	2.25	0.61	1740 (s), 1715 (s)
2	102–114	3.00	1.50	1740 (s), 1715 (s)
3	64.5–67	0.10	1.28	1740 (s), 1715 (w)
4	67–68	0.15	4.22	1740 (s), 1715 (m)
5	66	0.10	0.87	1740 (s), 1712 (s)
Residue			4.22	1760 (m), 1740 (s), 1712 (m)

The reaction of methyl acrylate with isopropylmagnesium bromide. The procedure of Lebedeva and Vainrub[3a] was repeated exactly, except that the material was not distilled but was placed on a 37-mm. bore column packed with five 150-g. portions of deactivated[12] alumina separated by 1″ plugs of glass wool. The following fractions were obtained:

Fraction Number	Eluent	Fraction Weight, G.	Infrared Maxima, Cm.$^{-1}$
5–7	10% Benzene in pet. ether	0.51	1740 (s), 1718 (s), 1025 (w)
8–16	25% Benzene in pet. ether	2.15	1740 (s), 1718 (m), 1025 (w)
17–21	50% Benzene in pet. ether	1.06	1740 (s), 1718 (m), 1025 (w)
22–26	75% Benzene in pet. ether	0.75	1740 (s), 1718 (m)
27–31	Benzene	0.34	1740 (s), 1718 (s), 1665 (w), 1622 (w)
32–37	10% Ether in benzene	0.23	1740 (s), 1718 (s), 1665 (w), 1622 (w)
53–58	Ether	0.47	1740 (s), 1718 (s), 1712 (w), 1665 (m), 1622 (m)
74–79	Chloroform	0.43	1740 (s), 1665 (w), 1622 (w)
80–89	50% Methanol in chloroform	3.10	1740 (s)
90–102	Methanol	0.26	1740 (s)

Fractions 27–29 had a maximum in the ultraviolet at 250 mμ.

Acknowedgment. The authors extend warm thanks and appreciation to Dr. A. R. Weiss for the mass spectroscopy determination, to Dr. W. R. Lyman for the preparation of the radioactive methyl methacrylate, and to Dr. K. Booman for the interpretation of the NMR spectrum.

BRISTOL, PA.

[CONTRIBUTION FROM THE U. S. ARMY QUARTERMASTER R & E COMMAND, PIONEERING RESEARCH DIVISION]

Triphenylgermane Addition Reactions

MALCOLM C. HENRY AND MARY F. DOWNEY[1]

Received November 8, 1960

The reactions of triphenylgermane with a number of organic compounds containing olefinic double bonds, with and without activating functional groups, have been studied. It is shown that, in the absence of solvent and catalyst, triphenylgermane adds to unsaturated carbon bonds. The addition products obtained contained the functional groups unchanged. By means of this reaction some new organogermanium compounds containing functional groups were synthesized.

This paper is concerned with the preparation of functional group-containing organogermanium compounds by means which do not require reactive organometallic intermediates or catalyts. As a result a series of organogermanium compounds, with and without functional groups, were synthesized in a simple and direct manner.

In the germanium series the germanium-hydrogen bond is expected to be less reactive than the correponding tin compounds. This should lead to fewer side effects resulting from exchange and reduction reactions which are frequently noticed with the organotin analog. Fuchs and Gilman[2] have carried out addition reactions with triphenylgermane using octene and cyclohexene, with an inert solvent, a peroxide catalyst or ultraviolet light. Lesbre and co-workers[3a,b] have investigatesd some addition reactions of trialkylgermanes utilizing peroxide or platinum catalysts and in this manner succeeded in preparing several β- or γ-substituted germanium compounds. In addition, they indicated that in the absence of catalyst, trialkylgermanes were added to acrylonitrile, acrylic acid, methyl acrylate, and ethyl acrylate. Subsequent work by the same authors[3c] showed that trialkylgermanes react quantitatively, in the presence of chloroplatinic acid, with acetylenic derivatives, and when phenylacetylene was used the reaction was possible in the absence of catalyst.

We have studied the reaction of triphenylgermane with various olefinic and acetylenic compounds in order to describe in greater detail the nature of this addition reaction. The functional group, when presented in the unsaturated molecule, was either conjugated with the unsaturated linkage or located terminal to it. In this manner, therefore, not only the effect of the Ge—H bond upon the functional group, but also the possibility of introducing functional groups by means of simple addition could be investigated. The following reactions were successfully completed:

$$(C_6H_5)_3GeH + CH_2{=}CHY \longrightarrow (C_6H_5)_3GeCH_2CH_2Y$$

where

$$Y = -C_6H_5,\ -OCOCH_3,\ -CN,\ -CONH_2,\ -COCH_3,\ -COOCH_3,\ -(CH_2)_5CH_3,\ -(CH_2)_2CH_2OH$$

In addition, the expected adducts were obtained by adding triphenylgermane to cyclohexene, 2-methyl-3-butyn-2-ol, and phenylacetylene.

No reducing properties of the triphenylgermane upon the functional groups were observed. Apparently, it is not a prerequisite that the unsaturation be activated by adjacent functional groupings. The results obtained are summarized in Table I.

EXPERIMENTAL

The addition reactions summarized in Table I were carried out in Schlenk tubes equipped with drying tubes and covered at all times by an oxygen-free, inert atmosphere. Infrared spectra of all the products were carried out on a Perkin-Elmer Infracord to check functional groupings and the characteristic absorption band at 1085 cm.$^{-1}$ for the phenylgermanium grouping as previously described.[4] Yields are based upon final recrystallized products. Melting points were taken with a Kofler hot stage. Triphenylgermane was prepared by converting germanium tetrachloride to tetraphenylgermane which in turn was brominated to triphenylbromogermane. The triphenylbromogermane was finally reduced with lithium aluminum hydride.[5]

Triphenyl(2-phenylethyl)germane. A mixture of 2.29 g. (7.5 mmoles) of triphenylgermane and 0.78 g. (7.5 mmoles) of freshly distilled styrene was heated overnight in an oil bath at 120°. The product was recrystallized from acetone and then from a methanol-acetone mixture m.p. 145–146°. The yield was 1.0 g. (40%).

Anal. Calcd. for $C_{26}H_{24}Ge$: Ge, 17.77. Found: Ge, 17.39.

Triphenyloctylgermane. A mixture of 1.12 g. (10 mmoles) of *n*-octene and 3.05 g. (10 mmoles) of triphenylgermane was heated in an oil bath for 5 days at 110–115°. Hexane was added to the reaction mixture which was warmed and allowed to cool. The white crystalline plates that precipitated were recrystallized from hexane and then from methanol, m.p. 62–66°. The yield was 1.2 g. (29%).

Anal. Calcd. for $C_{26}H_{32}Ge$: C, 74.95; H, 7.74; Ge, 17.42. Found: C, 74.54; H, 7.54; Ge, 17.40.

Triphenylstyrylgermane. A mixture of 1.02 g. (10 mmoles) of phenylacetylene and 3.05 g. (10 mmoles) of triphenyl-

(1) Research fellow sponsored by the Germanium Research Committee.

(2) (a) F. Fuchs and H. Gilman, *J. Org. Chem.*, **22**, 1009 (1957); (b) **23**, 911 (1958).

(3) (a) M. Lesbre and J. Satge, *Compt. Rend.*, **247**, 471 (1958); (b) P. Mazeroless and M. Lesbre, *Compt. Rend.*, **248**, 2018 (1959).

(3) (c) M. Lesbre and J. Satge, *Compt. Rend.*, **250**, 2220 (1960).

(4) J. G. Noltes, M. C. Henry, and M. J. Janssen, *Chem. & Ind. (London)*, 1959, 298.

(5) O. H. Johnson and D. M. Harris, *J. Am. Chem. Soc.*, **72**, 5566 (1950).

TABLE I. REACTIONS OF TRIPHENYLGERMANE WITH SOME UNSATURATED COMPOUNDS

Unsaturated Compound	Adduct	M.P.
Styrene	$(C_6H_5)_3GeCH_2CH_2C_6H_5$ Triphenyl(2-phenylethyl)germane	145–146
n-Octene	$(C_6H_5)_3Ge(CH_2)CH_3$ Triphenyloctylgermane	64–66[a]
Phenylacetylene	$(C_6H_5)_3GeCH{=}CHC_6H_5$ Triphenylstyrylgermane	146–149
Cyclohexene	$(C_6H_5)_3GeCH(CH_2)_4CH_2$ Triphenylcyclohexylgermane	144–147[a]
2-Methyl-3-butyn-2-ol	$(C_6H_5)_3GeCH{=}CHC(OH)(CH_3)_2$ Triphenyl(3-methyl-3-hydroxybuten-1-yl)germane	90.5–91.5
Vinyl acetate	$(C_6H_5)_3GeCH_2CH_2OCOCH_3$ Triphenyl(2-acetoxyethyl)germane	62–62.5
Acrylonitrile	$(C_6H_5)_3GeCH_2CH_2CN$ Triphenyl(2-cyanoethyl)germane	126–129
4-Pentene-1-ol	$(C_6H_5)_3Ge(CH_2)_4CH_2OH$ Triphenyl(5-hydroxypentyl)germane	51–61
Methyl vinyl ketone	$(C_6H_5)_3GeCH_2CH_2COCH_3$ Triphenyl(2-acetylethyl)germane	144–146
Acrylamide	$(C_6H_5)_3GeCH_2CH_2CONH_2$ Triphenyl(2-carbamylethyl)germane	176–178
Methyl acrylate	$(C_6H_5)GeCH_2CH_2COOCH_3$ Triphenyl(2-methoxycarbonylethyl)germane	60.5–62.0

[a] Fuchs and Gilman[2] report the triphenyl-(*n*-octyl)germane m.p. 72° and the triphenylcyclohexylgermane m.p. 143–146°, 147–149.5°.

germane was heated at 135° for 4 days in an oil bath. The thick viscous oil was chromatographed through a neutral alumina column with hexane. The first fraction to be eluted was recrystallized successively from petroleum ether (b.p. 60–80°), hexane, and finally from ethyl acetate, m.p. 146–149°. The yield was 0.5 g. (12%).

Anal. Calcd. for $C_{26}H_{22}Ge$: C, 76.75; H, 5.46; Ge, 17.85. Found: C, 76.76; H, 5.63; Ge, 17.63.

Triphenylcyclohexylgermane. A mixture of 0.82 g. (10 mmoles) of cyclohexene and 3.05 g. (10 mmoles) of triphenylgermane was heated for 5 days at 60–70° in an oil bath. Addition of hexane to the product yielded a white crystalline product that was recrystallized successively from methanol, cyclohexane, and methanol, m.p. 144–147°. The yield was 1.5 g. (39%).

Anal. Calcd. for $C_{24}H_{26}Ge$: C, 74.53; H, 7.03; Ge, 18.77. Found: C, 74.61; H, 6.78; Ge, 18.68.

Triphenyl(3-methyl-3-hydroxybuten-1-yl)germane. A mixture of 0.84 g. (10 mmoles) of 2-methyl-3-butyn-2-ol and 3.05 g. (10 mmoles) of triphenylgermane was heated 77 hr. at 50–60° in an oil bath. Hexane added to the product mixture yielded a white solid which was recrystallized from butanol and then from methanol, m.p. 90.5–91.5°. The yield was 1.81 g. (49%).

Anal. Calcd. for $C_{23}H_{24}OGe$: C, 71.00; H, 6.17; Ge, 18.67. Found: C, 70.90; H, 6.27; Ge, 18.82.

Triphenyl(2-acetoxyethyl)germane. A mixture of 0.86 g. (10 mmoles) of vinylacetate and 3.05 g. (10 mmoles) of triphenylgermane was heated in an oil bath for 6 hr. at 50–60°. Upon cooling, the mixture solidified. The solid product was crystallized successively from hexane, petroleum ether (b.p. 60–80°), and finally from an acetone-water solution, m.p. 62–62.5°. The yield of white crystals was 2.10 g. (54%).

Anal. Calcd. for $C_{22}H_{22}O_2Ge$: C, 67.64; H, 5.77; Ge, 18.58. Found: C, 67.75; H, 5.77; Ge, 18.70.

Triphenyl(2-cyanoethyl)germane. A mixture of 0.53 g. (10 mmoles) of acrylonitrile and 3.05 g. (10 mmoles) of triphenylgermane was heated in an oil bath at 50–60° for 6 hr. The solid product was taken up in methanol and recrystallized, m.p. 126–129°. The yield was 2.97 g. (83%).

Anal. Calcd. $C_{21}H_{17}NGe$: C, 70.57; H, 5.35; Ge, 20.29. Found: C, 70.55; H, 5.58; Ge, 20.20.

Triphenyl (5-hydroxy-n-pentyl)germane. A mixture of 0.86 g. (10 mmoles) of 4 pentene-1-ol and 3.05 g. (10 mmoles) of triphenylgermane was heated in an oil bath for 4 hr. at 50°. Hexane was added to the cooled product and after warming an oil settled out which crystallized upon standing. This product was then recrystallized again from hexane, m.p. 58–61°. The yield was 1.59 g. (41%).

Anal. Calcd. $C_{23}H_{26}OGe$: C, 70.69; H, 6.70; Ge, 18.58. Found: C, 70.87; H, 7.09; Ge, 18.70.

Triphenyl(2-acetylethyl)germane. A mixture of 0.70 g. (10 mmoles) of methyl vinyl ketone and 3.05 g. (10 mmoles) of triphenylgermane was heated in an oil bath for 18 hr. at 60–70°. Cooling precipitated a mass of white crystals. The filtered product was recrystallized first from petroleum ether (b.p. 60–80°) and finally from methanol, white rectangular plates, m.p. 144–146°. The yield was 2.0 g. (53%).

Anal. Calcd. for $C_{22}H_{22}OGe$: C, 70.45; H, 5.91; Ge, 19.37. Found: C, 70.30; H, 6.16; Ge, 19.39.

The 2,4-dinitrophenylhydrazone precipitated as yellow needles, m.p. 188–192°.

Anal. Calcd. for $C_{28}H_{26}N_4O_4Ge$: C, 60.58; H, 4.71. Found: C, 60.15; H, 4.96.

Triphenyl(2-carbamylethyl)germane. A mixture of 0.47 g. (10 mmoles) of acrylamide and 3.05 g. (10 mmoles) of triphenylgermane was heated in an oil bath for 21 hr. at 50–60°. The solid that separated out of the reaction mixture was filtered and recrystallized from dimethylformamide-water and then from acetone–petroleum ether (b.p. 60–80°) m.p. 176–178°.

Anal. Calcd. for $C_{21}H_{21}OGe$: C, 67.11; H, 5.59; Ge, 19.32. Found: C, 66.96; H, 5.73; Ge, 19.26.

Triphenyl(2-methoxycarbonylethyl)germane. A mixture of 0.86 g. (10 mmoles) of methyl acrylate and 3.05 g. (10 mmoles) of triphenylgermane was heated for 67 hr. at 60–70° in an oil bath. After cooling the resulting oil was taken up and recrystallized from a methanol-water mixture, m.p. 60.5–62.0°. The yield was 1.95 g. (50%).

Anal. Calcd. for $C_{22}H_{22}O_2Ge$: C, 67.62; H, 5.67; Ge, 18.58. Found: C, 67.35; H, 5.91; Ge, 18.42.

Acknowledgment. The authors are grateful to C. DiPietro for the microanalyses.

NATICK, MASS.

[CONTRIBUTION FROM THE DEPARTMENT OF INDUSTRIAL CHEMISTRY, FACULTY OF ENGINEERING, KYÔTO UNIVERSITY]

Direct Synthesis of Organotin Compounds. II. Diallyltin Dibromide and Its Derivatives

KEIITI SISIDO AND YOSIYUKI TAKEDA

Received November 9, 1960

Diallyltin dibromide was prepared by the reaction of allyl bromide with tin powder in boiling toluene. The catalytic effect of mercuric chloride and some organic bases on this reaction was examined and optimum conditions for preparation were determined. Allylic rearrangements in this reaction were investigated. The same reaction in boiling water or butanol yielded propylene.

In the previous paper[1] a direct preparation of di- or tribenzyltin chloride using toluene or water as a reaction medium, respectively, was reported. This reaction is considered to be of a radical nature.[1,2] In view of their similar behavior as radical sources, allyl halides were expected to react with tin in somewhat the same way,[3] if the high temperatures necessary for the initiation of the reaction could be reached.[1] When a solution of allyl bromide in toluene was refluxed for ten hours in the presence of tin powder diallyltin dibromide was obtained in a 14% yield. Addition of mercuric chloride accelerated this reaction to give the tin compound in a 44% yield. Search for a suitable catalyst led to the discovery that amines such as pyridine, triethylamine, dimethylaniline, or morpholine increased the yield of diallyltin dibromide to about 70%. Triphenylphosphine and -arsine also showed slight activities. Presumably mercuric chloride activated the tin powder by amalgamation, while the amines aided polarization of the carbon-bromine bond of allyl bromide so as to facilitate radical formation by the tin metal.

Triethanolamine did not act as a catalyst but inhibited the reaction. Sodium methoxide also inhibited the reaction.

Although the simultaneous addition of both mercuric chloride and an amine in toluene formed a curdy precipitate consisting of the addition complex,[4] which showed no catalytic effect, preliminary treatment of tin powder with mercuric chloride in boiling toluene followed by addition of triethylamine led to the production of the allyltin compound in a yield of 81.7%.

Presence of water in the reaction medium influenced the results due to the ready hydrolyzability of allyltin compounds. Under absolutely anhydrous conditions, in the absence of catalyst, the reaction gave the product in a 2% yield, whereas use of moistened tin powder[1] gave a yield of 14%. In a reaction catalyzed by mercuric chloride and triethylamine anhydrous toluene as a solvent furnished an 81.7% yield, while use of toluene saturated with water afforded only a 44% yield.

Recovered tin powder from these preparations could not be used again in another run, for it was always contaminated with a yellow gum which could not be removed by extraction with any solvent. This was probably formed by oxidation of an insoluble allyltin compound during filtration in air. In order to avoid a futile consumption of materials the use of tin and halide in a 1:2 molar ratio was examined, but it resulted in a lowering of the yield to 37%.

Results of these experiments are summarized in Table I.

For the identification of liquid diallyltin dibromide, its crystalline pyridine adduct,[5] (CH_2=

TABLE I

PREPARATION OF DIALLYLTIN DIBROMIDE[a]

Catalyst[b]	Reaction Time, Hr.	Diallyltin Dibromide[c] Yield	
		g.	%
None	10.0	0.6	2.2
None[d]	10.0	3.9	14.4
$HgCl_2$	8.0	12.0	44.4
C_5H_5N	4.0	19.0	70.2
$(C_2H_5)_3N$	4.0	19.1	70.3
$C_6H_5N(CH_3)_2$	4.0	18.9	69.4
Morpholine	4.0	19.0	69.8
$(C_6H_5)_3P$	4.0	15.8	58.3
$(C_6H_5)_3As$	4.0	10.7	39.9
$N(CH_2CH_2OH)_3$	4.0	(Recovery of materials)	
CH_3ONa	4.0	(Recovery of materials)	
$HgCl_2$,[e] C_5H_5N	1.5	21.6	79.9
$HgCl_2$,[e] $(C_2H_5)_3N$	1.5	22.3	81.7
$HgCl_2$,[e] $(C_2H_5)_3N$[f]	4.0	11.1	40.8
$HgCl_2$,[e] $(C_2H_5)_3N$[g]	4.0	10.1	37.4

[a] All reactions except the last one were carried out with 0.15 mole of allyl bromide and 0.15 mole of tin in 150 ml. of refluxing toluene (stored over sodium, unless otherwise stated) under a nitrogen atmosphere. [b] 2–3 millimoles of catalyst was used. [c] Fraction boiling at 77–79°/2 mm. [d] Tin powder containing 2–3% of water was used. [e] See details in Experimental. [f] Toluene saturated with water was used. [g] 0.075 mole of tin powder was used.

(1) K. Sisido, Y. Takeda, and Z. Kinugawa, *J. Am. Chem. Soc.*, **83**, 538 (1961).

(2) K. Sisido, Y. Udô, and H. Nozaki, *J. Am. Chem. Soc.*, **82**, 434 (1960).

(3) G. J. M. van der Kerk, J. G. A. Luijten, and J. G. Noltes, *Angew. Chem.*, **70**, 298 (1958).

(4) A. Naumann, *Ber.*, **37**, 4609 (1904); K. A. Hofmann and E. C. Marburg, *Ann.*, **305**, 202 (1899).

$CHCH_2)_2SnBr_2 \cdot 2C_5H_5N$, was utilized. This dipyridino adduct, when dissolved in such a solvent as an aromatic or paraffinic hydrocarbon, carbon tetrachloride, chloroform, or ethyl acetate dissociated into the monpyridino compound, $(CH_2{=}CHCH_2)_2SnBr_2 \cdot C_5H_5N$, which separated as a white precipitate. This precipitate dissolved again on addition of excess pyridine or such solvents as alcohols or dimethylformamide.

Reactions of tin with allylic *n*-butenyl bromides are of interest because of possible allylic rearrangements. In the case of Grignard reactions, studies on this rearrangement concerned only the final products[6] and the constitution of the intermediary organometallic compounds has scarcely been discussed. Recently, Gaudemar[7] has claimed, on the basis of absorptions at 1615–1645 cm.$^{-1}$, that all of the organomagnesium, aluminum, and zinc compounds of crotyl bromide consist exclusively of the primary crotyl isomer. Lanpher,[8] however, has not recognized any absorption in the normal double bond stretching region (1620–1680 cm.$^{-1}$) with crotyllithium, -sodium, and -magnesium bromide, but found a strong absorption due to a double bond stretching frequency at 1500–1560 cm.$^{-1}$

The reactions of both primary crotyl bromide and secondary methylvinylcarbinyl bromide with tin were carried out to give dibutenyltin dibromides. The products were separated by fractional distillation. Two distinctly different fractions were obtained from each in yields of 5 and 6% as well as 67 and 70%, respectively. Each corresponding fraction was proved to be the same by comparing the infrared spectra and in some cases mixed melting point determinations. Because of their instability, identification of these compounds could not be carried out by chemical methods such as oxidative degradation. Two strong absorptions at 915 and 985 cm.$^{-1}$ were found in the spectra of the lower boiling fraction. Since strong absorptions at 905 and 985 cm.$^{-1}$ were also found in diallyltin dibromide, these absorptions could be assigned to a vinyl group.[9] The higher boiling fraction showed a strong absorption at 955 cm.$^{-1}$ which was hardly recognized in the former and not in diallyltin dibromide. The absorptions could be assigned to a *trans*-disubstituted ethylene structure.[9] These facts indicated that both of the reactions gave the same products in the same proportions suggesting existence of an equilibrium. The main fraction consisted of dicrotyltin dibromide and the minor of bis(methylvinylcarbinyl)tin dibromide. Contamination with crotyl(methylvinylcarbinyl)tin bromide, however, was not absolutely excluded. Absorption bands arising from the double bond stretching were observed in both butenyltin compounds as well as in diallyltin dibromide in the 1635–1660 cm.$^{-1}$ region.

Allyl chloride showed practically no sign of reaction on heating with tin under various conditions. Due to difficulty in stirring, which must be very vigorous[1] in these reactions in order to keep the tin powder as a suspension, an attempt to use an autoclave was abandoned. Also allylic dodecenyl chloride[10] gave no product, although its higher boiling point permitted better contact with the tin.

Diallyltin dibromide is a pale yellow oil having a pungent leek-like odor. It was comparatively unstable in air but more stable in a nitrogen atmosphere. On storing in air for a day or in nitrogen for six months it gave a pale yellow jelly, in which the characteristic absorptions of a double bond were not recognized.

Catalytic hydrogenation of diallyltin dibromide was investigated for the purpose of finding a new synthetic route to dialkyltin dibromides. All attempts made using Raney nickel were unsuccessful.

Diallyltin dibromide and its homologs were readily hydrolyzed on shaking with water, forming bromide anion and a white curdy precipitate, the aqueous part becoming acidic to litmus. Taking advantage of this phenomenon, halogen bound to tin could easily be determined by a back-titration method as described in the Experimental. Volumetric analyses have recently been applied to the determination of acyl groups[11] and halogen atoms[12] in organotin compounds.

Attempted preparation of triallyltin bromide by the reaction of allyl bromide with dispersed tin powder in boiling water or in butanol at 100° resulted in the formation of propylene in yields of 84 and 67%, respectively. This may be accounted for by the decomposition of the allyltin compounds by the acids produced by hydrolysis of allyl bromide or stannous bromide. The fact that diallyltin dibromide, when boiled with hydrochloric acid, cleaved with elimination of propylene supports this explanation. This may also be in line with the easy cleavage of the allyl group from allyltin derivatives by acetic acid as reported by Rosenberg *et al.*[13]

EXPERIMENTAL[14]

Analyses of tin in organic compounds. Detection[15] and determination[16] of tin were performed by a method similar

(5) K. V. Vijayaraghavan, *J. Indian Chem. Soc.*, **22**, 135 (1945); *Chem. Abstr.*, **40**, 2787 (1946).

(6) R. H. DeWolfe and W. G. Young, *Chem. Revs.*, **56**, 753 (1956); M. S. Kharasch and O. Reinmuth, *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Inc., New York, N. Y., 1954, p. 1133.

(7) M. Gaudemar, *Bull. soc. chim. France*, 1475 (1958).

(8) E. J. Lanpher, *J. Am. Chem. Soc.*, **79**, 5578 (1957).

(9) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, 2nd ed., Methuen & Co., London, 1958, p. 34.

(10) Kindly supplied by Rohm & Haas Company, Washington Square, Philadelphia 5, Pa.

(11) H. H. Anderson, *J. Org. Chem.*, **22**, 147 (1957); T. M. Andrews, F. A. Bower, B. R. LaLiberte, and J. C. Montermoso, *J. Am. Chem. Soc.*, **80**, 4102 (1958).

(12) H. C. Clark and C. J. Willis, *J. Am. Chem. Soc.*, **82**, 1888 (1960).

to that previously[1] described. In the quantitative analysis the sample was wetted with a few drops of glacial acetic acid in a crucible before the addition of mixed acid.[16,17]

Analyses of ionically bound halogen. About 0.2 g. of a sample was weighed accurately and added to 30 ml. of 0.1*N* ethanolic potassium hydroxide solution in an Erlenmeyer flask. This was warmed with shaking in a water bath at 40° for 20 min. and unconsumed alkali was titrated on cooling with 0.1*N* aqueous hydrochloric acid solution using phenolphthalein as an indicator.

Tin powder. Chemically pure tin powder[18] or commercial tin powder was used after treatment as described in the previous paper.[1] There was no difference between the two.

Reaction of allyl bromide with tin in toluene; diallyltin dibromide. Results of reactions of allyl bromide with tin in the presence of various catalysts are summarized in Table I. All reactions and distillations were carried out in a nitrogen atmosphere. A representative procedure is as follows.

To 17.8 g. (0.15 mole) of tin powder in 150 ml. of toluene was added 0.5 g. (0.002 mole) of mercuric chloride and the resulting mixture was heated to reflux for 30 min. with stirring. After cooling 0.2 g. (0.002 mole) of triethylamine was added.

The mixture was again refluxed and to this was added dropwise 18.2 g. (0.15 mole) of allyl bromide with efficient stirring. After initial depression of the boiling point to 103°, the reaction temperature rose gradually, reaching a temperature of 111° in 1.5 hr. When the yield of the product was low, the final temperature was lower.

Unchanged tin together with an unidentified amorphous solid (10.4 g. in total) were filtered off and the filtrate was evaporated under reduced pressure. The residual oil (27.0 g.) was distilled *in vacuo* yielding 22.3 g. (81.7%) of diallyltin dibromide, b.p. 77–79°/2 mm., d_{20}^{20} 1.8640, (lit.[5] b.p. 77–79°/2 mm.), infrared absorptions (neat): 3090 (m), 2920 (w), 1810 (w), 1635 (vs), 1427 (m), 1395 (m), 1304 (w), 1182 (s), 1100 (m), 1030 (m), 985 (s), 905 (vs), 760 (s), and 740 (w) cm.$^{-1}$

The product gave correct analyses for tin and bromine.

Diallyltin dibromide gave a pyridine adduct, m.p. 101–103° (see below).

Removal of insoluble by-product from the recovered tin using various solvents was unsuccessful. Dimethylformamide dissolved the mass only incompletely; the extracted material consisted of an infusible organic matter containing tin and halogen.

Reaction of crotyl bromide with tin. Pure crotyl bromide,[19] b.p. 44–47°/90 mm., n_D^{25} 1.4788 (lit.[19] b.p. 49°/93 mm., n_D^{25} 1.4795), was prepared by the method of Young *et al.*[19] from the corresponding alcohol. To a suspension of 17.8 g. (0.15 mole) of tin powder treated with 0.5 g. (0.002 mole) of mercuric chloride in 150 ml. of toluene was added, in the presence of 0.2 g. (0.002 mole) of triethylamine, 20.1 g. (0.15 mole) of crotyl bromide following the same procedure as the preparation of diallyltin dibromide. After 1.5 hr. refluxing 24.3 g. of yellow oil was obtained on removal of the solvent. Distillation of this oil *in vacuo* gave two fractions: 1.5 g. (5.0%) of bis(methylvinylcarbinyl)tin dibromide, b.p. 60–63°/0.20 mm., infrared absorptions (neat): 3090 (m), 3010 (m), 2970 (vs), 2930 (s), 2660–80 (sh), 1660 (w), 1640 (m), 1520 (m), 1495 (w), 1453 (s), 1425 (sh), 1380 (vs), 1310 (m), 1260 (s), 1075 (s), 1035 (s), 985 (vs), 915 (vs), 807 (m), and 745 (s) cm.$^{-1}$

Anal. Calcd. for $C_8H_{14}Br_2Sn$: Sn, 30.54; Br, 41.12. Found: Sn, 29.86 Br, 40.79.

and 20.4 g. (70.2%) of dicrotyltin dibromide, b.p. 104–106°/0.20 mm., m.p. 30–31°, infrared absorptions (neat): 3020 (s), 2970 (s), 2930 (s), 2680 (m), 1660 (m), 1640 (w), 1450 (m), 1403 (m), 1380 (w), 1370 (w), 1303 (w), 1150 (m), 1100 (m), 1065 (m), 1035 (m), 955 (vs), 790 (m), 765 (m), and 730 (m) cm.$^{-1}$,

Anal. Calcd. for $C_8H_{14}Br_2Sn$:Sn, 30.54; Br, 41.12. Found: Sn, 30.01; Br, 40.94.

Reaction of methylvinylcarbinyl bromide with tin. Pure methylvinylcarbinyl bromide[19] b.p. 31–34°/93 mm., n_D^{25} 1.4610 (lit.[19] b.p. 31°/93 mm., n_D^{25} 1.4602) was prepared by the method of Young, *et al.*,[19] from the corresponding alcohol, and the same procedure was repeated as above using 20.1 g. (0.15 mole) of methylvinylcarbinyl bromide instead of crotyl bromide. The products were separated into 1.7 g. (6.0%) of bis(methylvinylcarbinyl)tin dibromide and 19.5 g. (67.2%) of dicrotyltin dibromide and were identified by the infrared absorptions, respectively, as well as the mixed melting point when the product was crystalline.

Reaction of allyl chloride with tin in toluene. In 150 ml. of toluene 17.8 g. (0.15 mole) of tin powder activated with 0.5 g. (0.002 mole) of mercuric chloride was caused to react with 11.5 g. (0.15 mole) of allyl chloride in the presence of 0.2 g. (0.002 mole) of triethylamine. After 40 hr. refluxing, unchanged tin (17.4 g.) was filtered off and the filtrate was fractionated to recover 10.7 g. of allyl chloride. Upon distillation of 1.1 g. of yellow oil which remained in the still no product containing tin was obtained.

Reaction of dodecenyl chloride with tin in toluene. To a suspension of 17.8 g. (0.15 mole) of tin powder activated with mercuric chloride in 150 ml. of toluene was added 26.1 g. (0.15 mole) of "dodecenyl chloride"[10] containing 92.5% of 1-chloro-5,5,7,7-tetramethyl-2-octene. After 40 hr. boiling 17.5 g. of tin powder and 25.8 g. of the starting halide were recovered.

Reaction of allyl bromide with tin in water. To a suspension of 17.8 g. (0.15 mole) of tin powder in 150 ml. of water was added dropwise 18.2 g. (0.15 mole) of allyl bromide under vigorous stirring over a period of 20 min. with such caution that loss of organic halide by steam distillation was avoided. Toward the end of addition the mixture became grayish and there was observed a vigorous evolution of gas which lasted for 15 min. The reaction apparatus had been fitted with a reflux condenser from whose upper end was connected a tube to two ice-cooled traps each containing 5 ml. of bromide in order to catch the gas. Resultant oil in the traps was freed from bromine, washed with sodium carbonate and water. Distillation gave 27.7 g. (84%) of 1,2-dibromopropane, b.p. 141–142°, n_D^{20} 1.5191 (lit.[20] b.p. 139–142°, n_D^{20} 1.5193), which gave the correct analytical values for carbon and hydrogen.

Another run with 17.8 g. (0.15 mole) of tin powder and 18.2 g. (0.15 mole) of allyl bromide using 1-butanol as a solvent also gave 22.1 g. (67.4%) of 1,2-dibromopropane.

Reaction of diallyltin dibromide with aqueous hydrochloric acid. To a stirred suspension of 10.3 g. (0.03 mole) of diallyltin dibromide in 30 ml. of water was added dropwise 30 ml. of 6*N* aqueous hydrochloric acid and the mixture was boiled for 30 min. Gaseous substances evolved was caught by bromine and treated as above to afford 8.7 g. (72.5%) of 1,2-dibromopropane.

Pyridine-adduct of diallyltin dibromide. Upon mixing of 5 g. (0.014 mole) of diallyltin dibromide and 5 g. (0.064 mole)

(13) S. D. Rosenberg, E. Debreczeni, and E. L. Weinberg, *J. Am. Chem. Soc.*, 81, 972 (1959).

(14) All temperatures are uncorrected.

(15) H. Gilman and T. N. Goreau, *J. Org. Chem.*, **17**, 1470 (1952).

(16) H. Gilman and S. D. Rosenberg, *J. Am. Chem. Soc.*, **75**, 3592 (1953).

(17) H. Gilman, B. Hofferth, H. W. Melvin, and G. E. Dunn, *J. Am. Chem. Soc.*, **72**, 5657 (1950).

(18) Assay: more than 99% Sn, 0.012% Cu, 0.006% Fe, 0.03% Pb, 0.031% As, 0.004% Sb, 0.011% Bi, 0.02% Zn.

(19) S. Winstein and W. G. Young, *J. Am. Chem. Soc.*, **58**, 104 (1936); W. G. Young, L. Richards, and J. Azorlosa, *J. Am. Chem. Soc.*, **61**, 3070 (1939).

(20) M. S. Kharasch, J. G. McNab, and M. C. McNab, *J. Am. Chem. Soc.*, **57**, 2743 (1935).

of pyridine there were precipitated crystals which were filtered, washed with pyridine, and allowed to stand over silica gel for 12 hr. to obtain 3.8 g. (52.8%) of dipyridino adduct, m.p. 101–103° (reported m.p. 99°[9]), which gave the correct analysis for tin.

On dissolving the dipyridino adduct in benzene there precipitated a white cloggy mass which could not be recrystallized from any solvent, but dissolved in ethanol or pyridine forming a clear solution. This monopyridino adduct decomposed on heating over 220°.

Anal. Calcd. for $C_{11}H_{15}Br_2NSn$: Sn, 26.99. Found; Sn, 26.53.

Attempted hydrogenation of diallyltin dibromide. In a usual hydrogenation apparatus a solution of 10.4 g. (0.03 mole) of diallyltin dibromide in 100 ml. of absolute ethanol was shaken with hydrogen in the presence of about 1 g. of Raney nickel (W-2[21]). During 8 hr. of shaking no absorption of gas was observed.

The same procedure using Raney nickel (W-6[21]) was also unsuccessful.

KYÔTO, JAPAN

(21) H. Adkins and H. R. Billica, *J. Am. Chem. Soc.*, **70**, 695 (1948).

[CONTRIBUTION FROM THE RAHWAY RESEARCH LABORATORY OF THE METAL AND THERMIT CORPORATION AND THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NEW HAMPSHIRE]

The Partial Hydrolysis of Dialkyltin Dihalides

A. J. GIBBONS, A. K. SAWYER,[1] AND A. ROSS

Received November 11, 1960

Some unexpected results obtained during recent work on various organotin compounds have led us to reexamine the products obtained by Johnson, Fritz, *et al.*,[3,4] from the reaction of dialkyltin dichlorides with certain amines and alcohols. These authors believe their products to be tetraalkyldichloroditins. We have repeated the reaction and closely studied the products. It is demonstrated that the products obtained are actually bis(dialkylchlorotin) oxides.

Hexaalkyl (aryl) ditins have been known for a good number of years[2] and the tin-tin bond in these compounds is widely accepted. The ditins readily react with bromine (or other halogens) at room temperature and give a metallic silver deposit on treatment with alcoholic silver nitrate. They are easily prepared by the reaction of the corresponding trialkyl (aryl) tin chloride with sodium, either in liquid ammonia or in high boiling solvents (1).

$$(C_6H_5)_3SnCl + 2Na \xrightarrow{(liq.\ NH_3)} (C_6H_5)_3SnNa + NaCl \quad (1)$$

$$(C_6H_5)_3SnNa + (C_6H_5)_3SnCl \longrightarrow (C_6H_5)_3Sn{-}Sn(C_6H_5)_3 + NaCl$$

I

The hexaarylditins (I) are generally solids and are oxidatively stable whereas the hexaalkyl ditins are generally high boiling liquids of lesser stability.

In 1954, Johnson and Fritz[3] reported a new type of tin compound, tetrabutyldichloroditin (II), from the reaction of an ethanolic solution of dibutyltin dichloride with sodium ethoxide (2).

$$(C_4H_9)_2SnCl_2 + NaOC_2H_5 \xrightarrow{C_2H_5OH} (C_4H_9)_2(Cl)Sn{-}Sn(Cl)(C_4H_9)_2 + 2NaCl \quad (2)$$

II

In 1955 the reaction was extended to several dialkyltin dichlorides and to diphenyltin dichloride.[4] It was also reported that various amines in combination with ethanol brought about the same reaction (3).

$$(C_4H_9)_2SnCl_2 + 2Et_3N + C_2H_5OH \xrightarrow{(C_2H_5)_2O} (C_4H_9)_2(Cl)Sn{-}Sn(Cl)(C_4H_9)_2 - 2Et_3N{\cdot}HCl \quad (3)$$

More recently Sawyer and Kuivila[5] have reported the preparation of similar ditin compounds with negative substituents on the tin atoms—*e.g.*, tetrabutylditin diacetate, tetraphenylditin dibenzoate. These preparations required the use of alkyltin hydrides to reduce the tin from a valence of four to a formal valence of three. These ditin products consumed stoichiometric amounts of bromine instantaneously.

In attempts to repeat the reaction of Johnson, Fritz, Halvorson, and Evans,[4] with di-*n*-butyltin dichloride, we have obtained yields of 95%, but the analyses of the products were consistently low in tin—*e.g.*, 42.8%, 42.6% as compared with a calculated value of 44.2%. These analyses were carried out in the Metal and Thermit laboratories where the procedure used has proved to be extremely reliable for many hundreds of tin compounds (see Experimental). The melting points, 110–112°, were sharp and identical with those obtained by Johnson, *et al.* Further recrystallization gave a material melting 1–2° higher but did not improve the analysis. Furthermore, this product

(1) University of New Hampshire, Durham, N. H.

(2) (a) E. Krause and R. Pohland, *Ber.*, **57**, 532 (1924). (b) *Cf.* E. Krause and A. Von Grosse, *Die Chemie der Metall-Organischen Verbindungen*, Gebrüder Borntrager, Berlin, pp. 356–361 (1937).

(3) O. H. Johnson and H. E. Fritz, *J. Org. Chem.*, **19**, 74 (1954).

(4) O. H. Johnson, H. E. Fritz, D. O. Halvorson, and R. L. Evans, *J. Am. Chem. Soc.*, **77**, 5857 (1955).

(5) A. K. Sawyer and H. G. Kuivila, *J. Am. Chem. Soc.*, **82**, 5958 (1960).

did *not* decolorize bromine, whereas tetraalkyldiacyloxyditins are known to take up bromine quantitatively.[5]

In order to identify the reaction product obtained, dibutyltin dichloride dissolved in methanol was treated with water, precipitating a white solid, m.p. 105–107°. Recrystallization from acetone gave white crystals, m.p. 111–112°, with 42.5% tin. This compound gave no depression in melting point when mixed with the product from the Johnson-Fritz reaction. Indeed, when dibutyltin dichloride was stirred with water alone, the insoluble material isolated was again identical to the previous products melting at 111–112°.

During attempts to prepare tetrabutylditindichloride from dibutyltin dihydride and dibutyltin dichloride, oxygen was bubbled through the mixture precipitating the same product as above, m.p. 112–114°.

The product obtained appears to be essentially the same material reported as $(C_4H_9)_2SnCl_2 \cdot (C_4H_9)_2SnO$,[6] m.p. 109–110°, and of the type discussed in a monograph by Luijten and van der Kerk.[7] Indeed, a comparison of the melting points of a number of products obtained by Johnson, Fritz *et al.*, with those of the corresponding complexes previously reported, brings out a distinct similarity as shown in Table I.

TABLE I

MELTING POINTS OF THE REACTION PRODUCTS FROM THE DIALKYLTIN DICHLORIDE–AMINE–ALCOHOL REACTION

R_2SnX_2		Reported by Johnson, Fritz,[3,4] *et al.*	Reported as $R_2SnX_2 \cdot R_2SnO$
R	X		
Ethyl	Cl	174–176°	176°[a]
Propyl	Cl	120.5–121.5°	124°[b]
Butyl	Cl	111–112°	109–110°[c] 114–115°[d]
Butyl	Br	102–103°	108°[c,e]
Phenyl	Cl	185–187°	187°[f]

[a] See ref. 7. [b] P. Pfeiffer and O. Brack, *Z. Anorg. U. Allgem. Chem.*, **87**, 229–234 (1941). [c] See ref. 6. [d] This work. [e] T. Harada, *Sci. Papers Inst. Phys. Chem. Research (Tokyo)*, **42**, 178–180 (1947) [now *J. Sci. Research Inst. (Tokyo)*]. [f] B. Aronheim, *Ann.*, **194**, 145–175 (1878).

As the melting point of our material is quite sharp and the analyses are consistently good, we regard the material as a pure compound, bis-(dibutylchlorotin) oxide, IV, and propose its formation as follows:

$$(C_4H_9)_2SnCl_2 + HOH \longrightarrow \underset{\text{III}}{(C_4H_9)_2(Cl)Sn{-}OH} + HCl \quad (4)$$

$$(C_4H_9)_2(Cl)Sn{-}OH + (C_4H_9)_2SnCl_2 \longrightarrow \underset{\text{IV}}{(C_4H_9)_2(Cl)Sn{-}O{-}Sn(Cl)(C_4H_9)_2} + HCl \quad (5)$$

$$2(C_4H_9)_2(Cl)Sn{-}OH \longrightarrow \underset{\text{IV}}{(C_4H_9)_2(Cl)Sn{-}O{-}Sn(Cl)(C_4H_9)_2} + H_2O \quad (6)$$

The intermediate dibutylchlorotin hydroxide, III, m.p. 105–107°, can be considered to be a hydrated form of IV. It is difficult to purify and characterize since it readily loses water to form IV when heated in solvents. Evidence for its existence is threefold: (1) Elementary analysis (see Experimental). (2) Molecular weight determination—calcd. for $C_8H_{19}ClOSn$: 285.4, Found: 250. 3) Karl Fischer titration: 0.500 moles H_2O per mole of III required by Equation (6); 0.508 moles H_2O found.

To demonstrate conclusively that the product of the dichlorotin-amine-alcohol reaction is not a ditin, the 1,1,2,2-tetrabutyl-1,2-dichloroditin (II) was successfully synthesized by the treatment of 1,1,2,2-tetrabutyl-1,2-diacetoxyditin with hydrogen chloride.[8] It has a melting point of 25–27°, a tin analysis of 44.0% (required—44.2%), and consumes 0.994 mole of bromine instantaneously.

TABLE II

REACTION PRODUCTS OF DIBUTYLTIN DICHLORIDE

Product	M.P.	% Sn	% Cl
$(C_4H_9)_2(Cl)Sn{-}Sn(Cl)(C_4H_9)_2$	Theory	44.22	13.2
$(C_4H_9)_2(Cl)Sn{-}O{-}Sn(Cl)(C_4H_9)_2$	Theory	42.95	12.8
$(C_4H_9)_2SnCl_2 + N(C_2H_5)_3 + C_2H_5OH$	110–112 115–116	43.97	13.06
Johnson, Fritz[3,4]		44.15	12.85
$(C_4H_9)_2SnCl_2 - N(C_2H_5)_3 + C_2H_5OH$	111–112	42.6	
This work		43.11	12.85
$(C_4H_9)_2SnCl_2 - (C_4H_9)_2SnO$	112–114	—	—
$(C_4H_9)_2SnCl_2 - H_2O$	112–113	—	—
$(C_4H_9)_2SnH_2 + (C_4H_9)_2SnCl_2 + O_2$	112–114	42.5	—
$(C_4H_9)_2(Cl)Sn{-}Sn(Cl)(C_4H_9)_2$	25–27	44.0	—
Sawyer[5]			
$(C_4H_9)_2Sn(Cl){-}Sn(Cl)(C_4H_9)_2 + O_2$	111–113	—	—
Sawyer[5]			

(6) British Patent 711,564, July 7, 1954; *Chem. Abstr.*, **49**, 14797 (1955).

(7) J. G. A. Luijten and G. J. M. van der Kerk, *Investigations in the Field of Organotin Chemistry*, Tin Research Institute, Fraser Road, Greenford, Middlesex, England, p. 8.

(8) A. K. Sawyer and H. G. Kuivila, soon to be published.

This product is oxidatively unstable, losing about 6% of its reducing capacity in one day in spite of special precautions to keep it away from air. When treated with oxygen, this ditin is converted quantitatively to IV.

CONCLUSION

All the data available on the products of the dibutyltin dichloride reaction are given in Table II. On the basis of these results it is concluded that the products of Johnson and co-workers are actually bis(dialkyl-halotin) oxides (IV), rather than ditin compounds as claimed. Furthermore, these oxides are very stable compounds, readily formed by partial hydrolysis of the disubstituted tin dichlorides. That this stability is representative of the class of compounds will be shown in further papers.

EXPERIMENTAL[9]

Dibutylchlorotin hydroxide (III). Dibutyltin dichloride (150 g.) was dissolved in 300 ml. of methyl alcohol and treated with a large volume of water. A white solid formed and was filtered, powdered with a mortar and pestle, and reslurried with more water. The solid was again filtered and dried under reduced pressure, yielding 132 g. (93%) of a white solid, m.p. 105–107°. The infrared spectrum showed a small band at 3509 cm.$^{-1}$

Anal. Calcd. for $C_8H_{19}ClOSn$: Sn, 41.75; Cl, 12.47. Found: Sn, 40.71; Cl, 12.39.

The molecular weight was determined in chloroform by the isopiestic method of Barger[10] except that the solutions were measured gravimetrically rather than volumetrically.

Anal. Calcd: 285.4; Found: 250. Attempts to recrystallize led to dehydration and yielded only compound IV.

Bis-(dibutylchlorotin) oxide (IV). (a) Using the procedure of Johnson, Fritz, *et al.*[3,4] 0.025 mole of dibutyltin dichloride in 50 ml. anhydrous ether reacted with 0.025 mole of triethylamine and 20 ml. of absolute ethanol. After removal of the amine hydrochloride, 5.27 g. of a white solid, m.p. 111–113°, was obtained. Recrystallization from acetone yielded 3.37 g., m.p. 112–114°.

Anal. Calcd. for $C_{16}H_{36}Cl_2OSn$: Sn, 42.95; Cl, 12.80. Found: Sn, 42.6, 43.11; Cl, 13.06, 12.85.

(b) When Compound III was recrystallized from acetone, a white solid resulted, m.p. 112–113°, which gave no depression in a mixed melting point determination with the product from (a).

(c) Dibutyltin dichloride 9 g. (0.03 mole) and 7.5 g. (0.03 mole) of dibutyltin oxide were melted to a clear solution and allowed to cool. The solid, when recrystallized from acetone, melted 112–114°.

(d) In the course of another investigation, dibutyltin dihydride and dibutyltin dichloride were mixed in equimolar quantities and oxygen bubbled into the mixture. A solid product was obtained which was shown by melting point and mixture melting point to be identical with the product obtained by the procedure of Johnson and Fritz.[4,5] Recrystallization from petroleum ether (b.p. 40–60°) gave a solid m.p. 112–114°.

Anal. Calcd. for $C_{16}H_{36}Cl_2OSn_2$: Sn, 42.95; Found Sn, 42.51, 42.44.

RAHWAY, N. J.
DURHAM, N. H.

(9) Melting (or decomposition) points are uncorrected. Tin analyses were done in duplicate by the method of Farnsworth and Pekola. This method has been extremely reliable for many hundreds of analyses (M. Farnsworth and J. Pekola, *Anal. Chem.*, **31**, 410–414 (1959).

(10) A. Steyermark, *Quantitative Organic Microanalysis*, Blakiston Co., Philadelphia, p. 292 *ff.* (1951).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Influence of the Metallic Cation of Certain Organometallic Compounds on the Courses of Some Organic Reactions[1,2]

WILLIAM IVO O'SULLIVAN,[3] FREDERIC W. SWAMER, WILBERT J. HUMPHLETT AND CHARLES R. HAUSER

Received August 22, 1960

The ratios of ionization of the α-hydrogen *versus* addition to the carbonyl group of acetophenone by phenylpotassium phenylsodium, and phenyllithium were approximately 10:1, 1.5–2:1 and 1:23, respectively. Similar results were obtained in certain related reactions. They are interpreted on the basis of the influence of the metallic cation. The 1,2- *versus* 1,4-addition of the reagents to benzalacetophenone was studied.

The courses of certain organic reactions with strongly basic or nucleophilic anions are known to be influenced considerably by the metallic cation associated with the anion. Two examples are the substitution *versus* elimination reactions of alkyl halides with alkali diethylamides or phenylalkalies[4] and the condensation of alkali esters with the carbonyl group of ketones *versus* the ionization of their α-hydrogen.[5] In both examples the lithium reagent favors the nucleophilic reaction at the carbon, and the sodium reagent the basic attack at the hydrogen.

(1) Supported by the Office of Ordnance Research, U. S. Army, and by the Office of Naval Research.

(2) A portion of this work was reported at the Philadelphia meeting of the American Chemical Society, April 1950.

(3) On leave from the University College, Dublin, Ireland.

(4) W. H. Puterbaugh and C. R. Hauser, *J. Org. Chem.*, **24**, 416 (1959).

(5) C. R. Hauser and W. H. Puterbaugh, *J. Am. Chem. Soc.*, **75**, 4756 (1953); C. R. Hauser and W. R. Dunnavant, *J. Org. Chem.*, **25**, 1296 (1960).

TABLE I

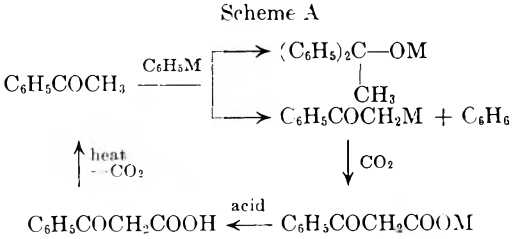
REACTIONS OF α-HYDROGEN COMPOUNDS WITH ORGANOMETALLIC REAGENTS FOLLOWED BY CARBONATION

Exp. No.	α-Hydrogen Compound	Organometallic Reagent	Solvent	Temp.	Time, Hr.	Regenerated α-H Compd. Yield, %[a]	Addition Product, Yield, %	Ratio of Ioniz. of α-H to Addition
1	Acetophenone	C_6H_5K	Isooctane	50	3	54	5	11:1
2	Acetophenone	C_6H_5K[b]	Hexane-octane	50	3	60	6	10:1
3	Acetophenone	C_6H_5Na[c]	Heptane	50	3	48	34	1.4:1
4	Acetophenone	C_6H_5Na[d]	Hexane-octane	50	3	36	24	1.5:1
5	Acetophenone	C_6H_5Na[d,e]	Hexane-octane	50	3	43	24	1.8:1
6	Acetophenone	C_6H_5Li	Ether	35	0.75	4	91	1:23
7	Acetophenone	C_6H_5MgBr	Ether	35	0.75	—[f]	90	Low
8	Acetophenone	$C_5H_{11}K$	Hexane-isooctane	50	3	48	—	High
9	Acetophenone	$C_5H_{11}Na$	Hexane-octane	50	3	38	12	3.2:1
10	Ethyl phenylacetate	C_6H_5Na[c]	Heptane	25–30	3	65	4	16:1
11	Ethyl phenylacetate	C_6H_5Li	Ether	25–35	3	6	70	1:12
12	Phenylacetonitrile	C_6H_5Na[c]	Benzene	40	1.5	90	5	18:1
13	Phenylacetonitrile	C_6H_5Li	Ether	35	8	45	9	5:1
14	Phenylacetonitrile	C_6H_5MgBr	Ether	35	5	15	33	1:2
15	Acetomesitylene	C_6H_5Na[c]	Heptane	50	3	80	—	High
16	Acetomesitylene	C_6H_5Li	Ether	35	2	all	—	High
17	Mesitylacetonitrile	C_6H_5Na[c]	Benzene	40	1.5	71	5	14:1
18	Mesitylacetonitrile	C_6H_5Li	Ether	35	4	—[g]	80	Low
19	Mesitylacetonitrile	C_6H_5MgBr	Ether	35	6	—	78	Low
20	Phenylacetonitrile	C_4H_9Li	Ether	35	2	28	—	High
21	Phenylacetonitrile	C_4H_9Li	Benzene	40	3	13	49	1:3.8
22	Mesitylacetonitrile	C_4H_9Li	Ether	35	6	35	21	1.7:1
23	Mesitylacetonitrile	C_4H_9Li	Benzene	40	4	14	51	1:3.6

[a] The regenerated α-hydrogen compounds generally boiled within a range of 2–5°. [b] The phenylpotassium–potassium methoxide reagent also contained a molecular equivalent of potassium chloride. [c] Reagent prepared by the earlier procedure. [d] Reagent prepared by newer procedure. [e] The phenylsodium–sodium chloride reagent also contained sodium methoxide. [f] No regenerated acetophenone was isolated but some of the magnesium bromide enolate of the ketone might have been formed and then condensed with unchanged ketone to give the aldol product. [g] The reaction product was not carbonated and thus regenerated mesitylacetonitrile was not expected.

We have found that, whereas phenyllithium and phenylmagnesium bromide add to the carbonyl group of acetophenone, phenylsodium, and especially phenylpotassium, react mainly with the α-hydrogen of this ketone effecting its ionization to form the alkali enolate. These two possible courses of reaction are shown in Scheme A, in which M represents potassium, sodium, lithium, or magnesium bromide.

Scheme A



As indicated in Scheme A, the relative extents of the two courses of reaction were determined by carbonation to convert the alkali enolate to the β-keto acid salt, which was separated from the carbinol. The free β-keto acid was liberated from the salt and decarboxylated to regenerate acetophenone, the yield of which represented the extent of ionization of the α-hydrogen. This yield as well as that of the carbinol from the addition reaction is given in Table I along with those from related reactions. Since 10–15% of the acetophenone was generally recovered in the reactions with the potassium and sodium reagents, the conversion yields would be correspondingly greater. The extent of the α-hydrogen reaction may be slightly higher than that indicated since the method did not take into account the possible aldol condensation.

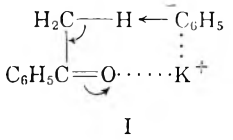
Since phenylpotassium was obtained from anisole and phenylsodium from chlorobenzene, their preparations produced as by-products potassium methoxide and sodium chloride, respectively. Attempts to prepare the former reagent from chlorobenzene and the latter reagent from anisole[6] under similar conditions were unsatisfactory. In experiments 2 and 5 of Table I, the phenylpotassium–potassium methoxide reagent contained an equivalent of potassium chloride, and the phenylsodium–sodium chloride reagent an equivalent of sodium methoxide (see Experimental). The presence of the potassium chloride in the former reagent had no appreciable effect on the two courses of reaction (compare Exps. 1 and 2) but that of the sodium methoxide favored slightly the α-hydrogen reaction (compare Exps. 3, 4, and 5).

The last column of Table I shows that the ratio of ionization of the α-hydrogen of acetophenone to reaction at the carbonyl group was approximately 10:1 with phenylpotassium, 1.5–2:1 with phenyl-

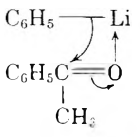
(6) See A. A. Morton and A. E. Brachman, *J. Am. Chem. Soc.*, **76**, 2975 (1954).

sodium and 1:23 with phenyllithium. Since the reactions with the potassium and sodium reagents were carried out under essentially the same conditions (Exps. 2 and 5), the considerable difference in the ratio of the two courses of reaction may be ascribed to the influence of the metallic cation. The great difference in the ratio of the two courses of reaction with the sodium and lithium reagents may be due not only to the influence of the metallic cation but also to the difference in solvents, which were an alkane and ether, respectively. An indication that the metallic cation is the more important factor is the observation that, in the related reactions of phenyl- and mesitylacetonitriles with butyllithium, the ratio of ionization of the α-hydrogen to addition was greater in ether than in benzene (Exps. 20–23). Consequently an even lower ratio in the two courses of reaction of acetophenone with phenyllithium might be expected if the solvent were a hydrocarbon instead of ether.

These results may be rationalized on the basis of the degree of ionization of the phenylalkalies, which should decrease as the metallic cation is varied in the order: K > Na > Li. Thus, phenylpotassium is effectively the strongest base attacking mainly the α-hydrogen, and phenyllithium the strongest nucleophilic reagent attacking largely the carbonyl carbon(indicated in I and II, respectively).

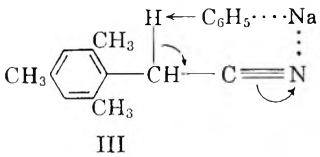


I

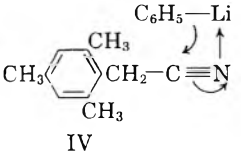


II

Similar results were obtained in several related reactions (see Table I). Interestingly, phenyllithium effected mainly ionization of the α-hydrogen of phenylacetonitrile but the addition reaction with mesitylacetonitrile lead to the formation of the corresponding ketone (Exps. 13 and 18). Phenylsodium, however, effected largely ionization of the α-hydrogen of both of these nitriles (Exps. 12 and 17). The predominant course of reaction of mesitylacetonitrile with the sodium and lithium reagents is indicated in III and IV, respectively.



III

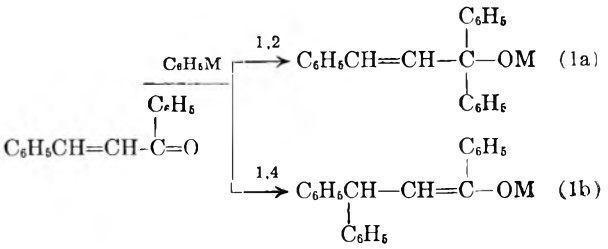


IV

As might be expected phenylsodium underwent the addition reaction with benzaldehyde to form benzhydrol. This reagent has previously been shown to add to benzophenone to give triphenylcarbinol.[7]

(7) S. F. Acree, *Am. Chem. J.*, 29, 588 (1903).

1,2-Versus 1,4-addition. Earlier workers have shown that benzalacetophenone undergoes mainly 1,2-addition with phenylpotassium, phenylsodium[8] and phenyllithium[8,9] in ether but largely 1,4-addition with phenylmagnesium bromide.[10] These two courses of reaction may be represented by equation 1a and 1b, respectively.



We have confirmed the predominant 1,2-addition with the three former reagents. Whereas the previous reaction with phenylpotassium and phenylsodium were carried out in ether,[8] we have employed appropriate hydrocarbon solvents. The reaction mixtures were carbonated to convert the metal enolate of the 1,4-addition product to the salt of the carboxylic acid which was separated from the carbinol. The results, including the earlier ones, are summarized in Table II.

TABLE II

1,2- VERSUS 1,4-ADDITION OF BENZALACETOPHENONE WITH PHENYLALKALIES AND PHENYLMAGNESIUM BROMIDE

Metallic Cation	1,2-Addition Yield, %	1,4-Addition Yield, %
K	67 (52)[a]	—
Na	60 (39)[a]	14 (3.5)[a]
Li	75 (69)[a]	14 (13)[a]
MgBr	—	94[b]

[a] Ref. (8). [b] Ref. (10).

EXPERIMENTAL[11]

Potassium and sodium reagents. Phenylpotassium was prepared from potassium and anisole[12] in an appropriate alkane employing a creased flask and high speed stirrer. Carbonation of the suspension gave benzoic acid in 55–60% yield.

Phenylsodium was prepared in an alkane or in benzene from chlorobenzene and commercially dispersed sodium[13] (earlier procedure) or dispersed sodium prepared in this laboratory with a high speed stirrer (newer procedure.)[14]

(8) H. Gilman and R. H. Kirby, *J. Am. Chem. Soc.*, **63**, 2046 (1941).

(9) A. Luttringhaus, Jr., *Ber.*, **67**, 1602 (1934).

(10) E. P. Kohler, *Am. Chem. J.*, **38**, 511 (1907).

(11) Boiling points and melting points are uncorrected.

(12) A. A. Morton and E. J. Lanpher, *J. Org. Chem.*, **23**, 1638 (1958).

(13) We are indebted to Dr. V. L. Hansley of Electrochemical Dept., E. I. du Pont de Nemours and Co., Niagara Falls, N. Y., and later of U. S. Industrial Chemical Co., Division of National Distillers, Cincinnati 37, Ohio, for generous samples.

(14) See U. S. Industrial Chemical Co., Division of National Distillers Production Corp., New York, N. Y., *Sodium Dispersions*, 1957, p. 36.

Carbonation of the suspension gave practically quantitative yields of benzoic acid.

n-Amylpotassium and *n*-amylsodium were prepared from *n*-amyl chloride and the alkali metal in an alkane.[15] An 80% yield of the reagent was assumed.[16]

Lithium and Grignard reagents. These reagents were prepared in ether in the usual mnner and transferred to the reaction flask under nitrogen pressure. Butyllithium was also prepared in benzene.[16]

Reactions of α-hydrogen compounds with reagents. (Table I.) (A) *With phenylpotassium.* In Exp. 1 of Table I, the phenylpotassium–potassium methoxide reagent prepared as described above was treated directly with acetophenone but, in Exp. 2, dry potassium chloride (11.17 g., 0.15 mole) was added with stirring to a 0.15 mole preparation of the reagent before adding 0.15 mole of the ketone. Experiment 1 is described below.

To the stirred reagent (0.2 mole preparation) was added a solution of 24.03 g. (0.2 mole) of acetophenone in 50 ml. of iso-octane during 20 min., maintaining the temperature at about 50°. After stirring for 3 hr. at this temperature, the reaction mixture was cooled and poured onto excess Dry Ice. When the excess Dry Ice had evaporated some isobutyl alcohol was added (to destroy potassium) followed by 200 ml. of water. After shaking, the two layers were separated. The aqueous layer was extracted three times with ether and the extracts were added to the organic layer. The two solutions were worked up as described below.

The aqueous solution was acidified and heated on the steam bath for 1 hr., cooled, and extracted three times with ether. The combined ether extracts were washed with a saturated solution of sodium bicarbonate, then with water, dried over anhydrous magnesium sulfate, and the solvent removed. The residual oil was distilled to give 13.0 g. (54%) of acetophenone, b.p. 90–92° at 19 mm.; 2,4-dinitrophenylhydrazone m.p. 248–249°.

The organic solution was washed with water, dried over anhydrous magnesium sulfate, and the solvent removed. The residual oil was distilled to give 3.05 g. (13%) of acetophenone, b.p. 91–94° at 19 mm. The residue was cooled and shaken with *n*-hexane. The mixture was filtered. The solid (0.85 g., 2.2%) was crude diphenylmethylcarbinol, m.p. 75–77° after recrystallization from benzene. It did not depress melting point of an authentic sample of the carbinol. The *n*-hexane filtrate was evaporated, and the residual oil was distilled to give 1.0 g. (2.8%) of 1,1-diphenylethylene, b.p. 142–147° at 19 mm., lit.[17] b.p. 147° at 16 mm. This olefin, which resulted from dehydration of the carbinol, readily decolorized bromine in carbon tetrachloride; total yield of carbinol is estimated to be 5%. A sample of the olefin, prepared by dehydration of the carbinol with concentrated sulfuric acid, boiled at 155–158° at 25 mm., lit.[18] b.p. 156° at 25 mm.

(B) *With phenylsodium.* In Exps. 3 and 4 of Table I, the phenylsodium–sodium chloride reagent prepared as described above was treated directly with acetophenone. In Exp. 5, methanol (6.4 g., 0.2 mole) was slowly added with cooling to a 0.4 mole preparation of phenylsodium to give 0.2 mole each of phenylsodium and sodium methoxide. Acetophenone (0.2 mole) in 50 ml. of *n*-hexane was then added. After stirring at about 50° for 3 hr., the reaction mixture was worked up as described for phenylpotassium.

The aqueous solution was acidified and heated on the steam bath to give 10.2 g. (43%) of acetophenone, b.p. 93° at 21 mm.; 2.4-dinitrophenylhydrazone, m.p. 249–250°.

The organic solution yielded 5.15 g. of diphenylmethylcarbinol, m.p. 78–81° (no depression on admixture with authentic sample), 1.6 g. of less pure carbinol, m.p. 66–73°, and 0.75 g. of 1,1-diphenylethylene, b.p. 115–120° at 11 mm., n_D^{25} 1.60C, lit.[17] n_D^{14} 1.610. The total yield of carbinol is estimated to be 24%. Acetophenone (9%) was obtained as a forerun.

The reactions of other α-hydrogen compounds with phenylsodium (Exps. 10, 12, 15, and 17, Table I) were carried out similarly. The product obtained from the organic solution in Exp. 10 was distilled to give 1.2 g. of recovered ethyl phenylacetate and 6.1 g. of higher boiling material which, after a week in the refrigerator, deposited 1.7 g. of phenyl benzyl ketone, m.p. 56–60° after recrystallization from ligroin (b.p. 90–120°), lit.[19] m.p. 60°, oxime m.p. 97–98°, lit.[19] m.p. 98°.

The product obtained from the organic solution in Exp. 12 was added to dilute hydrochloric acid and heated on a steam bath for 1–2 hr. (to hydrolyze the ketimine hydrochloride). There was obtained phenyl benzyl ketone m.p. 55°[19]; semicarbazone (recrystallized from methanol), m.p. 146–147°, lit.[19] m.p. 148°.

The product obtained from the organic solution in Experiment 17 yielded 2,4,6-trimethylbenzyl phenyl ketone (5%), m.p. 162° (see below).

(C) *With amylpotassium and amylsodium.* The reaction of these reagents with acetophenone (Exps. 8 and 9) was carried out as described for phenylpotassium.

The product obtained from the organic layer in Experiment 9 was distilled to give recovered acetophenone (14%). b.p. 92–95° at 20 mm. (2,4-dinitrophenylhydrazone m.p. 251–253°) and 2-phenylheptane-2-ol (12%), b.p. 81–82° at 0.4 mm., $n_D^{25.5}$ 1.5065, lit.[20] b.p. 169° at 50 mm. and 108° at 0.6 mm., n_D^{25} 1.5028. The infrared spectrum of this product was identical with that of the carbinol (b.p. 80° at 0.3 mm., n_D^{24} 1.5042) prepared from *n*-amylmagnesium bromide and acetophenone in ether.

(D) *With phenyllithium and phenylmagnesium bromide.* Experiment 17 is described below. To a stirred solution of approximately 0.4 mole of phenyllithium in 500 ml. of ether was added 35.8 g. (0.2 mole) of ethyl phenylacetate in 100 ml. of ether. The mixture was refluxed 2 hr., cooled, and poured onto excess Dry Ice. There was obtained 2.15 g. (6%) of regenerated ethyl phenylacetate, b.p. 178–190° at 20 mm. (identified by infrared spectrum), and 36.8 g. (70%) of 1,1,2-triphenylethanol, m.p. 81–88° and at 87–88° after recrystallization from *n*-hexane. A mixed melting point with an authentic sample showed no depression. Also 9.2 g. of residual gum was obtained.

Experiments 6, 7, 13, 14, 16, 18, and 19 were carried out similarly. In Exps. 6, 7, and 16, slightly more than a 1:1 mole ratio of reagent to active hydrogen compounds was used. In Exps. 13, 14, and 18, a 10–50% excess of the reagent was employed The products from Exps. 6, 7, and 16 were worked up as described in Exp. 1, and those from Exps. 13, 14, 18, and 19 as described in Exp. 12. In exps. 18 and 19, there was obtained 2,4,6-trimethylbenzylphenyl ketone, m.p. 162°.

Anal. Calcd. for $C_{17}H_{18}O$:C, 85.67; H, 7.61. Found: C, 86.06; H, 7.90.

(E) *With n-butyllithium.* These reactions (Exps. 20–23) were carried out essentially as described for Exp. 11, and the products were worked up as described for Exp. 12. In Exp. 20, no ketone was isolated under the conditions used and a considerable amount of the starting nitrile was recovered. In Exp. 21, *n*-butyl benzyl ketone (49%) was obtained, b.p.

(15) A. A. Morton, F. D. Marsh, R. D. Coomles, A. L. Jones, S. E. Penner, H. E. Ramsden, V. B. Baker, E. L. Little, and R. L. Letsinger, *J. Am. Chem. Soc.*, 72, 3785 (1950).

(16) H. Gilman, E. A. Zoellner, and W. M. Selby, *J. Am. Chem. Soc.*, 54, 1957 (1932).

(17) I. Heilbron, *Dictionary of Organic Compounds*, Vol. II, Oxford University Press, New York, 1953, p. 415.

(18) A. Klages, *Ber.*, 35, 2647 (1902).

(19) See Ref. 17, p. 12.

(20) W. C. Davies, R. S. Dixon, and W. J. Jones, *J. Chem. Soc.*, 471 (1930); M. Protiva, O. Exner, M. Borovick, and J. Pliml, *Chem. Listy*, 46, 37 (1952).

128–138° at 13 mm., lit.[21] 130–131° at 12 mm. This experiment was repeated at room temperature for 118 hr. to give 17% of *n*-butyl benzylketone, 5% of regenerated nitrile, and some high boiling residue. In Exp. 23, 2,4,6-trimethylbenzyl *n*-butyl ketone was obtained, b.p. 142–147° at 7 mm.; 2,4-dinitrophenylhydrazone (yellow needles), m.p. 99° (recrystallized from ethanol).

Anal. Calcd. for $C_{12}H_{26}O_4N_4 \cdot C_2H_5OH$: N, 14.17. Found: N, 14.03.

Addition of reagents to benzalacetophenone. (Table II). These reactions were carried out as described in Exp. 1 by addition of benzalacetophenone in an appropriate solvent to the stirred reagent; the reaction mixtures were carbonated and worked up essentially as described for the α-hydrogen compounds.

In the experiment with phenylpotassium, no 1,4-addition product was isolated. A 67% yield of crude diphenylstyryl carbinol was obtained. After recrystallization from ligroin, the product melted at 109–111° (lit.[9] m.p. 108–111°). Some unidentified residue was obtained.

In the experiment with phenylsodium, β,β-diphenylpropiophenone, m.p. 94–95° (lit.[10] m.p. 96°) was obtained on acidifying the aqueous solution and decarboxylating the product. Diphenylstyrylcarbinol was isolated from the organic solution.

Reaction of phenylsodium with benzaldehyde. This reaction was carried out with 0.3 mole of phenylsodium and 0.21 mole of benzaldehyde in heptane (2 hr. at room temperature, 1 hr. at 50°). There was obtained 28 g. (72%) of benzhydrol, b.p. 175–180° at 17 mm. The product solidified; after recrystallization from ligroin (b.p. 90–120°), it melted at 66–67°. A mixed melting point with an authentic sample showed no depression.

(21) D. Ivanov, *Bull. Soc. Chem.*, [5], 4, 682 (1937).

DURHAM, N. C.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

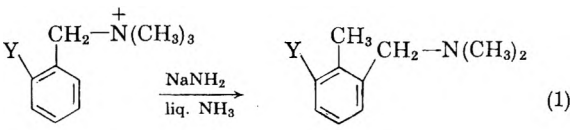
Ortho Substitution Rearrangement of Certain 3-Substituted and 3,5-Disubstituted Benzyltrimethylammonium Ions by Sodium Amide[1]

WILLIAM Q. BEARD, JR., DONALD N. VAN EENAM, AND CHARLES R. HAUSER

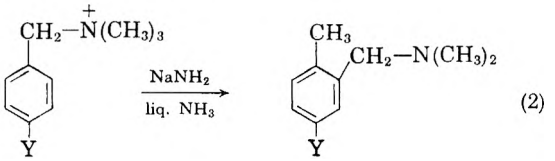
Received August 5, 1960

The 3-methoxy-, 3-methyl-, and 3-chloro-benzyltrimethylammonium ions underwent the ortho substitution rearrangement with sodium amide in liquid ammonia to form mixtures of the two possible types of isomeric amines in yields of 92, 90, and 16%, respectively. With the first two quaternary ions, rearrangement into the *ortho* position versus the *para* position occurred in the ratio of 2:1 and 1.2:1, respectively. The 3-bromo and 3-trifluoromethyl quaternary ions failed to yield isolable amounts of rearrangement products. The 3,5-dimethoxy- and 3,5-dimethyl-benzyltrimethylammonium ions underwent the rearrangement in 93% yield.

Previous papers[2–4] have described the *ortho* substitution rearrangements of several 2- and 4-substituted benzyltrimethylammonium ions (Equations 1 and 2, respectively) in which the substituents Y were such groups as alkyl, methoxy and chlorine.

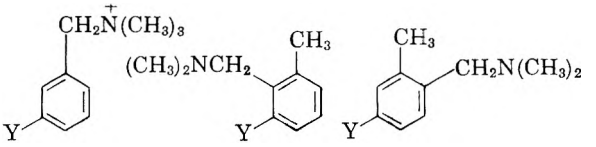


(1)



(2)

The present paper describes a similar study of certain 3-substituted and 3,5-disubstituted benzyltrimethylammonium ions with sodium amide in liquid ammonia. Whereas the rearrangement of a 2- or a 4- substituted benzyltrimethylammonium ion can form but a single amine (Equation 1 or 2), that of a 3-substituted quaternary ion of Type I (such as Ia) may afford a mixture of isomeric rearranged amines of Types II and III (such as IIa and IIIa). These isomers would arise through rearrangements into the *ortho-* and *para-* positions, respectively, relative to the 3-substituent.



Ia. Y = OCH_3 IIa. Y = OCH_3 IIIa. Y = OCH_3
Ib. Y = CH_3 IIb. Y = CH_3 IIIb. Y = CH_3
Ic. Y = Cl IIc. Y = Cl IIIc. Y = Cl
Id. Y = Br
Ie. Y = CF_3

Actually each of the three quaternary ions Ia–c produced a mixture of the possible isomeric amines of Types II and III. In Table I are summarized the yields of the amine mixtures and the relative proportions of the two isomers.

(1) Supported by the National Science Foundation.

(2) S. W. Kantor and C. R. Hauser, *J. Am. Chem. Soc.*, **73**, 4122 (1951).

(3) C. R. Hauser and A. J. Weinheimer, *J. Am. Chem. Soc.*, **76**, 1264 (1954).

(4) W. Q. Beard, Jr., and C. R. Hauser, *J. Org. Chem.*, **25**, 334 (1960).

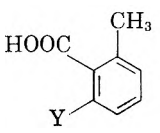
TABLE I

REARRANGEMENT OF 3-SUBSTITUTED BENZYLTRIMETHYLAMMONIUM IONS BY SODIUM AMIDE IN LIQUID AMMONIA

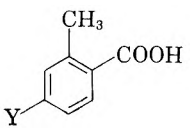
Quat. Ion	3-Substituent, Y	Amine Mixture, Yield %	Proportions of Isomers[a] Type II %	Type III %
Ia	OCH_3	92[b]	67 (IIa)	33 (IIIa)
Ib	CH_3	90	54 (IIb)	46 (IIIb)
Ic	Cl	16[c]	—	—

[a] These proportions of isomers were estimated from comparisons of infrared data (see Experimental). [b] An 86% yield was obtained on stopping the reaction after five minutes. [c] A 5% yield was obtained on stopping the reaction after five minutes.

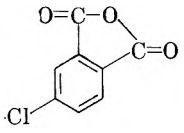
It can be seen from this table that the quaternary ions Ia–c produced mixtures of the corresponding isomeric amines IIa–c and IIIa–c in yields of 92, 90, and 16%, respectively. These isomers were not separated; they were oxidized with permanganate to form the known acids IVa–c and Va–c, respectively. These acids were readily separated, since those of type IV were considerably more soluble in water than those of type V. Acid Vc was further oxidized and dehydrated to give anhydride VI.



IVa. Y = OCH_3
IVb. Y = CH_3
IVc. Y = Cl



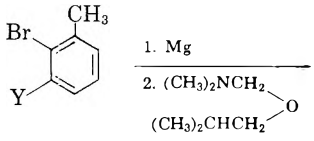
Va. Y = OCH_3
Vb. Y = CH_3
Vc. Y = Cl



The amine mixture from quaternary ion Ia was also converted to a mixture of the corresponding picrates, which were separated and identified as the picrates of amines IIa and IIIa.

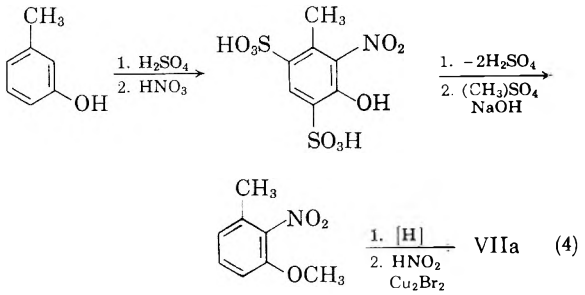
The infrared spectra of each of the three amine mixtures from quaternary ions Ia–c showed bands characteristic of the two isomeric amines of types II and III. Thus, the three adjacent aromatic hydrogens of amines of type II were indicated in each case by a strong band in the region 810–770 cm.$^{-1}$, and the two adjacent aromatic hydrogens and one isolated aromatic hydrogen of amines of type III were indicated in each case by a strong band in 860–800 cm.$^{-1}$ region and a weak band in the 900–860 cm.$^{-1}$ region, respectively.[5] Moreover, the spectra of the amine mixtures from quaternary ions Ia and Ib showed all of the bands (and no others) exhibited by samples of pure amines which were independently synthesized as described below. By adjusting the relative proportions of pairs of isomers it was found that mixtures of pure amines IIa and IIIa in the ratio of about 2:1 and of pure amines IIb and IIIb in the ratio of about 1.2:1 gave infrared spectra that were practically identical with the mixtures obtained from the rearrangements of Ia and Ib, respectively. The relative proportions of the two amine mixtures given in Table I were determined in this manner (see Experimental).

Rearranged amines IIa and IIb were independently synthesized by the condensations of dimethylaminomethyl isobutyl ether with the Grignard reagents of compounds VIIa and VIIb, respectively (Equation 3).

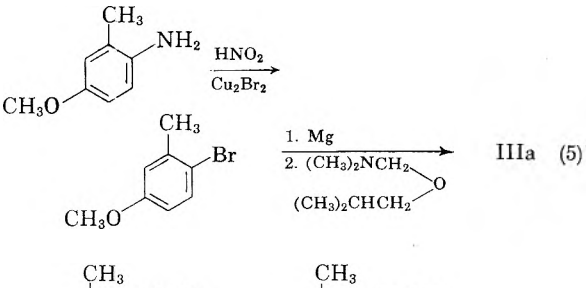


VIIa. Y = OCH_3
VIIb. Y = CH_3

Compound VIIa was prepared from *m*-cresol by a modification of the method of Gibson,[6] and compound VIIb from commercially available 2,6-dimethylaniline. Although the former method involved several steps (Equation 4), the structures in all steps had been established by earlier workers.



Rearranged amines IIIa and IIIb were independently synthesized from commercially available compounds as represented by equations 5 and 6, respectively.



The fact that the yield of rearrangement product from the chloro quaternary ion Ic was much lower than those from the methoxy and methyl quaternary ions Ia and Ib under similar conditions (see Table I) may have been due partly to the occurrence of a

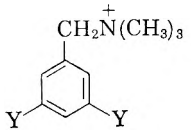
(5) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, 2nd ed., John Wiley & Sons, Inc., New York, N. Y., 1958, p. 78–79.

(6) G. P. Gibson, *J. Chem. Soc.*, 123, 1269 (1923).

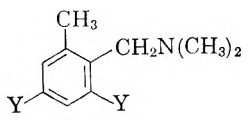
side-reaction involving the formation of a benzyne[7] (see Experimental). However, since some of the starting quaternary salt was recovered, the ion Ic evidently underwent the rearrangement more slowly than ions Ia and Ib.

Unsuccessful attempts were made to obtain the rearrangement products from the 3-bromo- and 3-trifluoromethyl quaternary ions, Id and Ie, respectively. The former ion evidently underwent mainly the benzyne reaction,[7] while the latter ion produced much tarry material although some of the starting quaternary salt Ie was recovered.

Next, consideration will be given to the 3,5-disubstituted benzyltrimethylammonium ions VIIIa and VIIIb, which, in contrast to the 3-substituted quaternary ions presented above, may undergo the ortho substitution rearrangement without forming isomeric mixtures. These quaternary ions both rearranged in 93% yield to form amines IXa and IXb, respectively.

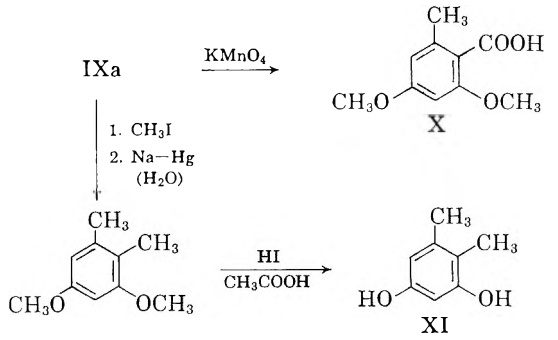


VIIIa. Y = OCH_3
VIIIb. Y = CH_3

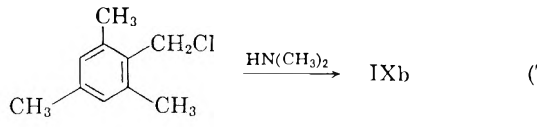


IXa. Y = OCH_3
IXb. Y = CH_3

The structure of the product from the rearrangement of VIIIa was established as IXa by oxidation to the known benzoic acid derivative X and by the Emde reduction of the methiodide of IXa followed by cleavage of the two methyl ether groups to form the known dihydroxy compound XI (Scheme A).



The structure of the product from the rearrangement of VIIIb was established as IXb by an independent synthesis from α^2-chloroisodurene (Equation 7).



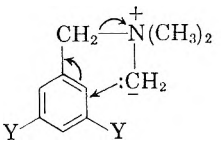
(7)

(7) See J. D. Roberts, H. Simmons, Jr., L. Carlsmith, and C. Vaughan, *J. Am. Chem. Soc.*, 75, 3290 (1953).

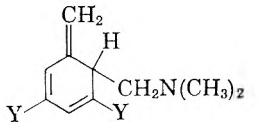
DISCUSSION

The predominant rearrangement of Ia and Ib into the 2-position relative to the 3-methoxy or 3-methyl substituent rather than into the 4-position is of interest. Apparently steric factors are not important, a conclusion supported by a consideration of molecular models.

The mechanism of the rearrangement has been considered[2] to involve the SNi′ type of displacement indicated in XII to form *exo*-methyleneamine (XIII), which undergoes a prototropic change to regenerate the aromatic ring. Actually the rearrangement of the



XII (Y = hydrogen of a substituent)



XIII

2,4,6-trimethylbenzyltrimethylammonium ion produces an isolable *exo*-methyleneamine that cannot undergo such a prototropic change.[8]

This mechanism suggests that the rearrangement would be retarded appreciably when Y in XII is methoxy or methyl, since such a group should increase the electron density at the position where the methyl carbanion attacks the ring. However, the rearrangement appears to be retarded just slightly. Thus the yields of rearranged amines from the unsubstituted benzyltrimethylammonium ion and the 3-methoxy substituted quaternary ion Ia were 90% and 86% within one minute and five minutes, respectively. Moreover, when an equimolar mixture of the unsubstituted and the 3,5-dimethylsubstituted salts was added to excess of the reagent and the reaction stopped in thirty seconds, the yield of rearranged amine from the former was 59% and that from the latter 49%. Even this slight retardation may not be real, since the quaternary salts were not entirely in solution.

Mechanism XII might also suggest that the rearrangement would be facilitated by a 3-chloro substituent as in Ic, but this is apparently not the case (see above).

These results may be reconciled with mechanism XII if it is assumed that substituents which increase the electron density at the point of attack also lower the energy of the transition state leading to the *exo*-methyleneamine XIII.

EXPERIMENTAL[9]

3-Methoxybenzyltrimethylammonium bromide (Ia). 3-Methoxybenzoic acid (110 g., 0.725 mole) was reduced with 38 g.

(8) C. R. Hauser and D. N. Van Eenam, *J. Am. Chem. Soc.*, 76, 1264 (1954).

(0.95 mole) of 95% pure lithium aluminum hydride[10] to give 89.7 g. (90%) of 3-methoxybenzyl alcohol, b.p. 129–131: at 9 mm., lit.[11] b.p. 129° at 9 mm.

This alcohol (89.3 g., 0.647 mole) was treated with 95 g. (0.35 mole) of phosphorus tribromide in 1500 ml. of absolute ether overnight. The mixture was hydrolyzed with ice water, and the layers separated. The ether layer was washed with sodium bicarbonate solution, dried, and distilled to give 116.8 g. (90%) of 3-methoxybenzyl bromide, b.p. 123–124° at 13 mm., lit.[11] b.p. 123.5° at 13 mm.

A solution of 116.8 g. (0.58 mole) of this bromide in 500 ml. of acetonitrile was cooled in an ice bath and treated with 51 g. (0.87 mole) of liquid trimethylamine. After stirring for several hours, 1500 ml. of dry ether was added to precipitate 147 g. (98%) of 3-methoxybenzyltrimethylammonium bromide (Ia), m.p. 171–171.5°. One recrystallization from acetonitrile raised the melting point to 172.5–173°.

Anal. Calcd. for $C_{11}H_{18}BrNO$: C, 50.75; H, 6.97; N, 5.38. Found: C, 50.65; H, 7.02; N, 5.35.

Rearrangement of bromide Ia. To a stirred suspension of 0.22 mole of sodium amide[12] in 600 ml. of liquid ammonia was added over a period of 10 min. 52.0 g. (0.2 mole) of 3-methoxybenzyltrimethylammonium bromide (Ia). The initial green color changed rapidly to brownish-red. After 30 min., 11.8 g. (0.22 mole) of ammonium chloride was added, and the ammonia was replaced by ether. Inorganic salts were removed by filtration, and the ether was evaporated. The residue was distilled to give 33.08 g. (92%) of a mixture of amines IIa and IIIa, b.p. 108.5–116° at 10.5 mm., n_D^{25} 1.5135.

Anal. Calcd. for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 74.01; H, 9.42; N, 8.08.

Treatment of a sample of the amine mixture with excess picric acid in 95% ethanol solution gave a picrate mixture which was recrystallized slowly from 95% ethanol. The resulting two types of crystals were separated mechanically and recrystallized to give the picrates of amines IIa and IIIa, m.p. 139–140° and 114–115°, respectively. Admixture with independently synthesized samples of these picrates (see below) did not depress the melting points.

Oxidation of a 2.0-g. sample of the amine mixture was effected by stirring with 3.0 g. of potassium permanganate and 2.0 g. of sodium hydroxide in 100 ml. of water at room temperature. When the purple color had disappeared, three 1.0-g. portions of permanganate were added, each after the color of the preceding portion had faded. After removing the precipitated manganese dioxide by filtration through a Super-cell mat, the colorless alkaline solution was acidified with concentrated hydrochloric acid to liberate 6-methoxy-2-methylbenzoic and 4-methoxy-2-methylbenzoic acids, IVa and Va, respectively. The latter acid, which precipitated, was collected on a funnel and recrystallized from ethanol-water; yield, 0.42 g. (23%), m.p. 175–175.5°, lit.[13] m.p. 176°. The m.p. was not depressed on admixture with acid Va obtained from the oxidation of independently synthesized amine IIIa (see below).

Acid IVa, which remained in solution, was isolated by saturating the hydrochloric acid filtrate with sodium sulfate and extracting with ether. The extract was dried, filtered, and evaporated. The residue was recrystallized from hexane-ethanol to give 0.49 g. (26%) of 6-methoxy-2-methylbenzoic acid (IVa), m.p. 137–138°, lit.[14] m.p. 139°. The melting point was not depressed on admixture with acid IVa obtained from the oxidation of independently synthesized amine IIa (see below).

Estimation of the composition of the rearrangement product of Ia. The infrared spectrum of a 5% solution of the rearrangement product of Ia in cyclohexane was compared with the spectra of two cyclohexane solutions containing a total of 5% of independently synthesized amines IIa and IIIa. One of these solutions contained a mixture of IIa and IIIa in a ratio of 7:3 and the other contained a mixture of IIa and IIIa in a ratio of 6:4. The relative intensities of the moderate bands at 710 $cm.^{-1}$ (IIIa) and 700 $cm.^{-1}$ (IIa) led to a composition estimate for the rearrangement product of 67% 6-methoxy-2-methylbenzyldimethylamine (IIa) and 33% 4-methoxy-2-methylbenzyldimethylamine (IIIa).

Independent synthesis of amine IIa. *2-Nitro-m-cresol*, b.p. 106–108° at 9.5 mm., was prepared in 42% yield from 69 ml. of *m*-cresol, 304 ml. of 20% fuming sulfuric acid, and 28 ml. of fuming nitric acid (sp. gr. 1.5) according to the modification of Hodgson and Beard[15] of the method of Gibson.[6]

2-Nitros-3-methylanisole, m.p. 48–49°, lit.[14] m.p 49°, was obtained in 93% yield by the treatment of 37.5 g. of 2-nitro-*m*-cresol with a sevenfold excess of dimethyl sulfate and sodium hydroxide.

2-Amino-3-methylanisole, b.p. 114.5–116.5° at 15 mm., lit.,[6] b.p. 124–126° at 15 mm., was obtained in 75% yield by the reduction of 37.9 g. of 2-nitro-3-methylanisole with iron powder in glacial acetic acid.

2-Bromo-3-methylanisole, m.p. 34–36°, lit.[16] m.p. 35.5–36.5°, was obtained in 86% yield by the Sandmeyer reaction on 23.4 g. of 2-amino-3-methylanisole using the sulfuric acid procedure.[16]

6-Methoxy-2-methylbenzyldimethylamine (IIa) was prepared in 61% yield from 9.2 g. (0.0458 mole) of 2-bromo-3-methylanisole, 1.22 g. (0.05 g.-atom) of magnesium turnings, and 6.65 g. (0.0458 mole) of α-dimethylaminomethyl isobutyl ether.[17,18] The product boiled at 106–108° at 10.5 mm., n_D^{24} 1.5140.

Anal. Calcd. for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.51; H, 9.54; N, 7.91.

The picrate (recrystallized from 95% ethanol) melted at 139–140°.

Anal. Calcd. for $C_{17}H_{20}N_4O_8$: C, 50.00; H, 4.94; N, 13.72. Found: C, 50.26; H, 4.73; N, 13.59.

The methiodide, m.p. 153–154°, was prepared from the amine and excess methyl iodide in acetonitrile, precipitated with ether, and recrystallized from acetonitrile and ether.

Anal. Calcd. for $C_{12}H_{20}INO$: C, 44.73; H, 6.25; N, 4.35. Found: C, 44.66; H, 6.37; N, 4.33.

Oxidation of 2.0 g. of the pure amine IIa was effected as described for the rearrangement product of Ia to give the water-soluble 2-methyl-6-methoxybenzoic acid (IVa), m.p. 138° (recrystallized from hexane-ethanol), lit.[14] m.p. 139°; yield 38%.

Independent synthesis of amine IIIa. 4-Methoxy-2-methylaniline (0.5 mole) in 175 ml. of 48% hydrobromic acid and 125 ml. of water was diazotized at 0° with a solution of 35 g. of sodium nitrite in 100 ml. of water. The solution was poured onto 0.30 mole of freshly prepared cuprous bromide[19] in 120 ml. of 48% hydrobromic acid and 60 ml. of water to

(9) Analyses are by Galbraith Microanalytical Laboratories, Knoxville, Tenn. All melting points and boiling points are uncorrected.

(10) See W. G. Brown, *Org. Reactions*, VI, 491–492 (1951).

(11) E. Späth, *Monatsh.*, **34**, 1998 (1913).

(12) See C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. Reactions*, VIII, 122 (1954).

(13) C. Schall, *Ber.*, **12**, 824 (1879).

(14) P. Cluit and F. Bolsing, *Bull. Soc. chim. France* [3], **35**, 143 (1906).

(15) H. H. Hodgson and H. G. Beard, *J. Chem. Soc.*, **127**, 498 (1925).

(16) A. I. Vogel, *Textbook of Practical Organic Chemistry*, 3rd ed., Longmans, Green and Co., New York, N. Y., 1956, p. 602.

(17) G. M. Robinson and R. Robinson, *J. Chem. Soc.*, 532 (1923).

(18) See A. T. Stewart and C. R. Hauser, *J. Am. Chem. Soc.*, **77**, 1098 (1955).

(19) J. L. Hartwell, *Org. Syntheses*, **Coll. Vol. III**, 186 (1955).

give (steam distilled) 69.75 g. (69%) of 5-methoxy-2-methylbromobenzene, b.p. 106–108.5° at 11 mm., lit.[20] b.p. 108.5° at 12 mm.

This halide (0.12 mole) was converted to its Grignard reagent, which was treated with 0.78 mole of dimethylaminomethyl isobutyl ether to give amine IIIa (49%), b.p. 113.5–115° at 9.5 mm., n_D^{25} 1.5136.

Anal. Calcd. for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.52; H, 9.63; N, 7.92.

The picrate (recrystallized from 95% ethanol) melted at 115–115.5°.

Anal. Calcd. for $C_{17}H_{20}N_4O_8$: C, 50.00; H, 4.94; N, 13.72. Found: C, 50.10; H, 4.99; N, 13.60.

The methiodide, m.p. 202.5–203°, was prepared from the amine and excess methyl iodide in acetonitrile, precipitated with ether, and recrystallized twice from acetonitrile-ether.

Anal. Calcd. for $C_{12}H_{20}INO$: C, 44.73; H, 6.25; N, 4.35. Found: C, 44.62; H, 6.02; N, 4.38.

Oxidation of 2.0 g. of pure amine IIIa was effected as described for the rearrangement product of Ia to give the water-insoluble 4-methoxy-2-methylbenzoic acid (Va), m.p. 174–175° (recrystallized from ethanol-water), lit.[13] m.p. 176°; yield 73%.

3-Methylbenzyltrimethylammonium bromide (Ib). This salt, m.p. 217–219°, prepared in 90% yield from 0.2 mole of α-bromo-*m*-xylene and excess trimethylamine as described for Ia. Recrystallization from acetonitrile raised the m.p. to 222–223°.

Anal. Calcd. for $C_{11}H_{18}BrN$: C, 54.10; H, 7.43. N, 5.73. Found: C, 54.04; H, 7.57; N, 5.76.

Rearrangement of bromide Ib. This rearrangement was carried out with 36.6 g. (0.15 mole) of 3-methylbenzyltrimethylammonium bromide (Ib) in a suspension of 0.30 mole of sodium amide in 500 ml. of liquid ammonia as described for the rearrangement of Ia. The initial bright green color faded in 45–60 seconds, indicating a rapid reaction. There was obtained a mixture of 21.86 g. (90%) of amines IIb and IIIb, b.p. 91.8–93.2° at 12 mm., n_D^{25} 1.5077.

Anal. Calcd. for $C_{11}H_{17}N$: C, 80.92; H, 10.50; N, 8.58. Found: C, 80.87; H, 10.52; N, 8.70.

Oxidation of 2.0 g. of the amine mixture was effected as described for the rearrangement product of Ia to give the water-insoluble 2,4-dimethylbenzoic acid (Vb) (28%), m.p. 127.5–128.5°, lit.[21] m.p. 128°, mixed m.p. with authentic sample, 128–128.5°, and the water-soluble 2,6-dimethylbenzoic acid (IVb) (3% impure). After five recrystallizations from hexane, the latter acid melted at 113.5–114.5°, lit.[22] m.p. 116°. The melting point was not depressed on admixture with the acid obtained from the oxidation of independently synthesized amine IIb (see below).

Estimation of the composition of the rearrangement product of Ib. The infrared spectrum of a 4% solution of the rearrangement product of Ib in cyclohexane was compared with the spectra of two cyclohexane solutions containing a total of 4% of independently synthesized amines IIb and III. One of these solutions contained a mixture of IIb and IIIb. in a ratio of 55:45 and the other contained a mixture of IIb and IIIb in a ratio of 50:50. The relative intensities of the moderate bands at 689 cm.$^{-1}$ (IIb) and 713 cm.$^{-1}$ (IIIb) led to a composition estimate for the rearrangement product of 54% 2,6-dimethylbenzyldimethylamine (IIb) and 46% 2,4-dimethylbenzyldimethylamine (IIIb).

Independent synthesis of amine IIb. 2,6-Dimethylbromobenzene, b.p. 91–93.5[4°] at 20 mm., n_D^{25} 1.5549, lit., 23 b.p. 98–99° at 20 mm., n_D^{25} 1.5552, was prepared from 2,6-dimethylaniline as described by Brown and Grayson.[23]

2,6-Dimethylbenzyldimethylamine (IIb) was prepared from 6.55 g. (0.05 mole) of dimethylaminomethyl isobutyl ether,[17] 11.59 g. (0.0625 mole) of 2,6-dimethylbromobenzene, and 3.04 g. (0.125 g.-atoms) of magnesium turnings[18] employing 9.4 g. (0.045 mole) of 1,2-dibromoethane to activate Grignard formation. Distillation of the product gave 5.87 g. (72%) of amine IIb, b.p. 91–92° at 10.3 mm., n_D^{25} 1.5100.

Anal. Calcd. for $C_{11}H_{17}N$: C, 80.92; H, 10.50; N, 8.58. Found: C, 80.70; H, 10.41; N, 8.56.

The methiodide, prepared as described for that of IIa, melted at 192–193° dec.

Anal. Calcd. for $C_{12}H_{20}IN$: C, 47.25; H, 6.56; N, 4.59. Found: C, 47.07; H, 6.47; N, 4.54.

Oxidation of 1.0 g. of amine IIb was effected with 3.0 g. of potassium permanganate to give 0.13 g. (14%) of 2,6-dimethylbenzoic acid (IVb), m.p. 111–113° and at 114–114.5° after another recrystallization from hexane, lit.[22] m.p. 116°.

Independent synthesis of amine IIIb. 2,4-Dimethylbenzoic acid (0.086 mole) was reduced with lithium aluminum hydride[10] to give 2,4-dimethylbenzyl alcohol (52%), m.p. 27–28° (recrystallized from petroleum ether (b.p. 30–60°), cooled in Dry Ice), lit.[24] m.p. 22°.

A solution of 0.45 mole of this alcohol in 50 ml. of dry ether was treated 3 hr with 0.023 mole of phosphorus trichloride in 10 ml. of dry ether. Water was added, and the ethereal layer was washed with sodium bicarbonate solution and water. After drying the ethereal solution was evaporated and the residue taken up in benzene. The benzene solution was added to 4.5 g. (0.10 mole) of dimethylamine in 50 ml. of benzene, 3 g. more of the amine being bubbled through the mixture. After 2 hr., the solution was extracted with 2*M* hydrochloric acid (total 200 ml.) and the extract made basic with solid sodium hydroxide. The liberated amine was extracted with ether, dried, and distilled to give 2.07 g. (29%) of 2,4-dimethylbenzyldimethylamine (IIIb), b.p. 91–92° at 10.3 mm., n_D^{25} 1.5040, was obtained.

Anal. Calcd. for $C_{11}H_{17}N$: C, 80.92; H, 10.50; N, 8.58. Found: C, 80.73; H, 10.42; N, 8.56.

The methiodide, prepared as described for that of Ia, melted at 215–216° dec.

Anal. Calcd. for $C_{12}H_{20}IN$: C, 47.25; H, 6.56; N, 4.59. Found: C, 47.38; H, 6.51; N, 4.72.

3-Chlorobenzyltrimethylammonium bromide (Ic). This salt was prepared in 96% yield from 24.7 g. (0.12 mole) of 3-chlorobenzyl bromide and excess trimethylamine by the procedure described for Ia. After one recrystallization from a mixture of ethanol, acetonitrile, and ether it melted at 224–225°.

Anal. Calcd. for $C_{10}H_{15}BrClN$: C, 45.39; H, 5.71; N, 5.29. Found: C, 45.25; H, 5.70; N, 5.24.

Rearrangement of bromide Ic. This rearrangement was carried out essentially as described for the rearrangement of Ia. The quaternary salt was added as rapidly as possible; the reaction period was 1 hr. There was obtained 2.98 g. (16%) of a mixture of rearranged amines IIc and IIIc, b.p. 100–106° at 12 mm., n_D^{25} 1.5233.

Anal. Calcd. for $C_{10}H_{14}ClN$: C, 65.82; H, 7.68; N, 7.63; Cl, 19.30. Found: C, 65.59; H, 7.49; N, 7.72; Cl, 19.14.

Much of the original quaternary salt Ic was recovered contaminated with a salt containing an aromatic primary amine group as indicated by a positive test on diazotization and coupling with α-naphthol. This was supported by an infrared spectrum which showed bands for the N-H bond.

In another experiment using inverse addition and a reaction period of only 5 min., the mixture of rearranged amines was obtained in 5% yield. The recovered salts gave a weak positive test for an aromatic primary amine.

Treatment of a small sample of the amine mixture with excess picric acid in ethanol produced two types of crystals, which were separated mechanically and recrystallized

(20) R. Pschorr, *Ann.*, **391**, 50 (1912).

(21) E. V. Meyer and F. Nabe, *J. Prakt. Chem.* [2], **82**, 537 (1910).

(22) W. A. Noyes, *Am. Chem. J.*, **20**, 813 (1898).

(23) H. C. Brown and M. Grayson, *J. Am. Chem. Soc.*, **75**, 20–24 (1953).

(24) W. Hindrichsen, *Ber.*, **21**, 3085 (1888).

separately from 95% ethanol. The main picrate melted at 165.5–166.5°.

Anal. Calcd. for $C_{16}H_{17}ClN_4O_7$: C, 46.56; H, 4.14; N, 13.56. Found: C, 46.50; H, 4.28; N, 13.50.

The other picrate, obtained in very small amount, melted at 152°.

Oxidation of 0.97 g. of the amine mixture with 2.9 g. of potassium permanganate gave the water-insoluble 4-chloro-2-methylbenzoic acid (Vc) (21%), m.p. 169–171° (recrystallized from ethanol-water), lit.[25] m.p. 171–172°, and much less of the water-soluble 6-chloro-2-methylbenzoic acid (IVc), m.p. 100–101° after three recrystallizations from hexane, lit.[26] m.p. 102°.

Further oxidation of acid Vc (0.2 g.) was effected with 0.37 g. of potassium permanganate in 10 ml. of water and enough 20% sodium hydroxide solution to dissolve the acid. After heating on the steam bath until the purple color faded, the precipitated manganese dioxide was removed by filtration through a Supercell mat. The filtrate was acidified with concentrated hydrochloric acid, and the small amount (0.03 g.) of unchanged acid Vc was removed by filtration. After saturating with sodium sulfate, the filtrate was extracted with several portions of ether. The ethereal solution was dried and evaporated to leave 0.19 g. (85%) of 4-chlorophthalic acid, m.p. 152–153°, lit.[27] m.p. 150–150.5°. A small sample of this acid was boiled in a test tube and allowed to resolidify. The 4-chlorophthalic anhydride (VI) produced melted at 97.5–98.5°, lit.[27] m.p. 98.5°.

3-Bromobenzyltrimethylammonium iodide (Id). To 49.6 g. (0.21 mole) of *m*-dibromobenzene in 100 ml. of dry ether was added gradually 5.34 g. (0.22 g.-atom) of magnesium turnings. One hour after refluxing had ceased, 25.8 g. (0.197 mole) of dimethylaminomethyl isobutyl ether[17] in an equal volume of dry ether was added. After 20 hr. the solution was poured onto 200 g. of ice and 40 ml. of concd. hydrochloric acid. The aqueous acid layer was separated and made strongly basic with solid sodium hydroxide. The resulting mixture was steam distilled, and the distillate was extracted with several portions of ether. The combined extract was dried and distilled to give 27.85 g. (66%) of 3-bromobenzyldimethylamine, b.p. 105–108° at 9.8 mm., n_D^{25} 1.5388.

Anal. Calcd. for $C_9H_{12}BrN$: C, 50.49; H, 5.65; N, 6.54. Found[28]: C, 52.56; H, 6.20; N, 7.04.

This amine (27.42 g., 0.128 mole) was treated 3 hr. with 35 g. (0.25 mole) of methyl iodide in 125 ml. of acetonitrile. Ether was added to precipitate 3-bromobenzyltrimethylammonium iodide (Id), m.p. 189–191° after recrystallization from acetonitrile-ether; yield 45.5 g. (98%). Two more recrystallizations from acetonitrile-ether raised the melting point to 191.5–192°.

Anal. Calcd. for $C_{10}H_{15}BrIN$: C, 33.77; H, 4.25; N, 3.94. Found: C, 33.60; H, 4.41; N, 3.74.

Treatment of bromide Id *with sodium amide.* To 35.5 g. (0.1 mole) of 3-bromobenzyltrimethylammonium bromide (Id) in 200 ml. of liquid ammonia was added during 15 min. a suspension of 0.101 mole of sodium amide in 300 ml. of liquid ammonia to produce yellow, orange, and finally dark red-brown colors. After 15 min., 5.40 g. (0.101 mole) of ammonium chloride was added and the ammonia replaced by ether. No ether-soluble amine was obtained. The ether-insoluble material (resinous salts) was diazotized and coupled with α-naphthol to give a brilliant water-soluble red dye indicating a considerable amount of primary amino quaternary salt.

3-Trifluoromethylbenzyltrimethylammonium iodide (Ie). 3-Trifluoromethylbenzyldimethylamine was obtained from 45.0 g. (0.20 mole) of *m*-bromobenzotrifluoride, 4.86 g. (0.20 g.-atom) of magnesium turnings, and 18.92 g. (0.148 mole) of dimethylaminomethyl isobutyl ether[17,18]; yield 20.4 g. (68%), b.p. 102–107° at 60 mm., n_D^{25} 1.4453.

Anal. Calcd. for $C_{10}H_{12}F_3N$: C, 59.09; H, 5.95; N, 6.89. Found: C, 58.93; H, 5.73; N, 6.82.

This amine (20.1 g., 0.099 mole) was treated with excess methyl iodide as described in the preparation of Id to give 33.2 g. (97%) of 3-trifluoromethylbenzyltrimethylammonium iodide (Ie), m.p. 163–164° and at 163.5–164° after recrystallization from acetone-ether.

Anal. Calcd. for $C_{11}H_{15}F_3IN$: C, 38.28; H, 4.35; N, 4.06. Found: C, 38.48; H, 4.51; N, 3.87.

Treatment of iodide Ie *with sodium amide.* This reaction was carried out with 13.8 g. (0.04 mole) of Ie and 0.041 mole of sodium amide as described for Id. The ether-soluble fraction was evaporated leaving a viscous black basic tar from which no pure compound was isolated. The ether-insoluble salts were triturated in acetonitrile and the mixture filtered. Ether was added to the filtrate to precipitate 6.4 g. (46%) of recovered quaternary salt Ie, m.p. 159–160°, mixed m.p. 161–162°.

3,5-Dimethoxybenzyltrimethylammonium chloride (VIIIa). This salt, m.p. 191–192°, was prepared in 93% yield from 67.5 g. (0.362 mole) of 3,5-dimethoxybenzyl chloride[29] (m.p. 46°) (obtained from 3,5-dimethoxybenzyl alcohol)[10] and excess trimethylamine as described for Ia. The picrate of this hygroscopic quaternary salt was prepared for analysis. After three recrystallizations it melted at 159–160°.

Anal. Calcd. for $C_{18}H_{22}N_4O_9$: C, 49.31; H, 5.06; N, 12.78. Found: C, 49.31; H, 4.92; N, 12.76.

Rearrangement of chloride VIIIa. This reaction was carried out with 24.6 g. (0.10 mole) of quaternary salt VIIIa and 0.20 mole of sodium amide as described for the rearrangement of Ia to give 19.6 g. (93%) of 2,4-dimethoxy-6-methylbenzyldimethylamine (IXa), b.p. 100–101° at 1.0 mm.

Anal. Calcd for $C_{12}H_{19}NO_2$: C, 68.86; H, 9.15; N, 6.69. Found: C, 69.05; H, 9.04; N, 6.63.

The picrate, recrystallized three times from ethanol, melted at 142–143°.

Anal. Calcd. for $C_{18}H_{22}N_4O_9$; C, 49.31; H, 5.06; N, 12.78. Found: C, 49.28; H, 5.16; N, 12.85.

Oxidation of 0.5 g. of amine IXa was effected as indicated for amine IIIa to give 0.2 g. (45%) of crude 2,4-dimethoxy-6-methylbenzoic acid (X) which, after one recrystallization from aqueous ethanol, melted at 140–141° dec., lit.,[30] m.p. 140 dec.

The methiodide of IXa was prepared from 43.8 g. (0.209 mole) of the amine and excess methyl iodide as described for Id. Recrystallization from ethanol gave 73 g. (99%) of 2,4-dimethoxy-6-methylbenzyltrimethylammonium iodide, m.p. 169–170° (shrinking and darkening, did not actually melt even at 250°). The quaternary picrate, recrystallized three times from water, melted at 172.5–173.5°.

Anal. Calcd for $C_{19}H_{24}N_4O_9$: C, 50.44; N, 5.35; N, 12.39. Found: C, 50.69; H, 5.31; N, 12.31.

Emde reduction of the methiodide of IXa was effected with 17.55 g. (0.05 mole) of the salt and 210 g. of 5% sodium amalgam in water by the *Org. Syntheses* procedure for the preparation of hemimellitene[31] to give 2.86 g. (35%) of 3,5-dimethoxy-*o*-xylene, b.p. 117.5–120° at 13 mm., n_D^{25} 1.5263.

Anal. Calcd. for $C_{10}H_{14}O_2$: C, 72.26;; H, 8.49. Found: C, 72.07; H, 8.48.

Ether cleavage of 3,5-dimethoxy-*o*-xylene was effected with 2.0 g. of the compound in 10 ml. of glacial acetic acid

(25) K. von Auwers and L. Harres, *Z. physik. Chem.* [A], **143**, 16 (1929).

(26) J. Kenner and E. Witham, *J. Chem. Soc.*, 119, 1458 (1921).

(27) W. Miersch, *Ber.*, 25, 2116 (1892).

(28) This analysis checks closely for an impurity of about 8.6% of *m*-bis(dimethylaminomethyl)benzene, which would arise from the formation of the di-Grignard reagent.

(29) R. Adams, S. MacKenzie, Jr., and S. Leowe, *J. Am. Chem. Soc.*, 70, 664 (1948).

(30) J. Herzig and F. Wenzel, *Monatsh.*, 24, 901 (1904).

(31) W. R. Brasen and C. R. Hauser, *Org. Syntheses*, 34, 56 (1954).

and 10 ml. of 47% hydriodic acid refluxing under an air condenser for 2 hr. The solvents were removed under reduced pressure leaving orange crystals which were recrystallized from water (Norite) to give 3,5-dihydroxy-*o*-xylene (XI), m.p. 136°, lit.[32] m.p. 136–137° (from water).

3,5-Dimethylbenzyltrimethylammonium bromide (VIIIb). 3,5-Dimethylbenzoic acid (30.0 g., 0.2 mole) was added slowly to a slurry of 10.0 g. (0.25 mole) of 95% pure lithium aluminum hydride in 500 ml. of anhydrous ether. The addition required about 1.5 hr. because of the unusually vigorous reaction. After 3 hr. of mechanical stirring the reaction was worked up by the usual procedure[10] to give 24 g. (88%) of 3,5-dimethylbenzyl alcohol, b.p. 115–117.5° at 10 mm., lit.,[33] b.p. 218–221.°

This alcohol, 26.7 g. (0.16 mole), was treated with 27.1 g. (0.10 mole) of phosphorus tribromide in 500 ml. of ether. After the usual work-up the product was recrystallized once from methanol at −70° to give 31.2 g. (80%) of 3,5-dimethylbenzyl bromide, m.p. 37.5–38°, lit.,[33] m.p. 37.5–38°.

Quaternary salt VIIIb, m.p. 238.5–239°, was prepared in 84% yield from 31.2 g. (0.157 mole) of this bromide and excess trimethylamine as described for Ia.

Anal. Calcd. for $C_{12}H_{20}BrN \cdot 1/2\ H_2O$[34]: C 54.01; H, 7.92; N, 5.25. Found: C, 54.17, 54.05; H, 8.13, 7.98; N, 5.17, 5.14.

Rearrangement of bromide VIIIb. This rearrangement was carried out with 30.5 g. (0.114 mole) of quaternary salt VIIIb and 0.24 mole of sodium amide as described for the rearrangement of Ia to give 19.6 g. (97%) of 2,4,6-trimethylbenzyldimethylamine (IXb), b.p. 108–109° at 10.5 mm., n_D^{25} 1.5109, lit.[2] b.p. 112–113° at 13 mm. The picrate melted at 148–149°, lit.[2] m.p. 149–150°. The methiodide melted at 195–196°, lit.[2] m.p. 196–197° dec.

Independent synthesis of amine IXb. To a solution of 9.0 g. (0.2 mole) of dimethylamine in 50 ml. of benzene was added 9.3 g. (0.0436 mole) of 2,4,6-trimethylbenzyl bromide in 25 ml. of benzene. After 1 hr., the mixture was shaken with 300 ml. of 2*M* hydrochloric acid and the layers separated. The aqueous phase was made strongly basic with solid sodium hydroxide, cooled, and extracted with ether. The ethereal solution was dried, filtered, and evaporated. Vacuum distillation yielded 5.68 g. (74%) of 2,4,6-trimethylbenzyldimethylamine (IXb), b.p. 107–108° at 10 mm., n_D^{25} 1.5109 (identical with that of the rearrangement product). The melting points of its picrate and methiodide were the same as those of the rearranged amine and mixed melting points were not depressed. In addition the infrared spectra of the two samples of amine were identical.

Rearrangement of a mixture of benzyltrimethylammonium iodide and 3,5-dimethylbenzyltrimethylammonium bromide (VIIIb). To a stirred suspension of 0.30 mole of sodium amide in 300 ml. of liquid ammonia was added during 1 min. a mixture of 25.8 g. (0.10 mole) of 3,5-dimethylbenzyltrimethylammonium bromide and 27.7 g. (0.10 mole) of benzyltrimethylammonium iodide in 1000 ml. of liquid ammonia. Most of the solid salts had dissolved in the ammonia before the addition. After 30 sec., 16 g. (0.3 mole) of ammonium chloride dissolved in liquid ammonia was added rapidly. The ammonia was replaced by ether and the mixture was filtered. The filtrate was distilled to give 8.72 g. (59%) of 2-methylbenzyldimethylamine, b.p. 80–85° at 14 mm. and 8.73 g. (49%) of 2,4,6-trimethyldimethylamine (IXb), b.p. 113–115° at 14 mm. Also a middle cut (2.16 g.), b.p. 85–113° at 14 mm., was obtained. These two amines were identified by comparison of their infrared spectra with those of authentic samples.

DURHAM, N. C.

(32) O. Simon, *Ann.*, **329**, 305 (1903).

(33) P. Wispek, *Ber.*, **16**, 1577 (1883).

(34) The yields of rearranged amine from salt VIIIb are nevertheless based on the anhydrous salt. The yields based on the hydrated form would be about 4% higher.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF FLORIDA]

Tetraphenylbutatriene from the Reaction of 1,1-Diphenyl-2-nitroethylene with Potassium *t*-Butoxide[1]

W. M. JONES AND C. D. BROADDUS[2]

Received November 23, 1960

Treatment of 1,1-diphenyl-2-nitroethylene with potassium *t*-butoxide gives, in addition to products resulting from *beta*-addition of base, small amounts (up to 10%) of tetraphenylbutatriene II. Employing spectrophotometric techniques, it was shown that this reaction does not involve an intermediate carbene. A mechanism for this reaction involving *alpha*-addition of a vinyl carbanion to the nitroolefin is suggested.

In the course of some examinations of the scope and mechanism of *alpha*-eliminations from vinyl systems (the Fritsch-Buttenberg-Wiechell rearrangement)[3,4] we felt that it would be interesting to investigate the reactions of 1,1-diphenyl-2-nitroethylene with strong base under typical *alpha*-elimination conditions. It was recognized from the outset that *beta*-addition of base to the nitroolefin[5,6] would certainly compete with *alpha*-elimination. We therefore selected the rather bulky base,

(1) Taken in part from the dissertation submitted by Charles D. Broaddus to the Graduate School of the University of Florida in partial fulfillment of the requirements for the degree of Doctor of Philosophy, 1960.

(2) Du Pont Teaching Fellow, 1959–60.

(3) P. Fritsch, *Ann.*, **279**, 319 (1894); W. P. Buttenberg, *Ann.*, **279**, 327 (1894); H. Wiechell, *Ann.*, **279**, 337 (1894). For a review of this type of reaction see T. L. Jacobs, *Org. Reactions*, V, 1 (1949). More recent references can be found in A. A. Bothner-By, *J. Am. Chem. Soc.*, **77**, 3293 (1955) and reference 4.

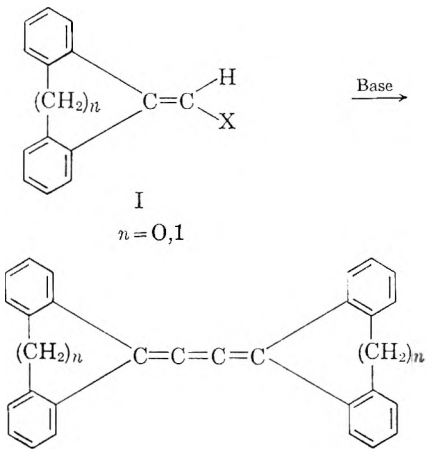
(4) J. F. Pritchard and A. A. Brothner-By, *J. Phys. Chem.*, **64**, 1271 (1960); D. Y. Curtin and E. W. Flynn, *J. Am. Chem. Soc.*, **81**, 4714 (1959).

(5) The addition of basic reagents to 1,1-diphenyl-2-nitroethylene is a well known reaction. *E.g.* see P. Lipp, W. Ludicke, N. Kalinkoff, and A. P. Pethoff, *Ann.*, **449**, 15 (1926); M. Konowalow and G. Jatzewitsch, *J. Russ. Phys. Chem. Ges.*, **37**, 542 in *Chem. Zent.*, **76**, II, 824 (1905).

(6) R. Anschutz and E. Romig, *Ann.*, **233**, 327 (1886).

potassium *t*-butoxide, for our initial investigations. It was found that, in addition to products which obviously arose from *beta*-addition to the nitroolefin, small amounts of 1,1,4,4-tetraphenylbutatriene II were consistently formed.

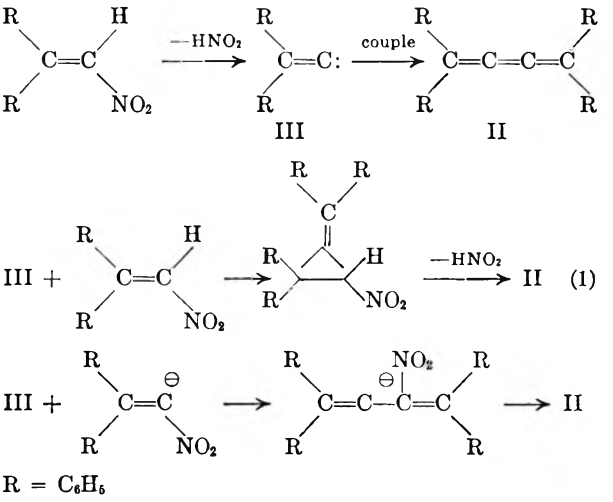
The formation of tetraphenylbutatriene from this reaction was particularly interesting to us in view of the recent observations by Hauser and Lednicer[7] as well as Curtin and Richardson[8] that certain vinyl halides give the dimeric product rather than the rearranged acetylene.



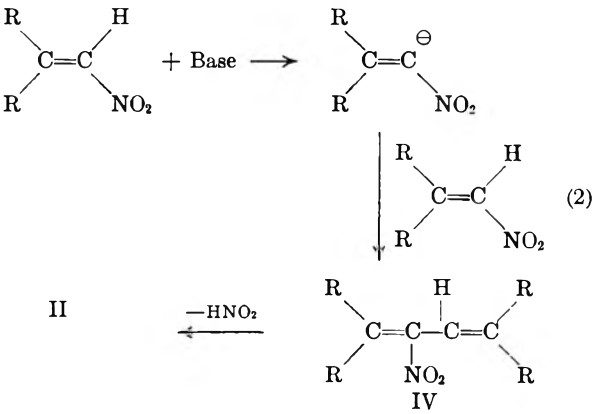
However, the characteristic which was common to all of these investigations was that the two phenyl rings were bonded together in such a way as to inhibit rearrangement. In fact, Curtin and Richardson[8] found that when the length of the chain bonding the two phenyls together was long enough (I. $n = 2$), again, rearrangement was observed. In the case of the nitroolefin, however, the dimeric product was formed despite the fact that the two phenyls were free to migrate. Furthermore, the crude product from this reaction was examined with gas chromatography and its was found that no detectable amount of diphenylacetylene had been formed.

In view of this interesting difference in the course of the reaction and in view of the possible theoretical implications, this reaction was studied in some detail. This paper will be confined to the reaction involving the *alpha*-carbon.

The two mechanisms suggested by both Hauser[7] and Curtin[8] for the formation of triene from the substituted methylenefluorenes and related compounds certainly appeared to apply to the system under investigation. Thus, the reaction could proceed *via* initial formation of the carbene III followed by various reaction paths leading to formation of the triene (Equation 1) or it could proceed by attack



of the vinyl carbanion on the *alpha*-carbon of 1,1-diphenyl-2-nitroethylene[9] to give the nitrobutadiene IV. This, in turn, could *beta*-eliminate to give the observed product (Equation 2).



In the attempt to distinguish between these two reaction paths, two approaches were employed. First, attempts were made to isolate intermediate IV. Isolation of this material followed by elimination under the reaction conditions would exclude carbene coupling as the sole source of triene. However, in view of the small proportion of this reaction which proceeded by reaction at the *alpha*-carbon (at most 9.4%) it was not too surprising that all attempts to isolate such an intermediate failed.

As a second method to distinguish between these two reaction paths, attempts were made to capture the carbene with an appropriate trapping agent and isolate and characterize such a product. The trapping agents which were employed were cyclohexene and diethylamine. Again all attempts failed.

In the course of this study, however, it was observed that as long as the conditions of the reaction (including the time interval between the prepara-

(7) C. R. Hauser and D. Lednicer, *J. Org. Chem.*, 22, 1248 (1957).

(8) D. Y. Curtin and W. H. Richardson, *J. Am. Chem. Soc.*, 81, 4719 (1959).

(9) This type of reaction has been discussed fully by Hauser and Lednicer[4] and Truce and his co-workers (*J. Am. Chem. Soc.*, 78, 2743, 2748 (1956); 80, 1916, 6450 (1958).

tion and use of the base) were held reasonably constant, the reaction gave consistent yields of the triene which could be determined quite accurately by employing spectrophotometric techniques. For example, see the first two entries in Table I. The yield of triene was therefore determined in the presence of various carbene trapping agents. In Table I it will be seen that the addition of a large excess of either cyclohexene or diethylamine caused no detectable change in the amount of triene formed (as compared with blanks run at the same time). These experiments make the carbene mechanism very unlikely for this particular reaction.

TABLE I

1,1,4,4-TETRAPHENYLBUTATRIENE FROM THE REACTION OF 1,1-DIPHENYL-2-NITROETHYLENE WITH POTASSIUM *t*-BUTOXIDE[a]

Moles of Nitroolefin	Moles of Reagent Added	Reaction Time, Hours	Nitroolefin Unreacted, %	Yield of Triene, %
2.2×10^{-4}	None	2	14	3.5[b]
2.2×10^{-4}	None	2	13	3.4[b]
8.8×10^{-5}	None	0.5	13	2.3
8.8×10^{-5}	1×10^{-2} Cyclohexene	0.5	14	2.3
2.2×10^{-4}	None	2	14	2.1[c]
2.2×10^{-4}	1×10^{-3} Diethylamine	2	17	2.1[c]
2.2×10^{-4}	None	2	18	4.0
2.2×10^{-4}	3.2×10^{-3} Methyl iodide	2	16	2.2
2.2×10^{-4}	None	1.5	21	5.4
2.2×10^{-4}	3.2×10^{-3} Methyl iodide	1.5	18	3.0[d]
2.2×10^{-4}	None	12	11	9.4[e]

[a] The reactions were made up to 10 ml. with heptane. Unless otherwise stated the potassium *t*-butoxide was added as a solution (0.8*M*) in 1 ml. of *t*-butyl alcohol. [b] These two runs were made under identical conditions for the purpose of comparison of triene yields. [c] The difference in yield between these two runs and the first two is typical of the differences observed when different batches of base were used. It was not determined why this reaction was so sensitive to either changes in batch or the length of time a single sample was stored before use. This difficulty was obviated in individual runs by comparison with blanks. [d] 4×10^{-3} moles of base. [e] 9×10^{-4} moles of freshly prepared dry potassium *t*-butoxide added to a solution of the olefin in heptane.

Finally, it should be mentioned that the formation of a carbanion intermediate was demonstrated by effecting the reaction in the presence of a tenfold excess of methyl iodide, a reagent that should be effective as a carbanion trapping agent (Table I). This mixture showed a 40–50% drop in the amount of triene formed. In another pair of runs, there was included in the reaction mixture containing the methyl iodide enough excess potassium *t*-butoxide to completely react with the methyl iodide and still retain the same mole ratio of 1,1-diphenyl-2-nitroethylene to potassium *t*-butoxide as was present in the blank. These conditions gave the same 40–50% drop in the amount of triene formed.

It is therefore suggested that the most likely path for the formation of the four-carbon chain is initial formation of the vinyl carbanion followed by *alpha*-addition to the nitroolefin (Equation 2).

There remains unanswered, however, the question of why the nitroolefin couples to give the triene whereas the corresponding halogenated olefin,[3,4] when possible, *only* rearranges to the corresponding diphenylacetylene. Since there is little doubt but that both reactions proceed *via* an anionic intermediate[4] this difference is particularly striking. One obvious contributing factor to this difference in reaction routes is the difference in electron density at the *alpha*-carbon to which the anion must couple. This, however, hardly seems to be sufficient to explain the difference in reaction routes since Curtin and Flynn[4] found that the vinyl halide anionic species were much too short-lived to expect appreciable coupling. For example, it was found that the anionic species generated from the reaction of 1,1-diphenyl-2,2-dibromoethylene underwent 80% rearrangement to the acetylene in just 30 seconds at −35°. Furthermore, in contrast to the nitroanalog, all attempts to trap the intermediate anion failed. Thus, there apparently exists within the anions inherent differences in tendencies to rearrange. One is tempted to conclude that this difference indicates that the *alpha*-elimination from vinyl type systems proceeds by migration of a phenyl without its electrons and that the nitro group retards this migration by dispersing the negative charge of the anion away from the carbon to which migration occurs (at least by an inductive effect and probably also by rehybridizing the carbon and placing the nonbonding electrons into a conjugated *p*-orbital). However, it is also possible that the *alpha*-elimination proceeds by migration of the phenyl with its electrons with concomitant loss of the halide and that the difference in these two reactions is simply due to the difference in ease of loss of the halide versus the nitro groups. The real difference must remain a mystery until further investigations which are under way are completed.

EXPERIMENTAL[10]

1,1-Diphenyl-2-nitroethylene. 1,1-Diphenyl-2-nitroethanol was prepared from 1,1-diphenylethylene[11] by the method of Anschutz and Romig.[6] The substituted ethanol was then dehydrated by the method of Wittig and Gauss[12] to give 1,1-diphenyl-2-nitroethylene, yellow crystals from hexane (33%), m.p. 86–87° (lit.[5] m.p. 86–87°).

(10) Melting points are uncorrected. Microanalyses were done by Galbraith Laboratories.

(11) C. F. H. Allen and S. Converse, *Org. Syntheses*, Coll. Vol. I, 226 (1951).

(12) G. Wittig and W. Gauss, *Ber.*, 80, 372 (1947).

Authentic 1,1,4-4-Tetraphenylbutatriene Authentic tetraphenylbutatriene was synthesized from 1,1,4,4-tetraphenyl-2,3-dihydroxybutyne-2 by the method of Kuhn and Wallenfells,[13] m.p. 236–237° (lit.[13] m.p. 236.5–237°).

Reaction of 1,1-diphenyl-2-nitroethylene with dry potassium t-butoxide. Dry potassium *t*-butoxide was prepared by adding *t*-butyl alcohol to a refluxing mixture of potassium in dry toluene or xylene. After 2 hr. reflux, the mixture was filtered under nitrogen and the residue of potassium *t*-butoxide was washed thoroughly with dry ether. The best yields of triene were obtained when this material was used as soon after preparation as possible. In a typical run, 1,1-diphenyl-2-nitroethylene (2.0 g., 8.8 mmoles) was dissolved in 150 ml. of dry heptane. The system was flushed with dry nitrogen and heated to reflux. To the refluxing solution was added in small portions 2.0 g. (18 mmoles) of dry potassium *t*-butoxide. After each addition, a red color developed in the reaction mixture. The mixture was refluxed for 5 hr. after completion of the addition. It was then filtered, while hot, through a Buchner funnel. Upon cooling, the heptane filtrate deposited 0.12 g. (7.6%) of yellow crystals, m.p. 236–237°; admixture with authentic 1,1,4,4-tetraphenylbutatriene showed no melting point depression.

Anal. Calcd. for $C_{28}H_{20}$: C, 94.37; H, 5.63. Found: C, 94.12; H, 5.60.

The infrared spectrum was identical with that of authentic tetraphenylbutatriene.

Evaporation of the heptane filtrate almost to dryness afforded 0.34 g. (17%) of the starting material.

Both the residue from the above filtration of the hot reaction mixture and the filtrate (after evaporation to dryness) were analyzed for diphenylacetylene. This was effected by gas chromatography of samples of each (chloroform extract of the residue) employing a six-foot column of Tide at 198° and 15 p.s.i. internal pressure in a Perkin-Elmer model 154-B vapor fractometer. Neither sample showed any peak near 7.4 min., the retention time of authentic diphenylacetylene.

Quantitative determination of tetraphenylbutatriene and unchanged 1,1-diphenyl-2-nitroethylene. The concentration of the triene and unchanged starting material were determined quantitatively by utilizing the Beckman DK-2 Spectrophotometer. Absorptions at 420 mμ (triene) and 360 mμ (starting material) were employed. Both compounds obeyed Beer's Law and no absorption from products resulting from *beta*-addition to the nitroolefin appeared at these wave lengths. It was therefore possible to analyze the reaction products for triene and nitroolefin directly. A typical run is given below. The other results are summarized in Table I.

Reaction of 1,1-diphenyl-2-nitroethylene with a t-butyl alcohol solution of potassium t-butoxide in the presence of cyclohexene. 1,1-Diphenyl-2-nitroethylene (0.02 g., 8.8 $\times 10^{-5}$ moles) was dissolved in 8 ml. of dry heptane. To this solution was added 1 ml. (1×10^{-2} moles) of cyclohexene. The three-necked flask was flushed well with dry nitrogen and 1.0 ml. of a *t*-butyl alcohol solution of potassium *t*-butoxide (8.0×10^{-4} moles) was added dropwise by means of a syringe. The solution was refluxed, with constant agitation, for 30 min. at which time the hot mixture was poured into 30 ml. of boiling chloroform. The solution was washed twice with 50-ml. portions of saturated salt solution and dried over anhydrous magnesium sulfate. The solution was made up to volume with chloroform in a 50-ml. volumetric flask followed by dilution with chloroform of 1:10. The amount of triene and starting material were then calculated directly from the ultraviolet spectrum to be 2.3% and 14%, respectively.

A blank, differing from the above reaction only in that 9 ml. of heptane was used as the solvent rather than 8 ml. of heptane and 1 ml. of cyclohexene also gave a 2.3% yield of triene.

(13) R. Kuhn and K. Wallenfells, *Ber.*, **71**, 783 (1938).

GAINESVILLE, FLA.

[CONTRIBUTION NO. 31 FROM THE EXPLORATORY RESEARCH LABORATORY, DOW CHEMICAL OF CANADA, LIMITED]

Aryldiazonium Tetrachloroborates and Tetrabromoborates

G. A. OLAH AND W. S. TOLGYESI

Received October 4, 1960

Aryldiazonium tetrachloroborates and tetrabromoborates were prepared from (1) the corresponding aryldiazonium halides and boron trihalides, (2) primary aromatic amines and nitrosonium tetrachloroborate, (3) the reaction of $N_2O_3 \cdot BCl_3$ and $N_2O_3 \cdot BBr_3$ with primary aromatic amines.

The first reference to diazonium tetrafluoroborates is that of Bart[1] in 1913 who prepared them by treating aromatic diazo compounds with complex fluoroboric acids and their salts. Owing to the great stability and practical application of the diazonium tetrafluoroborates, considerable research has since been carried out on these compounds.[2] As intermediates in the Schiemann reaction, aryldiazonium tetrafluoroborates are prepared either by diazotizing aromatic primary amines and then treating the prepared diazonium compounds with fluoroboric acid or fluoborates or by carrying out the diazotization directly in aqueous fluoboric acid.[3] Wannagat and Hohlstein[4] in an improved method prepared aryldiazonium tetrafluoroborates from primary aromatic amines and nitrosonium tetrafluoroborates. No aryldiazonium tetrachloroborates or tetrabromoborates, however, have been reported previously.

Tetrachloroborate and tetrabromoborate complexes are considerably less well known than the corresponding tetrafluoroborates. Muetterties[5] ob-

(1) H. Bart, Ger. Patent 281,055 (Oct. 7, 1913) [*Chem. Abstr.*, 9, 1830 (1915)].

(2) H. S. Booth and D. R. Martin, "Boron Trifluoride and Its Derivatives," Wiley, New York, 1949.

(3) G. Balz and G. Schiemann, *Ber.*, **60B**, 1186 (1927); E. Wilke-Dorfurt and G. Balz, *Ber.*, **60**, 115 (1927); A. Roe, *Org. Reactions*, 193–228 (1949).

(4) U. Wannagat and G. Hohlstein, *Chem. Ber.*, **88**, 1839 (1955).

(5) E. L. Muetterties, *J. Am. Chem. Soc.*, **79**, 6563 (1957).

tained potassium, rubidium, and cesium tetrachloroborates by the interaction of boron trichloride with alkali metal chlorides under pressure and high temperatures. Lappert[6] prepared pyridinium tetrachloroborates and tetrabromoborates from the corresponding pyridinium halides and boron trihalides. Gerard and Mooney[7] have observed that the reaction of boron trichloride with certain primary amines proceeds *via* disproportionation to give the tetrachloroborates $RNH_3 \cdot BCl_4$ and an aminoboron dichloride, $RNHBCl_2$, instead of giving the expected adduct, $RNH_2 \cdot BCl_3$. Herbert[8] studied the halogen exchange between boron trichloride and a number of chloride salts using Cl^{36} as a radiotracer. Both tetramethylammonium chloride and tetraethylammonium chloride exchange chloride rapidly with liquid boron trichloride. These results can be interpreted only on the basis of a mechanism which involves the formation of the tetrachloroborate anion. Alkylammonium tetrachloroborates and trifluorochloroborates[9] were prepared from the corresponding alkylammonium halides and boron trihalides in liquid hydrogen chloride. The electron acceptor properties of boron trichloride have been reviewed and findings suggesting the presence of the tetrachloroborate ion in some complexes are discussed. Infrared bands at 690 and 660 $cm.^{-1}$ were assigned to this ion.[10] The asymmetric stretching vibration of the BBr_4^- ion was observed at 593 $cm.^{-1}$.[11] Recently a comprehensive report on infrared investigation of tetrachloroborate complexes was published.[12] Tetrachloroborate complexes generally show a very broad strong band in the 630–750 $cm.^{-1}$ region.

To enable further investigation of the properties of organic tetrahaloborate complexes, aryldiazonium tetrachloro and tetrabromoborates were prepared. It was not possible to use the simple methods previously reported for the preparation of the aryldiazonium tetrafluoroborates. No aqueous chloro- or bromoboric acid exists, neither are their salts stable in aqueous solutions. Therefore, the preparation of the diazonium salts could not be effected through simple diazotization of the corresponding amines, with subsequent addition of the complex haloboric acid or its salts.

Nitrosonium tetrachloroborate ($NO^+BCl_4^-$), as such, has not been reported in the literature. Partington and Whynes[13] investigated the nitrosyl chloride–boron trichloride addition compounds and reported that a 1:1 compound $NOCl.BCl_3$ could be obtained. When formed from equimolar quantities of the starting materials, it is a lemon-yellow solid, melting in a sealed tube at 26–27° forming two liquid layers; the upper clear, reddish, the lower, orange or opaque. On heating to 65°, the lower layer disappears. This behavior corresponds with the phase diagram described by Roozeboom.[14] On the melting point curve, the maximum corresponding to compound formation, is not reached since a completely closed curve (probably similar to that of the nicotine-water system) cuts the apex and the compound does not melt without decomposition. No effort was made to clarify the structures of the 1:1 addition compound.

In our investigation of the nitrosyl chloride–boron trichloride system, it was found that it is possible to prepare a slightly yellow colored addition compound by treating difluorodichloromethane (Freon 12) solutions of the components at −50°. On evaporation of the solvent and any excess reagents at low temperatures in a vacuum system, the complex was obtained as a colorless, crystalline compound with a decomposition point of 24–25° (a considerable vapor pressure showing already at 20°). Analytical determinations are in accordance with a 1:1 composition $NOCl \cdot BCl_3$. The compound is insoluble in apolaric solvents but dissolves more readily in polaric solvents such as nitrobenzene. Decomposition at atmospheric pressure takes place quantitatively in the absence of moisture according to the equilibrium

$$NOCl \cdot BCl_3 \rightleftharpoons NOCl + BCl_3$$

By cooling, the addition complex is reformed, but needs further purification because it is yellow in color owing to absorbed nitrosyl chloride. Infrared investigation of the complex shows an absorption peak at 2123 $cm.^{-1}$ which could be assigned as the stretching frequency of the NO^+ ion. The absorption peak observed in the 1800 $cm.^{-1}$ region corresponds to NO in NOCl. From these data the solid complex was considered as nitrosonium tetrachloroborate ($NO^+BCl_4^-$) in equilibrium with its components and the oxygen coordinated polarized covalent complex

$$NOCl \cdot BCl_3 \rightleftharpoons NO^+BCl_4^-$$

Nitrosonium tetrachloroborate, upon reaction with primary aromatic amines at temperatures between −15 and −5°, gave the corresponding aryldiazonium tetrachloroborates

$$ArNH_2 + NO^+ BCl_4^- \longrightarrow ArN_2^+ BCl_4^- + H_2O$$

The aryldiazonium tetrachloroborates are considerably more sensitive to hydrolysis than the

(6) M. F. Lappert, *Proc. Chem. Soc.*, 121 (1957).
(7) W. Gerard and E. F. Mooney, *Chem. and Ind.*, 1259 (1958).
(8) R. H. Herbert, *J. Am. Chem. Soc.*, 80, 5080 (1958).
(9) T. C. Waddington and F. Klanberg, *Naturwissenschaften*, 20, 578 (1959).
(10) W. Kynaston and H. S. Turner, *Proc. Chem. Soc.*, 304 (1958).
(11) T. C. Waddington and J. A. White, *Proc. Chem. Soc.*, 1960, 85.
(12) W. Kynaston, B. E. Larcombe, and H. S. Turner, *J. Chem. Soc.*, 1960, 1772.
(13) J. R. Partington and A. S. Whynes, *J. Chem. Soc.*, 1949, 3135.
(14) H. W. B. Roozeboom, "Die heterogenen Gleichgewichte vom Standpunkt der Phasenlehre," Verlag Friedr. Vieweg, Braunschweig, 1919, 2, 175.

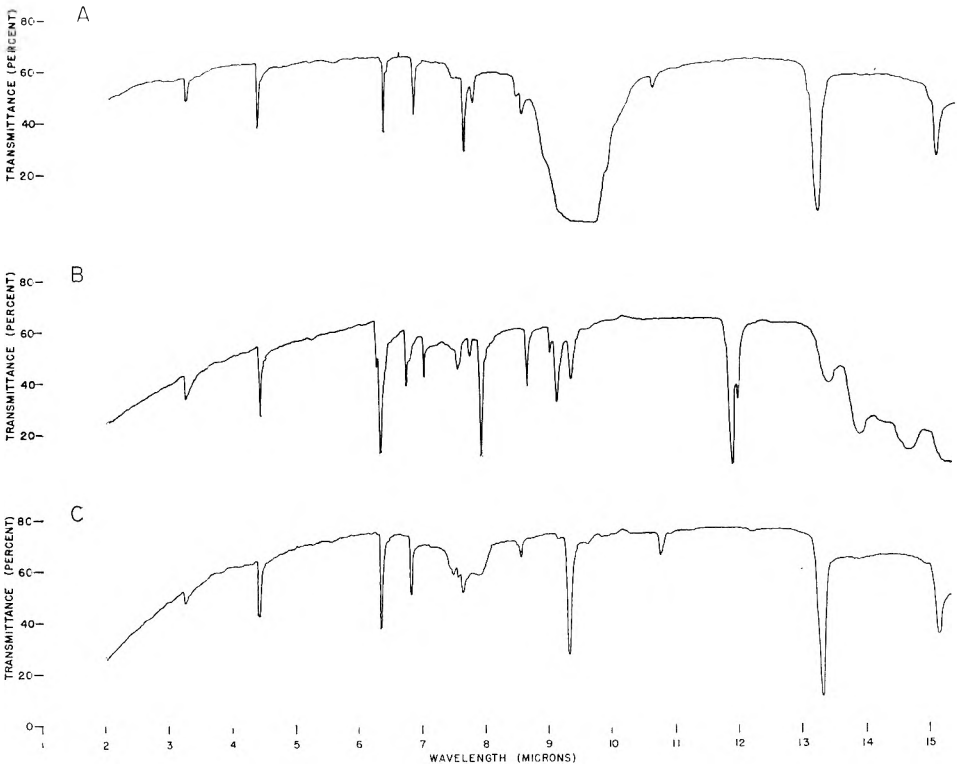
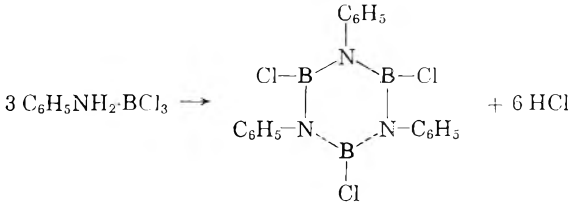


Fig. 1. (A) Phenyldiazonium tetrafluoroborate $C_6H_5N_2^+BF_4^-$, (B) phenyldiazonium tetrachloroborate $C_6H_5N_2^+BCl_4^-$, (C) phenyldiazonium tetrabromoborate $C_6H_5N_2^+BBr_4^-$

corresponding tetrafluoroborates. The equimolar amount of water, formed in the diazotization reaction, consequently tends to decompose the complexes. Therefore, it is necessary to control the temperature carefully and to remove the diazonium salts as quickly as possible from the reaction mixture. Another reason for the need of carefully regulating the temperature and not allowing it to rise above $-5°$ is related to the thermal decomposition of the nitrosonium tetrachloroborate to nitrosyl chloride and boron trichloride. The released boron trichloride reacts with aniline to form a 1:1 addition compound, which, on thermal decomposition, yields triphenyl trichloroborazole.[15]



An alternate way of preparation of aryldiazonium tetrachloroborates was found by treating primary aromatic amines with the 1:1 complex of nitrogen trioxide with boron trichloride. This complex, which is a crystalline white solid is easily formed by mixing at low temperatures dichlorodifluoromethane (Freon 12) solutions of nitrogen trioxide and boron trichloride. Its structure in analogy with the $N_2O_3 \cdot BF_3$ complex isolated and investigated by Backman[16] is suggested to be

$$BCl_3 + ON{:}NO_2 \longrightarrow (Cl_3B \longleftarrow NO_2)^-NO^+$$

and acts as a powerful nitrosating agent. The corresponding aryldiazonium tetrachloroborates are formed in high yields, but are difficult to obtain in pure form, because that equimolar amount of water formed in the diazotation reaction tends to hydrolyze the complexes and the products are consequently contaminated with boric acid. Boric acid contamination is also due to the fact that the $N_2O_3 \cdot BCl_3$ complex is fairly unstable, decomposes slowly at room temperature to nitrosyl chloride and boron trioxide.

To overcome the difficulty of the decomposing action of the water formed in direct diazotation a simple method was found for the preparation of diazonium tetrachloroborates. When primary aromatic amines react with nitrosyl chlorides, diazonium chlorides are formed.[17] The diazonium chlorides can be isolated as relatively stable solids and handled without difficulty under nonaqueous inert solvents such as hydrocarbons. When aryldiazonium chlorides were treated in a suspension of

(15) R. C. Jones and C. R. Kinney, *J. Am. Chem. Soc.*, 61, 1378 (1939).

(16) G. B. Bachman and T. Hokama, *J. Am. Chem. Soc.*, 79, 4370 (1957).

(17) Pabst and Girard, *Ber.*, 12, 365 (1879); Ger. Patent 6034; Brit. Patent 2811 (1878).

TABLE I

ARYLDIAZONIUM TETRACHLOROBORATES $ArN_2^+BCl_4^-$

Ar	Yield, %	Dec. Point	Cl %		N % (as N_2 in Diazonium Salt)	
			Calcd.	Found	Calcd.	Found
Phenyl	96	85–87	55.1	54.6	10.9	10.8
o-Tolyl	92	35–37	52.2	51.4	10.3	10.5
p-Tolyl	89	87	52.2	51.9	10.3	10.1
o-Nitrophenyl	91	90–92	46.9	45.8	9.2	9.8
m-Nitrophenyl	83	109	46.9	45.8	9.2	9.6
p-Nitrophenyl	89	101	46.9	46.0	9.2	9.3
m-Bromophenyl	78	33–35	42.1	41.3	8.3	8.5
p-Fluorophenyl	84	106	51.4	50.8	10.2	9.9

carbon tetrachloride and petroleum ether at −15 to −10° with boron trichloride, the corresponding aryldiazonium tetrachloroborates were formed with an almost quantitative yield.

$$ArN_2^+Cl^- + BCl_3 \longrightarrow ArN_2^+ BCl_4^-$$

Properties and yields of the preparation aryldiazonium tetrachloroborates are summarized in Table I. The infrared spectra of the diazonium tetrachloroborates resemble those of the aryldiazonium tetrafluoroborates having a characteristic N≡N stretching vibration at 2260 cm.$^{-1}$ and a broad band corresponding to the BCl_4^- between 630 and 750 cm.$^{-1}$

Lappert first proved the existence of the tetra bromoborate ion in pyridinium tetrabromoborate.[6] Alkylammonium tetrabromoborates were prepared[18] from alkylammonium bromide and boron tribromide in liquid hydrogen bromide. Consequently, an attempt was made by us to extend investigations on the preparation of aryldiazonium tetrabromoborates. Attempts to prepare nitrosonium tetrabromoborate from nitrosyl bromide and boron tribromide were unsuccessful. Although there is proof of complex formation upon mixing the components in Freon 12 solution, no uniform stable compound could be isolated. It was, therefore, not possible to try the reaction of primary aromatic amines with the nitrosonium salt.

Aryldiazonium tetrabromoborates were first successfully obtained when we reacted primary aromatic amines with the 1:1 complex of dinitrogen trioxide with boron tribromide. The complex, a crystalline solid, somewhat brownish in color due to possible bromine or nitrosyl bromide contamination, is formed in a very exothermic reaction when equimolar quantities of nitrogen trioxide and boron tribromide are treated in Freon 12 (CCl_2F_2) solution at low temperature. The complex decomposes slowly at room temperature to nitrosyl bromide and boric oxide. The obtained aryldiazonium tetrabromoborates were however not pure and contained always boric oxide as contamination, formed by hydrolysis through the water formed in the diazotation reaction or decomposition of the $N_2O_3 \cdot BBr_3$ complex.

To obtain aryldiazonium tetrabromoborates in pure form, an analogous way to the one applied for the preparation of aryldiazonium tetrachloroborates was found suitable.

Nitrosyl bromide makes it possible to prepare and isolate diazonium bromides in a manner similar to that used with nitrosyl chloride. Aryldiazonium bromides are formed when primary aromatic amines react with nitrosyl bromide.

$$ArNH_2 + NOBr \longrightarrow ArN_2^+Br^- + H_2O$$

The diazonium bromides can be isolated as relatively stable solids and handled without difficulty under an inert solvent such as a carbon tetrachloride–petroleum ether mixture. When aryldiazonium bromides reacted with boron tribromide in a suspension of carbon tetrachloride-petroleum ether mixture, the corresponding aryldiazonium tetrabromoborates were formed.

$$ArN_2^+Br^- + BBr_3 \longrightarrow ArN_2\,BBr_4^-$$

Properties and yields of the aryldiazonium tetrabromoborates prepared are shown in Table II. The infrared spectra of the aryldiazonium tetrabromoborates resemble those of the diazonium tetrafluoroborates and tetrachloroborates. The characteristic N≡N stretching vibration is at 2257 cm.$^{-1}$ Using sodium chloride optics, no characteristic band of the BBr_4^- anion was observed. The asymmetric stretching vibration of the anion is to be expected in the 590 cm.$^{-1}$ [11] region.

EXPERIMENTAL

All operations were carried out with the usual precautions to exclude moisture.

Nitrosonium tetrachloroborate. A solution of 6.5 g. (0.1 mole) nitrosyl chloride in 100 ml. of dichlorodifluoromethane (Freon 12) was added to a solution of 11.7 g. (0.1 mole) boron trichloride in 100 ml. Freon 12 over a period of 10 min. with constant stirring at −50°. An orange colored precipitate was formed. The solvent was evaporated and the product vacuum dried at −20° to remove any excess of the reagents. The yield was 16.2 g. (89%) of colorless, crystalline complex. Thermal decomposition of the material took place at 24–25° resulting in gaseous nitrosyl chloride and boron trichloride.

Anal. Calcd. for $NOBCl_4$ (182.7): Cl, 77.6; N, 7.7. Found: Cl, 76.9; N, 7.6.

(18) T. C. Waddington and J. A. White, *Proc. Chem. Soc.*, 85 (1960).

TABLE II

Ar	Yield, %	Dec. Point	Br %		N % (as N_2 in diazonium salt)	
			Calcd.	Found	Calcd.	Found
Phenyl	91	82	73.4	72.8	6.4	6.2
p-Tolyl	87	90–91	72.2	71.3	6.2	6.1
o-Nitrophenyl	83	100	66.5	65.8	5.8	5.5
p-Fluorophenyl	92	128–134	70.7	69.8	6.2	6.0

Phenyldiazonium tetrachloroborate from aniline and nitrosonium tetrachloroborate. To a stirred suspension of 20 g. (0.11 mole) of nitrosonium tetrachloroborate and 150 ml. of toluene maintained at −10° was added a solution of 9.3 g. (0.1 mole) of aniline in 100 ml. of toluene over a period of 20 min. Stirring was continued at −10° for 40 min. The pale yellow precipitate was filtered, washed with cold (0°) toluene and petroleum ether successively and dried in vacuum at 25° to remove solvents and any unchanged nitrosonium tetrachloroborate. The yield was 91%. Thermal decomposition point: 84–85°.

Anal. Calcd. for $C_6H_5N_2BCl_4$(257.8): Cl, 55.1; N, 10.9. Found: Cl, 54.4; N, 10.3.

$N_2O_3 \cdot BX_3$ (X = Cl, Br). A solution of 0.1 mole of boron trihalide in 100 ml. of difluorodichloromethane (Freon 12) was added dropwise to a continuously agitated solution of 7.6 g. (0.1 mole) of nitrogen trioxide in 100 ml. Freon 12 at −78°. Immediately an off yellow colored precipitate is formed in the strongly exothermic reaction. The solvent was then pumped off under slightly reduced pressure. A practically colorless crystalline complex remained, which based on gravimetric determination of the halogen content after hydrolysis is a 1:1 N_2O_3:BX_3 complex.

Phenyldiazonium tetrachloro- and tetrabromoborate from aniline and $N_2O_3 \cdot BX_3$. To a stirred suspension of 0.12 mole of $N_2O_3 \cdot BX_3$ complex and 150 ml. of Freon 12 maintained at −30° was added a solution of 9.3 g. (0.1 mole) of aniline in 100 ml. of Freon 12 over a period of 15 min. Stirring was continued for another half hour. The pale yellow precipitate was then filtered, washed with Freon 12 and dried in vacuum. No attempt was made to purify the obtained diazonium salts from boric acid impurity. N% for $C_6H_5N_2BCl_4$, calculated 10.9, found 10.2, for $C_6H_5N_2BBr_4$, calculated 6.4, found 5.8.

Anal. Calcd. for $C_6H_5N_2BCl_4$:N, 10.9. Found: 10.2. Calcd. for $C_6H_5N_2BBr_4$: N, 6.4. Found: 5.8.

Aryldiazonium chlorides. A solution of 9.3 g. (0.1 mole) of the corresponding aminobenzene in 50 ml. of chloroform was added with stirring to a solution of 9.8 g. (0.15 mole) of nitrosyl chloride in 100 ml. of chloroform and 100 ml. of petroleum ether at −15 to −18° over a period of 30 min. The resulting suspension was filtered, the solid diazonium salt washed successively with cold chloroform (−15 to −18°) and petroleum ether, yielding a white amorphous material. Aryldiazonium chloride dissolved in the filtrate was precipitated by the evaporation of excess nitrosyl chloride, in vacuum, below 0° and was added to the previously obtained material after filtering and washing. The salts could be handled and stored safely in an inert organic solvent such as petroleum ether below 0°. Yields, calculated on the amounts of amino benzene used, were 72–89%.

Aryldiazonium tetrachloroborates from aryldiazonium chlorides and boron trichloride. Boron trichloride (25.3 g., 0.22 mole) was introduced over a period of 30 min. into a stirred suspension of 0.1 mole of the corresponding aryldiazonium chloride, 100 ml. of chloroform and 100 ml. of petroleum ether maintained at −10 to −18°. Stirring was continued for 1 hr. while the temperature of the mixture was allowed to rise to 20°. The off-white product was filtered, washed with petroleum ether, and dried in vacuum. Data on the aryldiazonium tetrachloroborates obtained are given in Table I.

Nitrosyl bromide. A rapid stream of nitric oxide was introduced into 40 g. (0.25 mole) bromine at −7 to −18° for a period of 1 hr., resulting in a weight increase of 6.8 g. (0.23 mole). A fraction of the product boiling between −5 and + 10° was removed by distillation and refractionated giving a product b.p. −4–2°, which was found by infrared spectroscopy to be pure nitrosyl bromide. Yield, calculated on the amount of bromine used, was 14.3%.

Aryldiazonium bromides. A solution of 9.3 g. (0.1 mole) of the corresponding aniline in 50 ml. of chloroform was added to a solution of 16.5 g. of nitrosyl bromide in the mixture of 100 ml. chloroform and 100 ml. of petroleum ether at −15 to −18° during a period of 30 min. Excess nitrosyl bromide was evaporated from the solution in vacuum at −5° to 0° and the precipitate was removed by filtration and washed with cold (−18°) petroleum ether. Yields of the obtained diazonium bromides were 72–86%.

Aryldiazonium tetrabromoborates. A 30-g. (0.12 mole) sample of boron tribromide was added over a period of 30 min. to a stirred suspension of 0.1 mole aryldiazonium bromide, 100 ml. of chloroform and 100 ml. of petroleum ether at −18° to −10°. Stirring was continued for 1 hr. while the temperature was allowed to rise to 20°. The pale pink product was filtered, washed with petroleum ether and dried in vacuum. Data on the obtained aryldiazonium tetrabromoborates are given in Table II.

The infrared spectra were obtained on a Perkin-Elmer Model 221 Spectrometer, using sodium chloride optics, as Nujol Fuorolube mulls.

Acknowledgment. The authors are indebted to Dr. Denys Cook for obtaining and interpreting the infrared spectrum.

SARNIA, ONT., CANADA

[CONTRIBUTION FROM THE ORGANIC BASIC RESEARCH DEPARTMENT, THE DOW CHEMICAL CO.]

The Addition of Chlorine to Acrylonitrile

N. B. LORETTE

Received October 21, 1960

The type of products obtained when chlorine is added to acrylonitrile is dependent upon the presence or absence of hydrogen chloride during the reaction. The radiation of a tungsten lamp between 3000 and 4000 Å is the most effective radiation range for catalyzing the addition of chlorine to acrylonitrile.

The literature describing the conditions and products for the addition of chlorine to the double bond of acrylonitrile presents conflicting data. Sumner[1] has stated in a patent that chlorine reacts with acrylonitrile in the presence of visible light and in the absence of oxygen and water to give a 65 to 79% yield of 2,3-dichloropropionitrile. He reports that if solvents were used the desired molar amount of chlorine was about one third the amount of acrylonitrile present as the use of a higher ratio of chlorine favored the formation of by-products. Emphasis was placed on the need for anhydrous conditions. Yet the effect of a small amount of water did not appear to be a sufficient reason for the absence of 2,3-dichloropropionitrile in the products when the work of D'Ianni[2] is considered. In his study of the action of chlorine water on acrylonitrile, D'Ianni obtained a 26% yield of 2,3-dichloropropionitrile as a by-product when he added chlorine to a solution of one mole of acrylonitrile dissolved in twenty-two moles of water. Krzikalla and Flickinger[3] have stated that "chlorination of acrylonitrile with two atoms of chlorine does not yield 2,3-dichloropropionitrile as expected, but a mixture of about one half mole of 3-chloropropionitrile and one half mole of 2,2,3-trichloropropionitrile." A similar statement was made in a patent by Clifford and D'Ianni.[4]

Brintzinger, Pfannstiel, and Koddebusch[5] reported a 95% yield of 2,3-dichloropropionitrile and 100% acrylonitrile conversion when chlorine was added in the dark to acrylonitrile (1.04 moles) in the presence of pyridine (0.18 mole). This work has been repeated in this laboratory but their very high yield was not achieved. It is important in this procedure that all of the pyridine be removed by the water wash as only trace amounts of pyridine hydrochloride causes continuous dehydrohalogenation of 2,3-dichloropropionitrile to 2-chloroacrylonitrile during distillation.

Since published reports are conflicting, a detailed study of the chlorination of acrylonitrile was undertaken. It is now evident that the conditions of chlorination may be altered to obtain two kinds of products: (1) A mixture of 3-chloropropionitrile and 2,2,3-trichloropropionitrile, and (2) 2,3-dichloropropionitrile.

The concentration of hydrogen chloride in the chlorination mixture was an important factor in determining the nature of the product formed. When acrylonitrile was treated with chlorine and chlorination was continued after the mixture became saturated with hydrogen chloride, the product was a mixture of 3-chloropropionitrile and 2,2,3-trichloropropionitrile which on prolonged chlorination led to high yields of 2,2,3-trichloropropionitrile. When the reaction was stopped before the solution became saturated with hydrogen chloride, the major product was always 2,3-dichloropropionitrile.

EXPERIMENTAL

Influence of hydrogen chloride on the reaction. Since the reaction proceeds very slowly in the dark, visible light (150-watt Sylvania bulb with built-in reflector) was employed as specified by Sumner.[1]

Commercial acrylonitrile that contained 0.5 to 0.7% water was used in all experiments.

The experiments were carried out in a cylindrical Pyrex reactor that was placed in and against the side of a larger Pyrex beaker which contained ice water. A magnetic stirrer was used in the reactor. The light source was placed 6 inches away from the section where the beaker and reactor touched. Chlorine was added to a 200-ml. (3.3 moles) charge of acrylonitrile at a rate of 16–18 g./hr. and 8-ml. samples were withdrawn at half-hour intervals. These were analyzed by infrared spectroscopy by measuring the intensity of the band at 11.0 μ for 3-chloropropionitrile, 13.3 μ for 2,2,3-trichloropropionitrile, and 13.6 μ for 2,3-dichloropropionitrile. Several runs were made, and the results of a typical run are given in Fig. 1. In each run hydrogen chloride was evolved when, or just after, the maximum concentration of 2,3-dichloropropionitrile was reached. The 3-chloropropionitrile appeared at approximately the same time.

If the accumulation of hydrogen chloride is a major factor in determining the course of the reaction, the addition of a base to neutralize the acid as it forms should make possible a higher conversion of acrylonitrile to 2,3-dichloropropionitrile. An experiment was run exactly as before but with 20 ml. (0.25 mole) of pyridine added to the initial acrylonitrile charge. The point of attainment of saturation with hydrogen chloride and corresponding appearance of 3-chloropropionitrile and 2,2,3-trichloropropionitrile was delayed by more than 2 hr., as shown in Fig. 2.

To determine the effect of hydrogen chloride in a direct manner, 11 g. of the gas was added (with cooling) to 200 ml. of acrylonitrile in 2 min. This was immediately followed

(1) J. K. Sumner, U. S. Patent 2,390,470 (1945).

(2) J. D'Ianni, U. S. Patent 2,231,360 (1941).

(3) H. Krzikalla and E. Flickinger, Office of the Publication Board, PB Report 638.

(4) A. M. Clifford and J. D. D'Ianni, U. S. Patent 2,384,889 (1945).

(5) H. Brintzinger, K. Pfannstiel, and H. Koddebusch, *Angew. Chem.*, A60, 311 (1948).

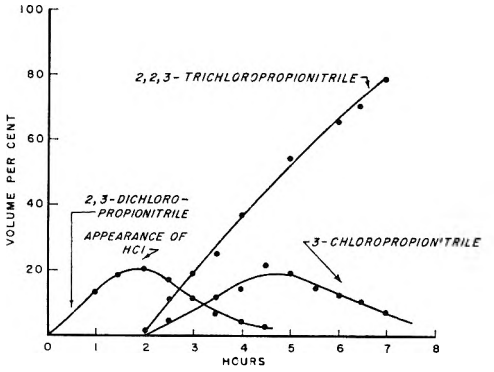


Fig. 1. Effect of time on distribution of products of the reaction of acrylonitrile and chlorine

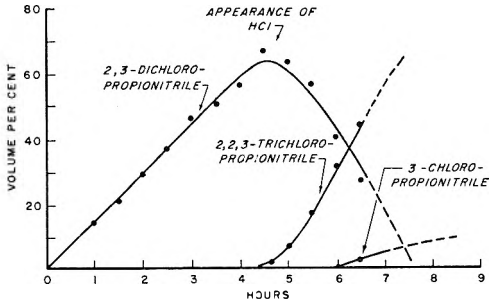


Fig. 2. Effect of time on distribution of products of the reaction of chlorine and acrylonitrile containing pyridine

by the addition of chlorine at a rate of 16–18 g./hr. in the presence of light from the 150-watt lamp. At the end of 30 min. the major product was 2,2,3-trichloropropionitrile, the minor product was 3-chloropropionitrile, and there was neither chlorine nor 2,3-dichloropropionitrile present.

In order to establish the effect of hydrogen chloride on further chlorination of 2,3-dichloropropionitrile, 6 g. of chlorine was dissolved in 200 g. of the compound. This solution was left at room temperature, in the dark, for 4 hr. and no reaction was noted. A like sample of 2,3-dichloropropionitrile was first saturated with hydrogen chloride and then chlorine was added (cooling was required immediately). In 4 hr. all of the 2,3-dichloropropionitrile was converted to 2,2,3-trichloropropionitrile. These two experiments were repeated starting with 3-chloropropionitrile and the results were the same.

Fig. 1 indicates that the relative rate of chlorination of 2,3-dichloropropionitrile is much higher than that of 3-chloropropionitrile. The 3-chloropropionitrile is chlorinated to 2,2,3-trichloropropionitrile but the concentration of the intermediate 2,3-dichloropropionitrile is not great enough to be detected by infrared spectrometry. Results of chlorinating a mixture of equal volumes of 2,3-dichloropropionitrile and 3-chloropropionitrile (mole ratio: 6.7 to 5.4, respectively) are plotted in Fig. 3. The reaction mixture was first saturated with hydrogen chloride and then chlorine was added at a constant rate in the absence of light. During the time (1 hr.) it took to chlorinate 30% by volume of 2,3-dichloropropionitrile only 2% of the 3-chloropropionitrile was chlorinated.

Identification of the photochemically effective radiation. Since the tungsten lamp that was used emitted radiation over a broad portion of the spectrum, standard glass radiation filters were used to locate the most effective portion of the spectrum. A piece of aluminum foil shaped like a funnel was used as a means of channeling the light through the filter. The 150-watt bulb was placed in the large end of the funnel and 6 inches away from the small end where one of

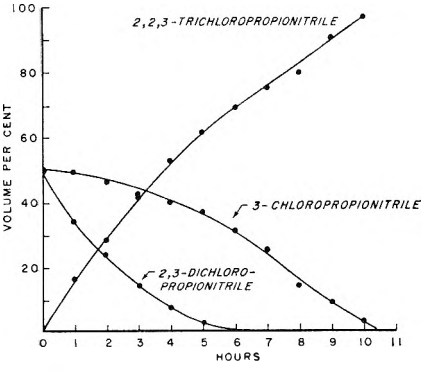


Fig. 3. Effect of time on distribution of the products of the reaction between chlorine and 2,3-dichloropropionitrile and 3-chloropropionitrile in the presence of hydrogen chloride and the absence of light

the standard 2″ × 2″ glass filters was placed. Thus the light passed through the filter, Pyrex beaker, and reactor. In each run 200 ml. of acrylonitrile was used and chlorine was added at a rate of 12–14 g./hr. for 35 min. In all runs there was an excess of chlorine. The composition of the sample was immediately determined by infrared measurements. The results are in Table I. (A small amount[6] of radiation is emitted by the tungsten lamp between 2800 and 3100 Å and no measure of its effectiveness was made.)

TABLE I

EFFECT OF LIGHT ON PRODUCT DISTRIBUTION

Filter No.	Wave Length[a]	Relative Concentration: 2,3-Dichloropropionitrile	Relative Concentration: 2,2,3-Trichloropropionitrile
Complete darkness	—	5	0
2540[b]	7500	5	5
3389[b]	4000	50	5
7380[b]	3400	65	0
Optical Pyrex	3100	100[c]	0

[a] The number indicates the lower limit in angstroms of 90% of the radiation. [b] Corning Glass Co. [c] The conditions of this experiment gave the highest concentration (actual 4% vol.) of 2,3-dichloropropionitrile and this was assigned an arbitrary value of 100.

Preparation of 2,3-dichloropropionitrile in a solvent. Three moles of chlorine was added in 1 hr. to 3 moles of acrylonitrile and 1 g. of hydroquinone dissolved in 500 ml. of carbon tetrachloride. An ice water bath was used to maintain a reaction temperature of 10–25°. The solution was illuminated with the lamp placed 4 inches from the reactor. The mixture was stirred an additional 0.5 hr. after the addition of chlorine was stopped. The carbon tetrachloride was removed by distillation at 200 mm. and then the distillation was continued at 7–10 mm. to obtain the product. The yield of 2,3-dichloropropionitrile was 75%.

Preparation of 2,3-dichloropropionitrile without a solvent. To a solution of 2 g. of hydroquinone in 11.9 moles of acrylonitrile was added 150 g. (2.1 moles) of chlorine in 70 min. The reaction mixture was cooled with an ice water bath and illuminated with a 150-watt bulb. The light was left on for 20 min. after the addition of chlorine was stopped.

(6) L. R. Koller, *Ultraviolet Radiation*, John Wiley and Sons, Inc., New York, N. Y., 1952, p. 101.

TABLE II

PHYSICAL PROPERTIES OF THE CHLOROPROPIONITRILES

	3-Chloropropionitrile	2,3-Dichloropropionitrile	2,2,3-Trichloropropionitrile
B.p. (10 mm.)	59°	58°	47°
B.p. (50 mm.)	93	91	79
B.p. (100 mm.)	110	108	96
d_{25}	1.137	1.327	1.426
n_D^{25}	1.4360	1.4633	1.4655
		(Literature)	
B.p.	75–76°/20 mm.[9]	61°/13 mm.[5]	53°/14 mm.[5]
		80°/25 mm.[2]	80–81°/63 mm.[8]
		86–87°/36 mm.[1]	156–157°/atm.[7]
Density	1.1272/20°[9]	1.303/25°[2]	
Refractive index	n_D^{20} 1.4370[9]	n_D^{26} 1.4638[2]	n_D^{20} 1.4677[7]

The reaction mixture was first distilled at 150 mm. and 8.5 moles of unchanged acrylonitrile was recovered. Then 1.5 moles of 2,3-dichloropropionitrile was obtained at 8 mm. pressure. The distillation residue appeared to be polymerized acrylonitrile. The 44% yield of 2,3-dichloropropionitrile based on unrecovered acrylonitrile undoubtedly could be improved.

Pyridine-catalyzed preparation of 2,3-dichloropropionitrile. Ten moles of chlorine was added at a rate of 1.5–2.0 moles/hr. to a stirred mixture of 10 moles of acrylonitrile and 100 ml. (1.24 moles) of pyridine. External cooling was used and the reaction was run in the dark. During the first hour a very viscous lower layer formed which was difficult to stir. This layer gradually disappeared. After all of the chlorine had been added, the crude reaction product was washed four times with 800-ml. portions of water, dried over calcium chloride and distilled at 8–10 mm.; yield of 2,3-dichloropropionitrile was 69%.

Preparation of 2-chloroacrylonitrile. The pyridine-catalyzed preparation was repeated but the reaction material was not water-washed. It was heated under reflux at 50 mm., the flask temperature was not allowed to exceed 90°. The 2-chloroacrylonitrile (b.p. 20°, 50 mm.) which was continuously formed was allowed to escape through the condenser and was collected in a large Dry Ice trap. The hydrogen chloride passed out of the system through a water aspirator as it was formed. The material caught in the Dry Ice trap was redistilled at 150 mm. to give a 60% yield of 2-chloroacrylonitrile, b.p. 44° (150 mm.), b.p. 88°, (760 mm.), d_{25} 1.088, n_D^{25} 1.4284 (lit.[7] b.p. 88°, n_D^{20} 1.4294).

Physical properties of the chloropropionitriles. The physical properties of the three chloropropionitriles prepared in this investigation are in Table II. The properties were determined on samples that were 99% pure as shown by vapor chromatography. The three chloropropionitriles did not form azeotropes with each other. Mixtures of 3-chloropropionitrile and 2,3-dichloropropionitrile could not be separated by distillation owing to the nearness of their boiling points. It is interesting to note that as the number of chlorine atoms in the molecule increased, the boiling point decreased.

DISCUSSION

The cursory use of light filters indicates that the most effective wave length for promoting the addition reaction between chlorine and acrylonitrile is between approximately 3000 to 4000 Å instead of the visible region as previously reported.[1] This presents a combination of opposed factors that must be considered when chlorine is added to the double bond of acrylonitrile. Without the radiation the addition is extremely slow. Radiation at about 3100 Å accelerates the addition, but it also promotes the undesired substitution of hydrogen by chlorine. Ultraviolet light is known also to cause acrylonitrile polymerization, which in this case is detrimental.

The use of pyridine[6] as a catalyst is unique because it both catalyzes the addition reaction and eliminates the hydrogen chloride. That pyridine hydrochloride will effect continuous dehydrohalogenation of 2,3-dichloropropionitrile to give 2-chloroacrylonitrile seems unusual; however, Spence[7] points out that a catalytic amount of an aliphatic amine hydrohalide will do the same.

When light was used for the reaction catalyst, the following scheme is proposed as the reaction path:

$$Cl_2 \xrightarrow{uv} 2Cl\cdot \quad (1)$$

$$CH_2{=}CHCN + Cl\cdot \longrightarrow CH_2ClC\dot{H}CN \quad (2)$$

$$CH_2ClC\dot{H}CN + Cl_2 \longrightarrow CH_2ClCHClCN + Cl\cdot \quad (3)$$

$$CH_2ClCHClCN + Cl\cdot \longrightarrow CH_2ClC\dot{C}lCN + HCl \quad (4)$$

$$CH_2ClC\dot{C}lCN + Cl_2 \longrightarrow CH_2ClCCl_2CN + Cl\cdot \quad (5)$$

$$CH_2ClC\dot{H}CN + HCl \longrightarrow CH_2ClCH_2CN + Cl\cdot \quad (6)$$

Step (1) can occur in the presence of ultraviolet radiation or blue visible light and is the initiation step. The chlorine radical then adds as in steps (2) and (3) to give 2,3-dichloropropionitrile. Step (4) leads to the formation of hydrogen chloride and loss of 2,3-dichloropropionitrile. Step (6) shows how as the concentration of hydrogen chloride builds up the formation of 3-chloropropionitrile becomes appreciable as does 2,2,3-trichloropropionitrile.

The presence of hydrogen chloride was shown to catalyze the chlorination of 3-chloropropionitrile and 2,3-dichloropropionitrile in the dark. (Kabisch[10] disclosed that acetonitrile saturated with hydrogen chloride was chlorinated readily in the dark to

(7) L. U. Spence, U. S. Patent 2,385,550 (1945).

(8) J. G. Lichty, U. S. Patent 2,231,838 (1941).

(9) A. Brylants, M. Tits, C. Dieu, and R. Gauthier, *Bull. soc. chim. Belg.*, **61**, 366–392 (1952).

(10) G. Kabisch, U. S. Patent 2,745,868 (1956).

trichloroacetonitrile.) These chlorinations may be interpreted on an ionic basis as follows:

$$HCl + CH_2{=}CHCN \longrightarrow CH_2ClCH_2CN \quad (7)$$

$$CH_2ClCH_2CN + H^+ \longrightarrow CH_2ClCH_2\overset{+}{C}{=}NH \overset{-H^+}{\rightleftharpoons} CH_2ClCH{=}C{=}NH \xrightarrow{Cl_2} CH_2ClCHClCN + HCl \quad (8)$$

$$CH_2ClCHClCN + H^+ \longrightarrow CH_2ClCHCl\overset{+}{C}{=}NH \overset{-H^+}{\rightleftharpoons} CH_2ClCCl{=}C{=}NH \xrightarrow{Cl_2} CH_2ClCCl_2CN + HCl \quad (9)$$

Step (7) is known to take place in the absence of light.[11] The rate of step (9) should be greater than step (8) because the carbonium ion of step (9) should eject a proton more readily than the corresponding carbonium ion of step (8). This is in agreement with the observation that the 2,3-dichloropropionitrile is chlorinated at a higher rate than 3-chloropropionitrile.

Acknowledgment. The author wishes to thank J. H. Brown, Jr., Professor Lewis Hatch, and Professor Harry Walborsky for their advice and help.

FREEPORT, TEX.

(11) R. Stewart and R. H. Clark, *J. Am. Chem. Soc.*, **69**, 713 (1947).

[CONTRIBUTION FROM THE MONSANTO CHEMICAL CO., RESEARCH AND ENGINEERING DIVISION]

Ozonation of Azo and Azomethine Double Bonds

ROBERT E. MILLER

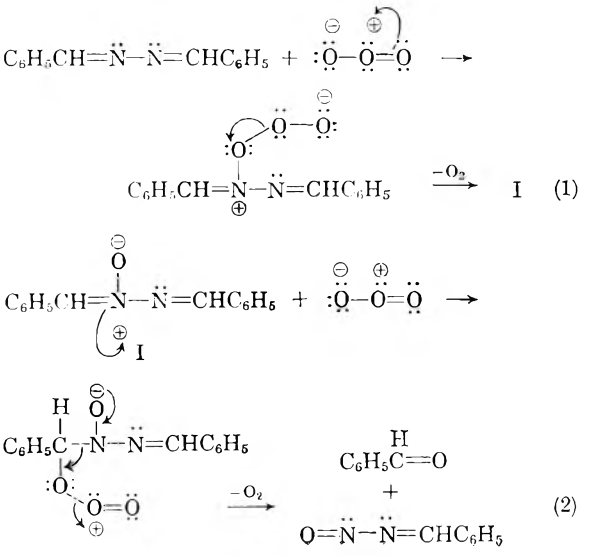
Received October 5, 1960

The ozonolysis of the azomethine double bond with ozone-oxygen mixtures has been investigated. Cleavage was the principal reaction with azines and Schiff bases. Carbonyl compounds were isolated in reasonably good conversions. These reactions were also accompanied by a variety of other products, which are best accounted for by an ozone-initiated autoxidation as a secondary reaction. Oxanilide, formanilide, and *s*-diphenylurea were isolated from the ozonolysis of *N*-cinnamylideneaniline. Azobenzene was unexpectedly resistant to ozonolysis.

The literature[1] indicates significant differences in the ease of ozonolysis of azo and azomethine linkages. An unsuccessful attempt in these laboratories to ozonize azobenzene prompted a further investigation of the reaction of azo and azomethine compounds with ozone-oxygen mixtures. Azobenzene was recovered nearly quantitatively on treatment with one, four and eight molar equivalents of ozone in oxygen mixtures at −40 to 34°. Trace amounts of glyoxal and a compound (isolated as the 2,4-dinitrophenylhydrazone, m.p. 252–255° dec.), possibly salicylaldehyde, were the only products isolated from the water-soluble oils obtained from these reactions (see table). Azoxybenzene formation was not detected. The ozonation reaction is in contrast to the peracetic acid oxidation of azobenzenes which yields azoxybenzenes.[2] However, it has been stated[3] that the ozonation of hydrazobenzene yielded azobenzene without "noteworthy" formation of other products.

The ozonation of benzalazine, on the other hand, resulted in a facile cleavage of the carbon-nitrogen double bond. An excellent conversion of benzaldehyde was obtained (see table). This reaction was characterized by the rapid development of a blue color, attributed to the formation of dinitrogen trioxide, which persisted throughout the oxonation. It has recently been observed that a blue to green color also resulted during the ozonation of nitrones, which was shown to be due to the formation of nitroso compounds.[1b]

Since this coloration does not result during ozonation of Schiff bases, the initial reaction of ozone with benzalazine must involve an electrophilic attack on the nitrogen atom of the carbon-nitrogen double bond followed by the loss of oxygen



(1) The literature is reviewed by (a) P. S. Bailey, *Chem. Revs.*, **58**, 925 (1958); (b) A. H. Riebel, R. E. Erickson, C. J. Ashire, and P. S. Bailey, *J. Am. Chem. Soc.*, **82**, 1801 (1960).

(2) (a) A. Angeli, *Atti. accad. Lincei*, 19, 794 (1910); (b) P. Gagnon and B. T. Newbold, *Can. J. Chem.*, **37**, 366 (1958).

(3) W. Strecker and M. Baltes, *Ber.*, **54B**, 2693 (1921).

TABLE I

OZONATION OF AZO AND AZOMETHINE COMPOUNDS

Compound	Moles	Solvent[a]	Ozone, Moles	Temp.	Products[b] Carbonyl	% Conv.	Other (% Conv.)
Azobenzene	0.05	B	0.06	22–26	—	—	[c,d]
	0.05	B	0.19	30–34	—	—	[d]
	0.02	C	0.17	–40	OCH—CHO[e]	—	—
Benzalazine	0.1	D	0.1	8–12	C_6H_5CHO[f]	61.4	N_2O_3[g]
Cyclohexanone ketazine	0.02	D	0.03	−45	$C_6H_{11}O$	60	N_2O_3[g]
	0.05	A	0.11	−40	$C_6H_{11}O$[h]	36	Dimethyl adipate (17.2)[i]
					$OCH(CH_2)_4CHO$[j]	18.4	
Cinnamalazine	0.05	C	0.1	25	C_6H_5CHO	61	"Cinnamal *N*-formylhydrazone"[k]; unknown, m.p. 196.5–197°[l]
					$C_6H_5CH{=}CHCHO$	—	
	0.59	D	xx	15	C_6H_5CHO	60.4	Benzoic acid (22.5)[m]
					OHC—CHO[e]	—	
N-Benzylideneaniline	0.1	A	0.11	−35	C_6H_5CHO	43	[n]
	0.05	A	0.05	2–6	C_6H_5CHO	60	
N-Benzylidene-*p*-chloroaniline	0.09	D	0.3	−18	C_6H_5CHO	36	*p*-Chloronitrobenzene (10)[o]; "4,4'-dichlorooxanilide"[p]
N-Benzylidene-*p*-nitroaniline	0.1	D	0.3	−18	C_6H_5CHO	41	1,4-Dinitrobenzene (14)[q]; "4,4'-dinitrooxanilide"[r]
N-Cinnamylideneaniline	0.12	D	0.12	18–21	C_6H_5CHO	60.6	Benzoic acid; nitrobenzene[t]; oxanilide (7.6)[u]; s-diphenylurea (28)[v]
					$C_6H_5CH{=}CHCHO$[s]	—	
	0.13	D	0.24	14–17	C_6H_5CHO	55.1	Benzoic acid (26.7); oxanilide (5.7); oxalic acid (16.8)[w]; formanilide (22.3)[x]
					$C_6H_5CH{=}CHCHO$	—	
					OHC—CHO[y]	—	
p-Nitroaniline	0.1	D	0.3	9	—	—	1,4-Dinitrobenzene (17.9); 4,4'-dinitroazobenzene (21.2)[z]

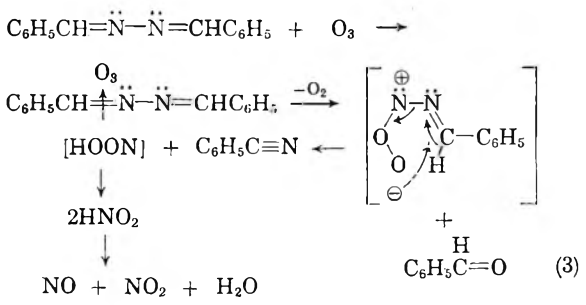
[a] A = methanol; B = acetic acid; C = chloroform; D = ethyl acetate. [b] Where conversion is not indicated only trace amounts of product were isolated. Identification of compounds enclosed in quotations is tentative. [c] Recovery of azobenzene was 78–95% in all three experiments. [d] A 2,4-dinitrophenylhydrazone was obtained from the water-soluble oil, m.p. 252–255° dec. *Anal.* Calcd. for $C_{13}H_{11}N_4O_5$: C, 52.71; H, 4.31; N, 17.62. Found: C, 52.55; H, 4.33; N, 18.31. Salicylaldehyde 2,4-dinitrophenylhydrazone has a reported melting point of 254–255° dec. N. R. Campbell, *Analyst*, **61**, 392 (1936). [e] Dioxime melted at 169–171°. E. C. Barany, E. A. Braude, and M. Pianka, *J. Chem. Soc.*, 1902 (1949), give m.p. 179°. *Anal.* Calcd. for $C_2H_4N_2O_2$: N, 31.85. Found: N, 30.81. [f] Distilled at 44–48° (4 mm.); 2,4-dinitrophenylhydrazone, m.p. 235–237°. [g] The solution developed a blue-green color, which is characteristic of solutions of N_2O_3 in nonpolar solvents. [h] Distilled at 36–40° (10 mm.); 2,4-dinitrophenylhydrazone, m.p. and mixed m.p. 162–163°. [i] Distilled at 96–99° (4 mm.). P. E. Verkade, J. Coops, and H. Hartman, *Rec. trav. chim.*, **45**, 590 (1926) give b.p. 107° (11 mm.). Infrared spectrum is identical with authentic sample. [j] Recovered from aqueous extracts; 2,4-dinitrophenylhydrazone, m.p. 238–240°. R. Pappo, B. S. Allen, R. V. Lemieux, and W. S. Johnson, *J. Org. Chem.*, **21**, 478 (1956), give m.p. 241.2–241.6°. [k] Melted at 150–153° dec. *Anal.* Calcd. for $C_{10}H_{10}N_2O$: N, 16.09. Found: N, 15.98, 15.83. K. v. Auwers and P. Heimke, *Ann.*, 408, 208 (1927), report m.p. of cinnamyl *N*-formylhydrazone as 155–156°. [l] Yellow crystals, insoluble in hot methanol, water, dioxane, ethyl acetate, benzene, and acetone. *Anal.* Calcd. for $(C_6H_7N_3O)_x$: C, 48.00; H, 5.60; N, 33.60. Found: C, 48.54; H, 5.27; N, 32.13, 32.74. [m] M.p. 121–122°. [n] The solid residue after removal of benzaldehyde was separated into two fractions: (A) soluble in benzene, m.p. 105–110° dec. *Anal.* C, 68.5; H, 5.6; N, 6.6. (B) benzene insoluble, m.p. 248–253° dec. *Anal.* C, 67.0; H, 5.7; N, 7.6. (See Ref. 1b, p. 1806.) [o] Melted at 81–83°. Infrared spectrum was identical with authentic specimen. [p] Melted at 289–291°. Infrared spectrum is consistent with this structure. F. D. Chattaway and W. H. Lewis, *J. Chem. Soc.*, **89**, 158 (1906), report m.p. 288°. [q] M.p. and mixed m.p., 174–175°. [r] Melting point, 357–359°. M. J. Bornwater, *Rec. trav. chim.*, **31**, 117 (1912), gives 358–359°. Infrared spectrum is consistent with this structure. [s] Distilled at 105° (4 mm.); 2,4-dinitrophenylhydrazone, m.p. and mixed m.p., 254–255° dec. (Ref. d.) [t] Indicated in benzaldehyde distillate by I.R. bands at 1530 and 1340 cm.$^{-1}$ [u] Melted at 246.5–248.5°. A. D. Macallum, *J. Soc. Chem. Ind.*, **42**, 469T (1923), gives 247–248°. *Anal.* Calcd. for $C_{14}H_{12}N_2O_2$: C, 70.00; H, 5.00; N, 11.68. Found: C, 69.44; H, 4.62; N, 11.25, 11.40. Infrared spectrum identical with reference standard (Sadtler No. 5856). [v] M.p. and mixed m.p., 238–241°. *Anal.* Calcd. for $C_{13}H_{12}N_2O_2$: C, 73.59; H, 5.66; N, 13.21. Found: C, 73.65; H, 5.53; N, 13.60. [w] M.p. 188–189°. [x] M.p. and mixed m.p., 47–48.5°. Distilled at 126–131° (3.5 mm.). O. Schmidt, *Ber.*, **36**, 2476 (1903), gives b.p., 166° (13 mm.); m.p., 47°. Infrared spectrum was identical with reference standard (Sadtler No. 1031B). [y] 2,4-Dinitrophenylhydrazone melted at 320–323° dec. H. J. Lucas and W. T. Stewart, *J. Am. Chem. Soc.*, **62**, 1794 (1940), report m.p. 323° dec. [z] Melted at 219–220.5°. Mixed m.p. with authentic sample was not depressed. O. N. Witt and E. Kopetschini, *Ber.*, **45**, 1134 (1912), report m.p. 222–223°.

to give a nitrone-like structure (I). The formation of the observed products is explained by a second, nucleophilic ozone attack[1b] on the carbon atom of the double bond followed by loss of oxygen (Equation 3).

Repeating the reaction described by Equation 3 on the remaining carbon-nitrogen double bond would yield oxides of nitrogen. Formation of the trioxide, N_2O_3, could occur by two alternate routes. It may be formed directly by oxidation of lower nitrogen oxides (analogous to the formation of nitro compounds from their nitroso precursors[1b,4]),

or indirectly through the decomposition of dinitrogen pentoxide,[5] which can arise by the action of ozone on dinitrogen tetroxide.[6]

The alternate possibility of ozone addition to the carbon-nitrogen double bond, similar to that which occurs on reaction with carbon-carbon double bonds, has been examined. In this event, phenyl cyanide should be formed, according to the sequence:

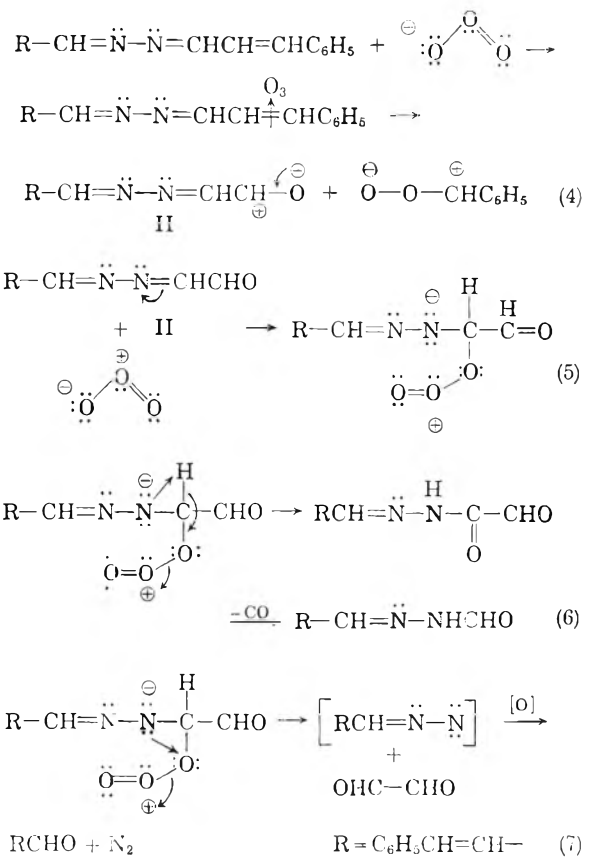


(3)

Phenyl cyanide, however, was not found among the products of this reaction. This result is in accord with the evidence presented by Bailey,[1b] *i.e.*, only one atom of the ozone molecule is utilized during the ozonolysis of Schiff bases and nitrones.

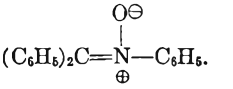
The ozonation of cyclohexanone ketazine in ethyl acetate also produced a blue solution; cyclohexanone was the only isolable product. However, when the ozonation was conducted in methanol, no color developed. This result is consistent with the behavior of dinitrogen trioxide in polar solvents. The isolation of adipaldehyde and dimethyl adipate together with cyclohexanone, indicated a further ozone-initiated radical oxidation of the cyclohexanone by oxygen. The ability of ozone to function as a radical initiator in autoxidations, and especially with ketones, has been reported.[7]

In contrast, the ozonation of cinnamalazine did *not* develop a distinctive blue coloration. Presumably, the initial ozone reaction involved addition to the carbon-carbon double bond. Benzaldehyde and benzoic acid resulted from this reaction (Equation 4). A subsequent nucleophilic attack by ozone at the carbon atom of the carbon-nitrogen double bond of the intermediate (II) is then postulated. This intermediate might undergo (1) loss of oxygen and shift of a proton to yield cinnamal *N*-formylhydrazone (Equation 6), or (2) loss of oxygen and cleavage of the double bond to give glyoxal and cinnamaldehyde (Equation 7). Actually, trace amounts of all three products were isolated.



(4) (5) (6) (7)

Ozonation of *N*-cinnamylideneaniline was investigated in a further attempt to evaluate the differences in the reactivities of exocyclic carbon-nitrogen and carbon-carbon double bonds towards ozone-oxygen mixtures. Ozonolysis of the carbon-carbon double bond was the major reaction, as evidenced by the excellent conversions (55–60%) of benzaldehyde obtained. The formation of small amounts of cinnamaldehyde and nitrobenzene indicated that cleavage of the carbon-nitrogen double bond had also taken place. Nitrobenzene has previously been isolated from the ozonation of benzal nitrone[1b] and from benzophenone nitrone,[8]



Formanilide (III) was isolated in significant amounts from this reaction. The formation of this compound must arise from the nucleophilic attack of ozone on the carbon atom of the carbon-nitrogen double bond of the fragment produced by ozonolysis of the carbon-carbon double bond. Shift of a proton, followed by loss of oxygen, and subsequently, of carbon monoxide, yields formanilide (Equation 9).

An ozone-initiated autoxidation of formanilide (Equation 10) is postulated to account for the

(4) J. S. Belew and J. T. Person, *Chemistry and Industry*, 40, 1246 (1959).

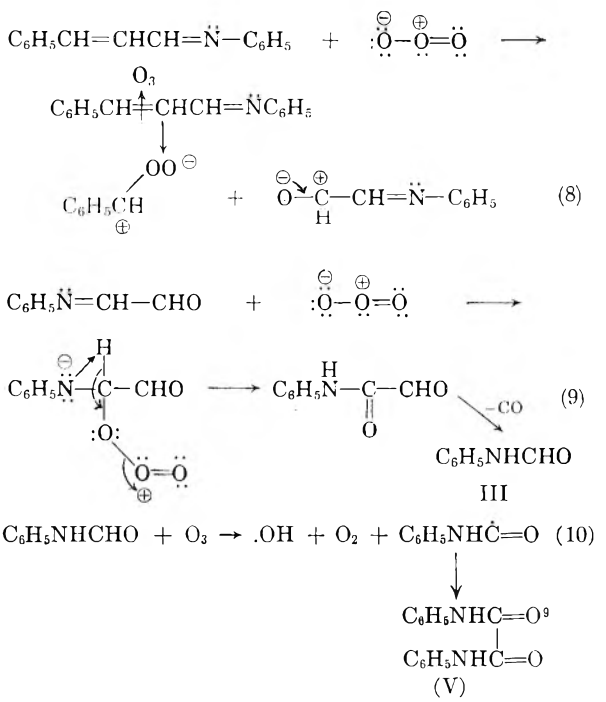
(5) M. Bodenstein, *Z. Phys. Chem.*, 104, 51 (1923).

(6) (a) T. M. Lowry and J. T. Lemon, *J. Chem. Soc.*, 695; (1935) (b) O. R. Wulf, F. Daniels, and S. Karrer, *J. Am. Chem. Soc.*, 44, 2398 (1922); (c) F. Foerester and M. Koch, *Angew. Chem.*, 21, 2216 (1908).

(7) (a) C. C. Schubert and R. N. Pease, *J. Am. Chem. Soc.*, 78, 2044, 5553 (1956); (b) E. Briner, *Advances in Chem. Ser.*, 21, 184 (1959).

(8) H. Staudinger and K. Mischer, *Helv. Chim. Acta*, 2, 554 (1919).

derivation of oxanilide (V) from this ozonation reaction.



(8)

(9)

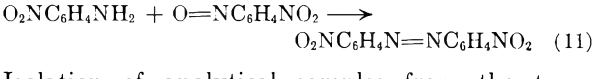
(10)

(V)

s-Diphenylurea was obtained from a single experiment during the ozonation of *N*-cinnamylideneaniline. The formation of this product was not confirmed in subsequent experiments, however.

Ozonolysis of the azomethine bond was also observed with *N*-benzylidene-*p*-chloroaniline and *N*-benzylidene-*p*-nitroaniline. *p*-Chloronitrobenzene and 1,4-dinitrobenzene, respectively, were obtained (10–14%), together with larger amounts (36–56%) of benzaldehyde. Products presumably derived from an ozone-initiated cleavage of the carbon-nitrogen single bond, *i.e.*, 4,4′-dichlorooxanilide and 4,4′-dinitrooxanilide, were isolated in trace amounts. In agreement with previous investigators,[1b,10] 2-phenyloxaziranes were not isolated.

The reaction of *p*-nitroaniline with an ozone-oxygen mixture gave 1,4-dinitrobenzene and *trans*-4,4′-dinitroazobenzene, possibly formed by the reaction:



(11)

Isolation of analytical samples from the tarry reaction product produced by the reaction of ozone-oxygen mixtures with *N*-benzylaniline failed. Previous investigators[4,11] have noted the decomposition of primary and secondary amines by the action of ozone.

EXPERIMENTAL

Materials. Azobenzene, benzalazine (m.p. 92–93°), and cyclohexanone ketazine (m.p. 36–37°) were purchased and recrystallized before use. *N*-Cinnamylideneaniline (m.p. 109°), cinnamalazine (m.p. 175–176°), *N*-benzylideneaniline (m.p. 53–54°), *N*-benzylidene-*p*-chloroaniline (m.p. 64–66°),[12] and *N*-benzylidene-*p*-nitroaniline (m.p. 117–118°)[13] were synthesized by known methods.

Apparatus. The reactor was a cylindrical flask of 300 ml. capacity with a T/S 45/50 joint at the top. Connections for a stirrer, thermometer, and Dry Ice condenser were built into a T/S joint which fitted the top of the reactor flask. A fritted gas inlet tube entered the reactor at the bottom. The ozone source was a Welsbach Model T-3 ozonator. Oxygen pressure to the ozonator was controlled at 8 p.s.i.g. by a Matheson 70A regulator. Oxygen-ozone flow rates from the ozonator were usually 0.25–0.35 cfm. Ozone concentrations were measured by a Welsbach ozone meter, which had previously been standardized by the potassium iodide–sodium thiosulfate procedure for determining ozone concentrations.

General procedure. The reactor was charged with 27 g. (0.13 mole) of *N*-cinnamylideneaniline dissolved in 150 ml. of dry ethyl acetate. The ozonolysis was conducted at 14–17° since the anil crystallized from the solution at lower temperatures. An oxygen-ozone mixture, containing 33–34 mg. ozone/l. of oxygen, was passed through the solution until 0.24 mole of ozone had been absorbed. The yellow solution gradually turned orange; a slight precipitate formed. The reaction mixture was flushed with dry nitrogen and evaporated at room temperature under reduced pressure to about one-third its volume. Ether was added (precipitation occurred) and the solution extracted with 100 ml. of 20% sodium hydroxide solution. In other experiments a 20% sodium sulfite solution was also used. Acidification of the aqueous alkaline solution caused precipitation of benzoic acid (4.2 g.). Oxalic acid (2.0 g.) was recovered by ether extraction of the aqueous acid solution. The residual aqueous solution was treated with 2,4-dinitrophenylhydrazine reagent. A trace of glyoxal bis-2,4-dinitrophenylhydrazone was isolated (see Table I).

The original ether-ethyl acetate extracts were dried over magnesium sulfate. During evaporation of the solvents under reduced pressure, oxanilide (0.8 g.) precipitated. This material was filtered from the liquid residues and recrystallized from benzene. The filtrate was distilled. Benzaldehyde (7.6 g.), cinnamaldehyde (1.0 g.) and a fraction distilling at 126–131° (3.5 mm.) were obtained. A portion of the latter fraction crystallized. This material (2.7 g.) was recrystallized from benzene, and subsequently identified as formanilide.

DAYTON 7, OHIO

(9) The author is indebted to the referee for indicating this possibility. A mechanism analogous to that proposed by Schubert and Pease[7a] might also pertain.

(10) W. D. Emmons, *J. Am. Chem. Soc.*, **79**, 5739 (1957).

(11) W. Strecker and H. Thieneman, *Ber.*, **53**, 2096 (1920).

(12) H. D. Law, *J. Chem. Soc.*, **101**, 160 (1912).

(13) W. v. Miller, J. Plöchl, and G. Rohde, *Ber.*, **25**, 2053 (1895).

[CONTRIBUTION FROM THE METCALF CHEMICAL LABORATORIES OF BROWN UNIVERSITY]

The Action of Diazomethane on Schiff's Bases

PANKAJA K. KADABA AND JOHN O. EDWARDS

Received December 5, 1960

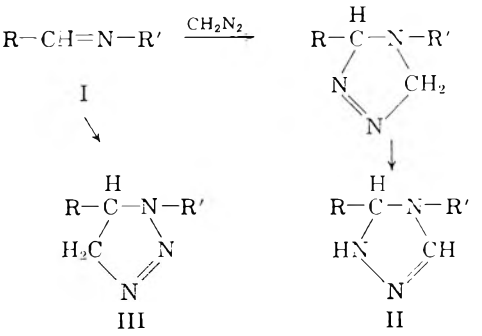
A study of the reaction of diazomethane with various Schiff's bases has been carried out in the hopes of obtaining ethylenimines; the results were largely negative. The addition of diazomethane to benzalanilines to give 1,2,3-triazolines has been investigated with emphasis on the conditions for good yield and on the kinetics. The mechanism of this addition reaction is discussed.

INTRODUCTION

The formation of three-membered ring systems from the reaction of double bond containing compounds and diazomethane derivatives has long been known. From certain olefins, a pyrazoline ring may be formed first and this may then be pyrolyzed to give a cyclopropane.[1] It has also been found[2] that both carbene and dichlorocarbene react with olefins to give cyclopropane derivatives. It is also known that diazomethane adds to the carbonyl group of aldehydes and ketones[3] to give an ethylene oxide or the higher homologous aldehydes and ketones. From the above considerations, the double bond in a Schiff's base might be expected to react with diazomethane either directly or indirectly to form an ethylenimine; with this in view an investigation of the action of diazomethane on Schiff's bases, both aliphatic and aromatic, was undertaken.

The reaction of aliphatic Schiff's bases with diazomethane itself and also with carbenes was studied; the carbene was generated either photolytically or catalytic decomposition of diazomethane was effected by use of boron trifluoride etherate.[4] In none of the cases studied here was it possible to obtain a definite reaction product corresponding to an ethylenimine. Also, no ethylenimine was detected in a petroleum ether solution of benzalaniline and diazomethane which had been exposed to light for four and a half hours. This anil, however, has been shown[5] to add dichlorocarbene (obtained from chloroform and sodium methoxide) to give 1,2-diphenyl-3,3-dichloroethylenimine. Dichlorocarbene obtained by the action of sodium methoxide on hexachloroacetone[6] also reacts with benzalaniline to yield the same ethylenimine.

Diazomethane itself reacts with some anils to give stable addition products. Mustafa[7], who first noticed the reaction, assigned to the addition product a 1,2,4-triazoline structure (*II*) solely on the basis of his observation that when heated or hydrolysed with acid these compounds decomposed with evolution of diazomethane and regeneration of I.



However, the triazoline addition product was later shown to have a 1,2,3-triazoline structure (III) by Buckley.[8] He compared the products obtained by Mustafa with those obtained by the addition of phenyl azide to olefins and found them to have identical melting points and infrared absorption spectra.

Kinetic studies of the addition reactions of diazomethane with various anils have now been carried out along with the synthesis of various substituted triazolines. It was found that water and methanol both catalyze the otherwise slow reaction in ether. The solvents used have a considerable effect on the yield of the reaction; *e.g.*, addition takes place to a greater extent in dioxane than in diethyl ether.

Wolff[9] and later Alder and Stein[10] suggested that the thermal decomposition of 1,5-diphenyl-1,2,3-triazoline yields a mixture of 1,2-diphenylethylenimine and the anil of acetophenone. The ethylenimine as such was not, however, isolated and characterized by these workers. Their conclusion was based on the observation that the product obtained by the pyrolysis of the triazoline had two nitrogen atoms less than the original compound and also that the triazoline was hydrolyzed by acid with evolution of nitrogen and formation

(1) *Cf.* E. P. Kohler and L. L. Steele, *J. Am. Chem. Soc.*, **41**, 1093 (1919).

(2) *Cf.* (a) W. von E. Doering and A. K. Hoffmann, *J. Am. Chem. Soc.*, **76**, 6163 (1954); (b) P. S. Skell and A. Y. Garner, *J. Am. Chem. Soc.*, **78**, 3409 (1956).

(3) F. Arndt and B. Eistert, *Ber.*, **61**, 1107, 1118 (1928); **68**, 196 (1935).

(4) H. Meerwein, *Angew. Chem.*, **A60**, 78 (1948).

(5) E. K. Fields and J. M. Sandri, *Chem. & Ind.*, 1216 (1959).

(6) P. K. Kadaba and J. O. Edwards, *J. Org. Chem.*, **25**, 1431 (1960).

(7) A. Mustafa, *J. Chem. Soc.*, 234 (1949).

(8) G. L. Buckley, *J. Chem. Soc.*, 1850 (1954).

(9) K. L. Wolff, *Ann.*, **394**, 68 (1912).

(10) K. Alder and G. Stein, *Ann.*, **501**, 1 (1933).

of an amino alcohol, which could have been formed from an ethylenimine intermediate. A reinvestigation by us of the pyrolysis of 1,5-diphenyl-1,2,3-triazoline failed to give 1,2-diphenylethylenimine. Careful fractional crystallization of the hydrochlorides obtained by treatment of the pyrolysis product with gaseous hydrogen chloride in ether solution gave only aniline hydrochloride. Thermal decomposition of 1-phenyl-5-(*o*-nitrophenyl)-1,2,3-triazoline in *o*-dichlorobenzene at 140–150° also did not yield an ethylenimine. The reaction product after acid hydrolysis consisted only of aniline, as shown by infrared spectra.

EXPERIMENTAL

Materials. The anils were synthesised by known methods, using condensation of the appropriate aldehydes with the amines. In the case of benzal-*p*-nitroaniline[11] a modified method was used. The mixture of *p*-nitroaniline and benzaldehyde was heated at 150–160° for 8 hr. in the presence of dry nitrogen in an open round-bottom flask, and the water formed in the reaction was allowed to evaporate continuously. The water, if allowed to condense back into the reaction mixture, caused hydrolysis of the anil and a deep yellow product with a considerably lower melting point resulted, from which the pure anil could not be obtained even after repeated recrystallization. All the anils were crystallized from suitable solvents shortly before use and air dried. Benzal-*p*-chloroaniline was dried *in vacuo* at 40–45° for 2 hr. The *o*-nitrobenzaldehyde needed in the preparation of the *o*-nitrobenzal-anilines was made by oxidation of *o*-nitrotoluene.[12]

Syntheses of 1,2,3-triazolines. In a typical reaction, the anil (0.05 mole) was dissolved in an ethereal solution (200 ml.) of diazomethane (0.1 mole) (not dried)[13] and 6 ml. of methanol (reagent grade) added as catalyst. The reaction mixture was then allowed to stand in a stoppered flask at room temperature for 4 days. At the end of this period, the major portion of the ether and unchanged diazomethane was removed by careful distillation. The residue was then cooled, and the sparingly soluble triazoline crystallized out first in preference to the unchanged anil. The triazolines were recrystallized from appropriate solvents as indicated below. All the triazolines melted with vigorous decomposition, evolving gas and forming deep orange-red melts.

When dioxane was used as solvent for the reaction, the anil was dissolved in dioxane containing diazomethane (not dried) and, at the end of 4 days, the reaction mixture was diluted with water until a heavy cloudiness appeared. It was then cooled in ice, when the triazoline was thrown out as a fine crystalline material.

The compounds 1,5-diphenyl-1,2,3-triazoline and 1-phenyl-5-*p*-chlorophenyl-1,2,3-triazoline are known compounds[7,8]; the melting points of our products agreed with the literature values. The six triazolines listed below with their properties are new compounds.

1-p-Nitrophenyl-5-phenyl-1,2,3-triazoline. Pale yellow glistening needle-like crystals from acetone; m.p. 152–153°.

Anal. Calcd. for $C_{14}H_{12}N_4O_2$: C, 62.68; H, 4.48; N, 20.89. Found: C, 62.75; H, 4.51; N, 21.09.

1-Phenyl-5-p-nitrophenyl-1,2,3-triazoline. Pale yellow fluffy needle-like crystals from benzene or from acetone-petroleum ether mixture; m.p. 130–130.5°. Turns orange on exposure to air.

Anal. Calcd. for $C_{14}H_{12}N_4O_2$: C, 62.68; H, 4.48; N, 20.89. Found: C, 62.55; H, 4.29; N, 20.93.

1-Phenyl-5-o-nitrophenyl-1,2,3-triazoline. Stout, yellow crystals from benzene; m.p. 149–150°.

Anal. Calcd. for $C_{14}H_{12}N_4O_2$: C, 62.68; H, 4.48; N, 20.89. Found: C, 61.84; H, 4.62; N, 21.06.

1-p-Chlorophenyl-5-phenyl-1,2,3-triazoline. Very pale yellow, stout hexagonal crystals from ether; m.p. 130–132°.

Anal. Calcd. for $C_{14}H_{12}N_3Cl$: C, 65.24, H, 4.69; N, 16.31; Cl, 13.76. Found: C, 64.14; H, 4.59; N, 16.71; Cl, 13.14.

1-p-Methoxyphenyl-5-o-nitrophenyl-1,2,3-triazoline. Bright orange-yellow crystals from acetone; m.p. 140–140.5°.

Anal. Calcd. for $C_{15}H_{14}N_4O_3$: C, 60.40; H, 4.70; N, 18.79. Found: C, 60.36; H, 4.80; N, 18.88.

1-p-Nitrophenyl-5-p-methoxyphenyl-1,2,3-triazoline. Shiny yellow gritty crystals from acetone; m.p. 157–158°.

Anal. Calcd. for $C_{15}H_{14}N_4O_3$: C, 60.40; H, 4.70; N, 18.79. Found: C, 60.66; H, 4.66; N, 18.99.

Rate measurements. The kinetic runs were carried out in dioxane solution at 24.95° ± 0.10°. The reaction course was studied as follows: 10-Ml. aliquots (in duplicates) at appropriate time intervals were quenched into a measured volume of a cold solution of benzoic acid (U.S.P. grade recrystallized form ethanol) of known strength in dioxane. The diazomethane reacted rapidly with the benzoic acid and there was no need to shake the mixture for more than 3 min. The solution was then diluted with 100 ml. of cold distilled water and the excess benzoic acid was titrated with standard alkali using phenolphthalein as indicator. This is essentially the procedure used in determining diazomethane concentrations in ethereal solution.[13] The same amount (10 ml.) of dioxane was used for rinsing the sides of the flask during titration in all the runs. The end point of the titration is indicated by a dull orange-yellow color in the case of anils with yellow color, and by a pink color in the case of colorless anils. The amount of benzoic acid reacting with the diazomethane can be used to calculate the diazomethane concentration at a given time. At the end of each run, duplicate aliquots were quenched in benzoic acid; one was titrated immediately and the other was allowed to stand for 40 min. in the cold (10–15°) and then titrated. Both gave identical results; thus under these conditions, no hydrolysis of anil or triazoline by benzoic acid occurred.

Dioxane (Eastman Kodak, white label) was left overnight over potassium hydroxide pellets and then distilled, b.p. 98–99°. The same dioxane was used in all the kinetic runs. Diazomethane solution of approximately 2% strength was prepared by slow distillation of a dilute ethereal solution of diazomethane and collecting the distillate in an equal volume of dioxane. The amount of diethyl ether present in a run was thus reduced to a minimum.

Solutions for the runs were prepared by dissolving weighed amounts of anil in 80 or 230 ml. of dioxane in 100 or 250 ml. volumetric flasks, respectively, and allowing them to stand at 24.95° for 1–2 hr. An approximately 2% solution of diazomethane, also at 24.95°, was then added to the anil solution and the mixture made up to total of 100 or 250 ml. as the case may be. The amount of diazomethane used was such

TABLE I

REACTION OF DIAZOMETHANE WITH BENZAL-*p*-NITROANILINE[a]

$[CH_2N_2]$[b]	[Anil][b]	k_1[c]	k_2[d]
0.0338	0.451	0.204	0.45
0.0141	0.429	0.198	0.46
0.0048	0.399	0.193	0.48
0.0186	0.496	0.327	0.66[e]
0.0154	0.248	0.139	0.56
0.0094	0.111	0.071	0.64

[a] In dioxane at 24.95°. [b] Units are mole liter.$^{-1}$ [c] Units are hr.$^{-1}$ [d] Units are liter mole^{-1} hr.$^{-1}$ [e] Using a different dioxane sample.

(11) W. v. Miller and J. Plöchl, *Ber.*, 25, 2020 (1892).

(12) S. M. Tsang, E. H. Wood and J. R. Johnson, *Org. Syntheses*, **Coll. Vol. III**, 641 (1955).

(13) Prepared from nitrosomethyl urea; *cf.*, F. Arndt, *Org. Syntheses*, **Coll. Vol. II**, 165 (1943).

TABLE II

YIELDS[a] AND RATES[b] FOR TRIAZOLINE FORMATION

Substituent					
C-Phenyl	*N*-Phenyl	Time[c]	Catalyst[d]	Yield, %	k_2[e]
H	H	240	M	10	3.5×10^{-2}
H	*p*-NO_2	21[f]	W	64	4.5×10^{-1}
		42[f]	W	75	
H	*p*-Cl	96	M	22	6.4×10^{-2}
H	*p*-CH_3	—	—	—	1.2×10^{-2}
p-NO_2	H	25	W or M	0	7.6×10^{-2}
		96	M	25	
		96[f]	W	45	
o-NO_2	H	18	None	5	—
		21	M or W	25	
		21	M plus W	25	
		96	M	56	
p-Cl	H	240	M	<10	1.5×10^{-2}
o-NO_2	*p*-OCH_3	21	M or W	7	—
		96	M or W	20	
p-OCH_3	*p*-NO_2	96[f]	W	53	—

[a] The data in the columns labelled time, catalyst and yield are for experiments in diethyl ether at room temperature to test for best synthetic conditions. [b] Rates are for dioxane solution at 24.95°. [c] Time in hours. [d] M is methanol and W is water. [e] Units are liter mole^{-1} hr.$^{-1}$ [f] In dioxane as solvent.

that the concentration of the latter permitted accurate measurements by the titration procedure adopted. The standard alkali solutions used were diluted (0.03–0.05*N*) to permit greater accuracy in the experimental procedure.

Pseudo first order rate constants k_1 were calculated by dividing the factor 0.693 by the half-life of the reaction; this was obtained from the plot of log CH_2N_2 concentration against time. The second-order rate constants k_2 were obtained by dividing the k_1 values by the anil concentration which was in large excess. Some data which illustrate concentrations, etc., of the kinetic runs are shown in Table I.

RESULTS AND DISCUSSION

Ethylenimine synthesis. The initial purpose of the present investigation was to find new ways to prepare ethylenimines (aziridines). Methods tried included: (a) reaction of diazomethane with anils under a variety of conditions including boron trifluoride catalysis and light activation, (b) reaction of aliphatic Schiff's bases with dichlorocarbene, and (c) pyrolysis of the 1,2,3-triazolines formed by the direct addition of diazomethane to aromatic anils. No ethylenimine was isolated nor was any identified (in the liquid product mixtures) by either infrared or gas chromatography. It seems safe to conclude that the reaction of diazomethane or other carbene-formers with anils to give ethylenimine shows little promise as a general synthetic route. The only exception presently known is the formation of 1,2-diphenyl-3,3-dichloroethylenimine.[5,6]

In view of the nature of the results obtained on ethylenimine synthesis, we have merely listed general areas of experimentation that were carried out. Details may be obtained from the authors as to conditions and results; however, publication of these details seems to be unwarranted at the present time.

Triazoline synthesis. The method of synthesis of triazolines was mentioned previously. It was observed during these preparations that the yields depended significantly on the reaction time and on the substituent groups of the aromatic rings. This strongly suggested that the reaction of diazomethane with a benzalaniline has a rate convenient for measurment. In Table II data on yields for eight triazolines are presented; among the factors studied were solvent, catalyst (water or methanol), and time. These results will be discussed after the kinetic data are presented.

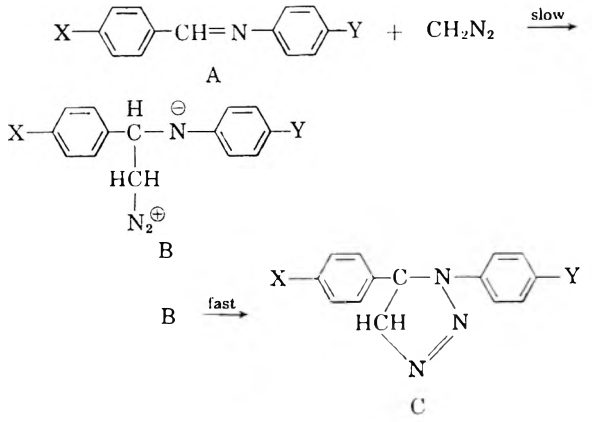
Kinetics. The results are summarized in the tables. In Table I are presented the first and second order rate constants for the addition reaction of diazomethane with benzal-*p*-nitroaniline at 24.95° at several different anil concentrations (always in excess). The reaction in first order in diazomethane concentration as good straight lines were obtained when the logarithm of the concentration of diazomethane was plotted against time; also the rate constant is independent of diazomethane concentration. The first order rate constants are dependent on first power of the anil concentration as seen from the data in Table I; the reaction thus follows simple second order kinetics.

The last column of Table II gives the second order rate constants for the reaction of diazomethane with benzal aniline and five anils having substituents on the *N*-phenyl and C-phenyl groups. Also given for comparison are the yields of triazolines obtained in the synthetic experiments; the parallelism between rate and yield is striking.

These results indicate conclusively that the diazomethane molecule is acting as a nucleophile in attacking the anil for the rate of reaction is increased by placing electron-withdrawing groups on the benzene rings of the anil and is decreased by the presence of electron-releasing groups. The results also show that substituents on the *N*-phenyl

group of the anil have a large polar effect whereas those on the C-phenyl have only a small polar effect. But the results do not of themselves indicate the site of attack, as either end of the diazomethane molecule could conceivably add to the anil in the rate step. It is possible, however, to give a satisfactory answer to this question of site, for several pieces of evidence (chemical data and kinetic studies) agree with a single mechanistic postulation.

Mechanism. Consider the mechanism



where the reaction is made of two steps, a slow and rate-determining step (A → B) and a subsequent rapid ring closure (B → C). There is a zwitterion intermediate B formed in the first step, which step is the nucleophilic attack by the carbon in diazomethane on the double bond carbon of the anil. It is pertinent to note here that the carbon of diazomethane has often been postulated to have nucleophilic character.[8,14] Also, double bonds are usually attacked at the position β to the activating group,[15] which certainly in our case is the *N*-phenyl group. There is little doubt that it is the carbon-carbon bond which is formed in the rate step.

The reaction coordinate diagram may be represented as shown in Fig. 1. The transition state is presumably close in energy content to the intermediate B, which fact suggests that the Hammond postulate[16] can be employed in discussion of the mechanism. One would, on the basis of this postulate, expect the transition state to have properties similar to the zwitterion intermediate. Some of the observations consistent with this are as follows: (a) The rate is dependent on solvent nature and the addition of a little water or methanol has a definite accelerating effect on the rate. (b) Electron-withdrawing substituents on the *N*-phenyl have a strong effect because of the high electron density on the nitrogen attached to this ring. The results should be, and are, particularly striking where conjugation of the type can occur. (c) The resonance

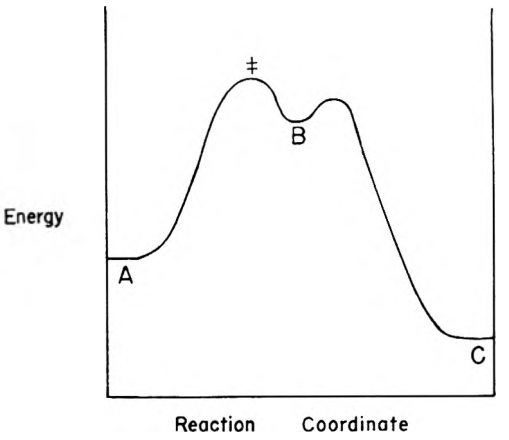
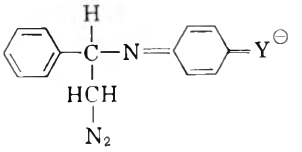
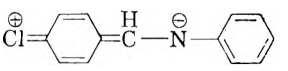


Fig. 1. Proposed reaction coordinate diagram for the reaction of aromatic Schiff's bases with diazomethane. Letters A, B, and C refer to reactants, zwitterion intermediate and product, respectively



between the C-phenyl ring and the double bond is broken as the new carbon-carbon bond is formed; thus electron-withdrawing substituents on C-phenyl should enhance the rate but not to a large extent. Such is the observation. The low rate (slower than benzalaniline itself) observed in the case of *p*-chlorobenzalaniline is presumably due to mesomeric double-bonding of the type which would



result in a lowering of the energy of the ground state A.

The observation that a comparatively high yield is obtained when the nitro-group on C-phenyl is in the *ortho* position is interesting. One possible explanation is that steric inhibition of resonance in the *ortho* case has raised the ground state energy, thus decreasing the activation energy. Unfortunately it was not possible for us to do any further experiments; therefore we were not able to test this particular hypothesis or to evaluate activation parameters for the addition reaction.

General significance. The mechanism of the addition of diazomethane to anils as postulated here is of general significance for certain other reactions have related mechanisms. One of these is the Michael addition,[15] which involves the attack of a carbanion on an activated double bond. Another is the attack of peroxy anions on double bonds.[17] In each case the site of attack by the nucleophile is the carbon which is *beta* to the acti-

(14) E. R. Alexander, *Ionic Organic Reactions*, Wiley, New York, 1950, p. 52.

(15) E. S. Gould, *Mechanism and Structure in Organic Chemistry*, Henry Holt, New York, 1959, p. 393.

(16) G. S. Hammond, *J. Am. Chem. Soc.*, **77**, 334 (1955).

(17) H. E. Zimmerman, L. Singer, and B. S. Thyagarajan, *J. Am. Chem. Soc.*, **81**, 108 (1959).

vating group. A related mechanism applies for the addition of diazomethane and diphenyldiazomethane to the double bond in maleic and fumaric esters[18] and maleic anhydride. The same addition product is obtained from the two esters and these when heated split off nitrogen to yield a *trans*-cyclopropane dicarboxylic acid. However, addition of diphenyldiazomethane to maleic anhydride yields a pyrazoline from which a *cis*-cyclopropane dicarboxylic acid is obtained. These results can be explained on the basis of an intermediate zwitterion addition product. In the case of the esters, as the C=C double bond is converted to a single bond in the intermediate, freedom of rotation is achieved resulting in identical pyrazolines, whereas in the case of the anhydride, no rotational freedom is achieved in the intermediate because of its cyclic nature. It has also been shown recently that the addition reactions of *p*-substituted diphenyldiazomethane to maleic ester and related compounds have rates consistent with the diazomethane acting as a nucleophile[19] and with there being an intermediate present in the reaction.

Acknolwecgment. We are grateful to the National Institutes of Health for financial support, and to Dr. Francis Smyth, Dr. Richard Baltzly and Mr. Ronald Brooks for helpful suggestions.

PROVIDENCE 12, R. I.

(18) *Cf.* J. van Alphen, *Rec. Trav. Chim.*, **62**, 210 (1943).

(19) N. B. Mehta, R. E. Brooks, and R. Baltzly, A.C.S. Meeting, Sept. 1960, New York City; paper #89, Abstracts of the Organic Chemistry Division.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF VIRGINIA]

2-Phenylcyclobutylamine

COLIN BEARD[1] AND ALFRED BURGER

Received November 30, 1960

The DL-*cis* and -*trans* isomers of 2-phenylcyclobutylamine have been synthesized in a sequence of reactions involving DL-*cis*- and -*trans*-2-phenylcyclobutanecarboxylic acids and 2-phenylcyclobutanone. An improved route to 2-phenylcyclobutane-1,1-dicarboxylic acid is also reported.

The discovery[2] of the potent inhibition of monoamine oxidases[3] by 2-phenylcyclopropylamine[4] (tranylcypromine) made it of interest to compare the effect of ring-homologous phenylcycloalkylamines on such enzymes. 2-Phenylcyclopentylamine,[5] 2-phenylcyclohexylamine,[6] and 2-phenylcycloheptylamine[7] have been described in the literature and 3-phenylcyclobutylamine has recently been reported.[8] This article describes the synthesis of *cis*- and *trans*-2-phenylcyclobutylamines.

Since cyclobutanecarboxylic acids have been successfully degraded to amines,[9] 2-phenylcyclobutanecarboxylic acid appeared to be a suitable starting material for our purpose. An oily 2-phenylcyclobutanecarboxylic acid,characterized as the *p*-toluidide, has been synthesized by Burger and Hofstetter[10] by decarboxylation of 2-phenylcyclobutane-1,1-dicarboxylic acid. However, the yields both in the lengthy synthesis of this dicarboxylic acid and in the decarboxylation were so low that they severely limited that sequence for preparative purposes. A new and more rewarding synthesis of 2-phenylcyclobutane-1,1-dicarboxylic acid has therefore been developed.

Diethyl cinnamylmalonate (I) was prepared by the alkylation of diethyl malonate with cinnamyl chloride.[11] Addition of hydrogen bromide to this unsaturated ester gave diethyl (3-bromo-3-phenylpropyl)malonate (II) and this was cyclized to diethyl 2-phenylcyclobutane-1,1-dicarboxylate (III) with sodium hydride in tetrahydrofuran. Alkaline hydrolysis of III led to 2-phenylcyclobutane-1,1-dicarboxylic acid (IV) in a yield of 80% based on I. The compound was identical with that previously reported.[10]

$$C_6H_5CH{=}CHCH_2Cl \xrightarrow{Na^+\bar{C}H(CO_2C_2H_5)_2} C_6H_5CH{=}CHCH_2CH(CO_2C_2H_5)_2 \quad (I) \xrightarrow{HBr}$$

[1] Smith, Kline & French Laboratories Postdoctoral Fellow, 1959–61.

(2) R. E. Tedeschi, D. H. Tedeschi, P. L. Ames, L. Cook, P. A. Mattis, and E. J. Fellows, *Proc. Soc. Exptl. Biol. Med.*, **102**, 380 (1959).

(3) S. Sarkar, R. Banerjee, M. S. Ise, and E. A. Zeller, *Helv. Chim. Acta*, **43**, 439 (1960).

(4) A. Burger and W. L. Yost, *J. Am. Chem. Soc.*, **70**, 2198 (1948).

(5) See, for example, T. R. Govindachari, K. Nagarajan, B. R. Pai, and N. Arumugan, *J. Chem. Soc.*, 4280 (1956).

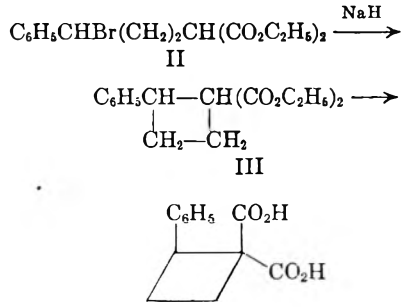
(6) See, for example, R. T. Arnold and P. N. Richardson, *J. Am. Chem. Soc.*, **76**, 3649 (1954).

(7) A. Burger, C. R. Walter, W. B. Bennett, and L. B. Turnbull, *Science*, **112**, 306 (1950).

(8) A. Burger and R. Bennett, *J. Med. and Pharm. Chem.*, **2**, 687 (1960).

(9) E. R. Buchmann, A. O. Reims, T. Skei, and M. J Schlatter, *J. Am. Chem. Soc.*, **64**, 2696 (1942).

(10) A. Burger and A. Hofstetter, *J. Org. Chem.*, **24**, 1290 (1959).



II

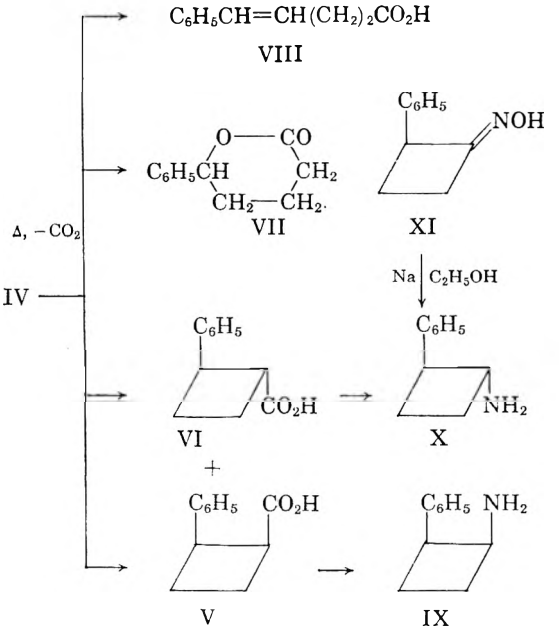
III

IV

Various conditions for the decarboxylation of the dicarboxylic acid (IV) have been examined. The most satisfactory methods proved to be those involving solvents, rather than the usual thermal decarboxylation of the molten malonic acid derivatives. Thus, chromatography of the mixture from a decarboxylation in refluxing mesitylene yielded two isomeric 2-phenylcyclobutanecarboxylic acids, the first a crystalline solid, and the second a liquid. Ozonization has been employed successfully in the configurational determination of 2-phenylcycloalkanecarboxylic acids, *e.g.* 2-phenylcyclopropanecarboxylic[12] and 2-phenylcyclohexanecarboxylic acids.[13] When applied to the crystalline 2-phenylcyclobutanecarboxylic acid, the major product was succinic acid, arising from fission of the 1-2 bond in the cyclobutane ring. However, there was also formed a small amount of *cis*-cyclobutane-1,2-dicarboxylic acid, demonstrating the *cis* configuration (V) of the solid acid. The isomeric oily acid is by inference the *trans* isomer (VI), and this assignment is supported by the results of reduction of 2-phenylcyclobutanone oxime (see below).

In addition to the stereoisomeric 2-phenylcyclobutanecarboxylic acids, a small amount (< 5%) of 5-phenyl-5-valerolactone (VII) was usually isolated from the decarboxylation mixture. A fourth component of this mixture was cinnamylacetic acid (VIII). This formed the bulk of the reaction product if the molten dicarboxylic acid (IV) was subjected to prolonged heating, and some polymer formation appeared to occur under these conditions. These components were practically absent if a solvent was used. That the cinnamylacetic acid did not arise through decomposition of the monocarboxylic acid (at least not the *cis* isomer), was shown by heating a sample of the acid (V) at 170–180° for one hour. The compound remained essentially unchanged under these conditions.

On the whole, the isolation of the pure (oily) *trans*-2-phenylcyclobutanecarboxylic acid proved quite laborious. As expected, the hindered *cis* acid is eluted first chromatographically and is easily purified by crystallization. In contrast, it is difficult to free the oily *trans* acid from traces of the *cis* isomer even by repeated chromatography. Although quantitative estimations are limited because of these difficulties, the *trans* acid appears to be the predominant isomer in the decarboxylation mixture, and this is confirmed by examination of the infrared spectrum of this mixture.[14]



Curtius degradation of the stereoisomeric 2-phenylcyclobutanecarboxylic acids V and VI yielded the corresponding 2-phenylcyclobutylamines IX and X in good yield. The intermediate azides were prepared advantageously from the acids by way of mixed ethyl carbonate anhydrides rather than from the acyl chlorides.[16] This method greatly improved preparative expediency although it was not needed to avoid the danger of isomerization of the *cis*- to the *trans*-series by way of the acid chlorides as is observed in the case of the 2-phenylcyclopropanecarboxylic acid.[4] In the cold at least, *cis*-2-phenylcyclobutanecarboxylic acid is not isomerized by thionyl chloride since the two

(11) D. Barnard and L. Bateman, *J. Chem. Soc.*, 926 (1950).

(12) G. W. Perold and H. L. DeWaal, *Chem. Ber.*, 85, 574 (1952).

(13) R. P. Linstead, S. R. Davis, and R. R. Whetstone, *J. Am. Chem. Soc.*, 64, 2009 (1942).

(14) M. Julia and A. Rouault[15] claimed to have cyclized ethyl 5-chloro-5-phenylvalerate to ethyl 2-phenylcyclobutanecarboxylate which on hydrolysis gave a crystalline acid of m.p. 90–91°. Through the courtesy of Prof. Julia we obtained a sample of this acid which we established to be cinnamylacetic acid by mixture melting point with an authentic sample, and comparison of the infrared spectra. In fact, prior to publication of the paper by Julia and Rouault we had attempted to cyclize ethyl 5-bromo-5-phenylvalerate with potassium isobutoxide but observed only ethyl cinnamylacetate as a reaction product.

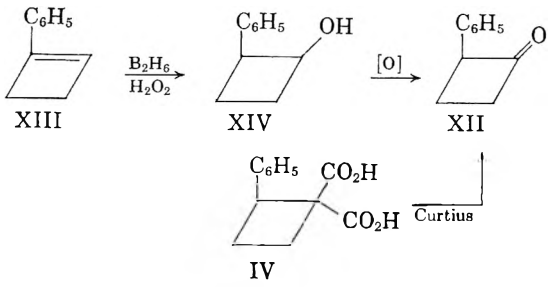
(15) M. Julia and A. Rouault, *Bull. soc. chim. France*, 1833 (1959); *Bull. soc. chim. France*, 979 (1960).

(16) We are obliged to Dr. Joseph Weinstock of Smith, Kline & French Laboratories for suggesting this modification. See J. Weinstock, *J. Org. Chem.*, in press.

acids, V and VI, give different *p*-toluidides *via* the acyl chlorides without extensive purification.

A second approach to 2-phenylcyclobutylamines started with 2-phenylcyclobutanone oxime (XI) which was reduced with sodium and ethanol to *trans*-2-phenylcyclobutylamine, identical with that obtained by Curtius degradation of the oily acid (VI). The reduction of ketones and oximes with metal combinations usually gives the thermodynamically more stable product,[17,18] and this is in accord with the formation of *trans*-2-phenylcyclobutylamine in this case.[19]

2-Phenylcyclobutanone (XII) was prepared by two routes. 1-Phenylcyclobutene[8] (XIII) was treated with diborane according to the general procedure of Brown[21] and the resulting adduct was oxidized and hydrolyzed to 2-phenylcyclobutanol (XIV), differing from 1-phenylcyclobutanol previously described.[8] A second, somewhat shorter and more convenient sequence, utilized the Curtius degradation[22] of 2-phenylcyclobutane-1,1-dicarboxylic acid.



EXPERIMENTAL

All melting points are corrected. Microanalyses by Mrs. Dolores Ellis.

Diethyl (3-bromo-3-phenylpropyl)malonate (I). Dry hydrogen bromide was passed through diethyl cinnamylmalonate[11] (276.3 g., 1.0 mole) over a period of 2 hr. The temperature rose to *ca.* 55° and was kept between 40 and 45° when the exothermic reaction ceased. The product was treated with ice water, and extracted with a mixture of benzene and ether. After washing the benzene solution with water and ice-cold 2% sodium bicarbonate solution, it was dried over sodium sulfate and the solvent removed at 90° (50 mm.). The product so obtained was used without further purification in the next step, as distillation caused decomposition.

2-Phenylcyclobutane-1,1-dicarboxylic acid (III). To a suspension of sodium hydride (48.0 g., 1.0 mole, 50% in oil) in tetrahydrofuran (1 l., distilled from lithium aluminum hydride) was added, slowly with stirring and cooling, under nitrogen, diethyl (3-bromo-3-phenylpropyl)malonate (1 mole) in tetrahydrofuran (100 ml.), at 0–5° over a period of 50 min. It is important that hydrogen starts to evolve early, otherwise the reaction becomes suddenly uncontrollable. The mixture was allowed to stand at 20° overnight and tetrahydrofuran was distilled off over a 75-min. period, until the internal temperature reached 80°. Ice was added and the mixture diluted with water. After separating the organic layer, the aqueous phase was extracted three times with ether and the combined organic layers were washed once with water. The solvent was removed and the residue saponified by treatment with refluxing potassium hydroxide solution (168 g., 3.0 moles in 500 ml. of 50% ethanol) over 3 hr. Most of the solvent was removed under vacuum on a water bath and the residue was taken up in water. The aqueous solution was washed twice with ether to remove the oil from the sodium hydride, and acidified with 37% hydrochloric acid (300 ml.). The organic acid which separated was isolated by ether extraction and crystallized from chloroform, yielding 2-phenylcyclobutane-1,1-dicarboxylic acid (173.7 g., 79% based on diethyl cinnamylmalonate), m.p. 173–174°, undepressed on admixture with a sample prepared by Burger and Hofstetter.[10] A further 11.4 g. of material, m.p. 169–172°, was collected from the mother liquor.

In a separate run, part of the crude diethyl 2-phenylcyclobutane-1,1-dicarboxylate was converted into the dihydrazide by refluxing with a solution of anhydrous hydrazine in butanol. The ether-washed product after crystallization from ethanol melted at 136–139°.

Anal. Calcd. for $C_{12}H_{16}N_4O_2$: C, 58.04; H, 6.49; N, 22.56. Found: C, 58.14; H, 6.61; N, 22.27.

Decarboxylation of 2-phenylcyclobutane-1,1-dicarboxylic acid. (a) 2-Phenylcyclobutane-1,1-dicarboxylic acid (40 g.) was heated in a retort at 10 mm. pressure and a bath temperature of 205–210°. Distillation set in and ceased after 15 min. The distillate (25.4 g.) was dissolved in a mixture of ether (30 ml.) and hexane (170 ml.), decanted from some insoluble oil, and chromatographed through a 53 × 145 mm. column of 100-mesh silica gel. Elution was carried out with a 15:85 mixture of ether-hexane, fractions of 100 ml. each being collected.

Fractions No. 4–12 consisted of a mixture of oil and crystals from which, by trituration with pentane, 5.5 g. of *cis*-2-phenylcyclobutanecarboxylic acid, m.p. 84.5–85°, was obtained. Rechromatographing the oily residue from these fractions on Fisher alumina (80–200 mesh) with an acetic acid–hexane mixture (2:98) yielded another 1.8 g. of the same material. For analysis, it was recrystallized from hexane. Characteristic infrared absorptions (in potassium bromide): 697, 730, 787 cm.$^{-1}$

Anal. Calcd. for $C_{12}H_{12}O_2$: C, 74.97; H, 6.86. Found: C, 74.85; H, 6.60.

After some oily mixed materials, the last fractions eluted with the acetic acid–hexane mixture yielded 2.5 g. of an oily acid which, from its infrared spectrum (700, 753 cm.$^{-1}$ as a smeared film) was judged to be pure *trans*-2-phenylcyclobutanecarboxylic acid.

Fractions No. 17–22 yielded 90 mg. of a solid which, after crystallization from hexane, melted at 90.5–91° and proved to be cinnamylacetic acid by comparison of melting points, infrared spectra and mixture melting point with an authentic sample.[23] After the elution of cinnamylacetic acid, the concentration of ether in the eluant was increased to 50%. Some of the next fractions contained unchanged 2-phenylcyclo-

(17) D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953).

(18) D. H. R. Barton and C. H. Robinson, *J. Chem. Soc.*, 3045 (1954).

(19) Any possibility that the 2-phenylcyclobutyl group might have isomerized *inter alia* to 2-phenylcyclopropylmethyl[20] during the Curtius degradation of the acids V or VI was discounted by the properties of 2-phenylcyclopropylmethylamine (hydrochloride, m.p. 187–188°) (private communication, Dr. Charles L. Zirkle). The hydrochloride of *cis*-2-phenylcyclobutylamine melts at 224–226° (dec.), that of the *trans* isomer at 210–213° dec. (see Experimental). Likewise, hydrogenolysis of the cyclobutane ring of 2-phenylcyclobutanone oxime could be eliminated from consideration, since the material expected from such a reaction would be 4-phenylbutylamine, and its hydrochloride is known to melt at 164.5–165.5°.[8]

(20) J. D. Roberts and V. C. Chambers, *J. Am. Chem. Soc.*, 73, 5030, 5034 (1951).

(21) H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, 81, 247 (1959).

(22) T. Curtius and G. Grandel, *J. prakt. Chem.*, 94, 339 (1916).

(23) E. Erlenmeyer and A. Kreutz, *Ber.*, 38, 3503 (1905).

butane-1,1-dicarboxylic acid, but fractions No. 31–42 yielded 5-phenyl-5-valerolactone[24] (1.75 g.) which crystallized from pentane as colorless needles, m.p. 73–75°, and was identified with an authentic sample by mixture melting point and comparison of the infrared spectra.

Anal. Calcd. for $C_{12}H_{12}O_2$: C, 74.97; H, 6.86. Found: C, 74.82; H, 6.87.

(b) A solution of 2-phenylcyclobutane-1,1-dicarboxylic acid (40 g.) in mesitylene (150 ml.) was refluxed for 1.5 hr., cooled, and extracted with 70 ml. of ice-cold 15% sodium hydroxide solution. After being washed twice with ether, the alkaline solution was acidified at a temperature below 10°, the oil which separated was extracted with ether and chromatographed on silica gel as described under (a). Fractions No. 4–13 yielded *cis*-2-phenylcyclobutanecarboxylic acid (8.5 g.) on trituration with pentane. Rechromatography of the oily portion (13 g.) from fractions No. 4–7 on alumina using hexane-4% acetic acid gave another 1.2 g. of the *cis* isomer, and then 6.4 g. of pure *trans*-2-phenylcyclobutanecarboxylic acid.

(c) When 2-phenylcyclobutane-1,1-dicarboxylic acid was heated under reflux for 15 min. at 10 mm. pressure in a bath of 165–170°, or in 6*N* hydrochloric acid for 11 hr., and the reaction mixtures were worked up and chromatographed, cinnamylacetic acid was the only pure product which could be isolated.

Cis- and trans-2-Phenylcyclobutanecarboxy-p-toluidides. The respective acids (0.2 g.) were allowed to react with 1 ml. of thionyl chloride at 20° overnight, unchanged thionyl chloride was removed at 20° under reduced pressure, and the crude acyl chlorides were treated with a solution of 0.4 g. of *p*-toluidine in ether. The ether solutions were washed with dilute hydrochloric acid and water and evaporated.

The *cis*-*p*-toluidide crystallized from aqueous ethanol or from benzene-hexane as needles, m.p. 137–138°.

Anal. Calcd. for $C_{18}H_{19}NO$: N, 5.28. Found: N, 5.52.

The *trans*-*p*-toluidide crystallized from benzene-hexane, m.p. 162.5–164.5°.

Anal. Calcd. for $C_{18}H_{19}NO$: N, 5.28. Found: N, 5.36.

A mixture melting point with a sample of a 2-phenylcyclobutane-carboxy-*p*-toluidide previously described[10] gave no depression, and the infrared spectra of the two compounds were superimposable.

Cinnamylaceto-*p*-toluidide, prepared from cinnamylacetic acid in the same fashion, crystallized from benzene as plates, m.p.165.5-167°.

Anal. Calcd. for $C_{18}H_{19}NO$: N, 5.28. Found: N, 5.46.

A mixture melting point with *trans*-2-phenylcyclobutanecarboxy-*p*-toluidide was 135–142°.

Ozonization of cis-2-phenylcyclobutanecarboxylic acid. A solution of 1.23 g. of the *cis*-acid in 25 ml. of acetic acid was ozonized for 4 hr., then 30 ml. of 10% hydrogen peroxide was added, and the solution left at 25° overnight. It was evaporated almost to dryness on a water bath, the residue again treated with three 9-ml. portions of 10% hydrogen peroxide, and the solution evaporated. The gummy residue was divided into two portions. One portion was brought to crystallization on a porous plate; the solid was recrystallized from water, m.p. 189–189.5°, undepressed by admixture with succinic acid (m.p. 189–189.5°).

The other half was extracted thoroughly with hot benzene. The residue from the benzene extracts consisted of a mixture of oil and crystals. The latter were charcoaled in benzene solution, and furnished colorless material, m.p. 138.5–140.5°. A mixture melting point with authentic[9] *cis*-cyclobutane-1,2-dicarboxylic acid (m.p. 139.5–140.5°) was undepressed, and the infrared spectra of the two materials were identical.

(24) The 5-phenyl-5-valerolactone needed for comparison was prepared by reduction of 4-benzoylbutyric acid with sodium borohydride. It was vacuum distilled and crystallized from hexane as needles, or from ether-hexane as prisms, m.p. 75–76°. *Cf.* also M. Julia and A. Rouault.[15]

2-Phenylcyclobutanol. Diborane, generated[21] from boron trifluoride–ether complex (23.0 g., 0.16 mole) in Diglyme (48 ml.) by the addition of a solution of sodium borohydride (2.3 g., 0.06 mole) in Diglyme (60 ml.) was carried by a stream of nitrogen into a solution of 1-phenylcyclobutene[8] (15.4 g., 118 mmoles) in tetrahydrofuran (36 ml.) at 0–3° over a 1-hr. period. After another hour at 25°, ice was added cautiously keeping the temperature below 10°. This was followed by 3*N* sodium hydroxide solution (27 ml.) and then, after 20 min., by 15 ml. of 30% hydrogen peroxide below 10°. After another hour at 25° the mixture was diluted with water (90 ml.) and extracted three times with ether. The combined ether extracts were washed with water, dried over sodium sulfate, and fractionated. The fraction (14.4 g., 82%) boiling at 78–81°/0.27 mm., n_D^{25} 1.5480 was collected.

Anal. Calcd. for $C_{10}H_{12}O$: C, 81.04; H, 8.16. Found: C, 80.63; H, 8.45.

The *phenylurethane* derivative melted at 118–120°.

Anal. Calcd. for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.09; H, 6.37; N, 5.59.

2-Phenylcyclobutanone. (a) A solution of 2-phenylcyclobutane-1,1-dicarboxylic acid (2.20 g., 0.01 mole) in acetone (4 ml.) and water (5 ml.) was treated at −5° to 0° with triethylamine (2.4 g., 24 mmoles) in acetone (20 ml.) followed by a solution of ethyl chloroformate (2.60 g., 24 mmoles) in acetone (5 ml.) as described above for *cis*-2-phenylcyclobutanecarboxylic acid. After conversion to the azide with sodium azide (1.96 g., 0.03 mole) in water (6 ml.) the mixture was stirred and worked up by ether extraction. The dried ether solution of the azide was then treated with 50 ml. of absolute ethanol. The ether was fractionated off, the ethanolic solution refluxed for 2 hr. and the solvent was removed. The residual orange oil was treated with 50 ml. of 2% sulfuric acid and steam-distilled, yielding 0.7 g. (48%) of colorless solid, b.p. 116°/7 mm., m.p. 27°.

Anal. Calcd. for $C_{10}H_{10}O$: C, 82.16; H, 6.90. Found: C, 81.77; H, 6.73.

The *semicarbazone* melted at 164–166°, and did not depress the melting point of the semicarbazone obtained by method (b).

(b) A solution of 2-phenylcyclobutanol (4.45 g., 0.03 mole), aluminum *t*-butoxide (4.9 g., 0.02 mole), and benzoquinone (16.2 g., 0.15 mole) in dry toluene (300 ml.) was stirred at 60–65° for 17 hr., then 1 ml. of water was added and the mixture filtered through a Celite pad. The filtrate was washed with three 100-ml. portions of 1*N* sodium hydroxide solution, then with water, the solvent was removed under reduced pressure and the residue extracted exhaustively with petroleum ether (b.p. 30–60°). This solvent was removed and the residual oil distilled, yielding 1.9 g. of colorless material, b.p. 65–68°/1–2 mm., $n_D^{22.5}$ 1.5464. This product did not analyze quite correctly but gave a solid sodium bisulfite adduct which was decomposed with 10% sodium carbonate solution. The ketone recovered from the adduct solidified when seeded with 2-phenylcyclobutanone obtained by method (a).

The *semicarbazone* melted at 163–165°.

Anal. Calcd. for $C_{11}H_{13}N_3O$: C, 65.00; H, 6.45; N, 20.68. Found: C, 65.24; H, 6.54; N, 20.41.

The oxime was obtained by refluxing a solution of 2-phenylcyclobutanone (3.0 g., 0.02 mole), hydroxylamine hydrochloride (4.2 g.), and potassium hydroxide (2.2 g.) in 50% aqueous ethanol (30 ml.) for 15 hr., removing most of the solvent under reduced pressure and extracting the remaining suspension with ether. After washing, drying, and evaporating, the ether solution left 2.7 g. of a thick oil which did not crystallize. The infrared spectrum showed strong absorption at *ca.* 3300 cm.$^{-1}$ and medium absorption at *ca.* 1690 cm.$^{-1}$ It was reduced directly to *trans*-2-phenylcyclobutylamine as described below (method b).

cis-2-Phenylcyclobutylamine. To a stirred solution of *cis*-2-phenylcyclobutanecarboxylic acid (6.16 g., 35 mmoles) in acetone (15 ml.) and water (7.5 ml.) was added, at −5°, a solution of triethylamine (4.05 g., 5.55 ml., 40 mmoles) in

acetone (30 ml.) and then a solution of ethyl chloroformate (4.35 g., 3.85 ml., 40 mmoles) in acetone (10 ml.). After stirring the mixture at −5° to 0° for 30 min., a solution of sodium azide (3.25 g., 50 mmoles) in water (20 ml.) was added and stirring continued for another hour. The mixture was poured into 500 ml. of ice-cold saturated sodium chloride solution and 250 ml. of ice water, and extracted with five 75-ml. portions of ether. The combined ether extracts were dried over calcium sulfate, evaporated in a vacuum at 30°, and the residual azide was dissolved in 50 ml. of toluene. This solution was warmed slowly to 100° until nitrogen evolution ceased, the solvent removed under reduced pressure, and the residual isocyanate refluxed with 18% hydrochloric acid (35 ml.) for 12 hr. The cooled solution was made basic with 10% sodium hydroxide solution, the amine extracted with ether, the ether extracts were dried over sodium sulfate and evaporated. The oily amine (4.55 g.) boiled at 69°/0.8 mm., 68°/0.55 mm., n_D^{25} 1.5498. The yield was 4.15 g. (81%).

The *hydrochloride*, prepared in ether, crystallized from chloroform, m.p. 224–226° (sealed tube).

Anal. Calcd. for $C_{10}H_{13}N.HCl$: C, 65.37; H, 7.68; N, 7.63; Cl, 19.30. Found: C, 65.42; H, 7.71; N, 7.93; Cl, 19.07.

trans-2-Phenylcyclobutylamine. (a) This was prepared from *trans*-2-phenylcyclobutanecarboxylic acid as described for the *cis* isomer above. The yield was 63%, b.p. 72°/0.55 mm., n_D^{25} 1.5464. The *hydrochloride* was precipitated with ethereal hydrogen chloride and crystallized from ethanol-ether, m.p. 210–213° dec.

Anal. Calcd. for $C_{10}H_{13}N.HCl$: C, 65.37; H, 7.68; N, 7.63. Found: C, 65.09; H, 7.56; N, 7.75.

The *N-benzoyl derivative* was prepared by the Schotten-Baumann method and crystallized from ethanol, m.p. 167.5–168.5°.

Anal. Calcd. for $C_{17}H_{17}NO$: N, 5.57. Found: N, 5.66.

(b) A solution of oily 2-phenylcyclobutanone oxime (1.6 g.) in absolute ethanol (70 ml.) was reduced by rapid addition of 6 g. of sodium. After the main reaction had ceased (15 min.), the mixture was refluxed for 35 min., the solvent removed under reduced pressure, the residue was treated with water (70 ml.) and the mixture extracted with ether. Basic material was extracted from the ether into 5% hydrochloric acid, the acid solution washed with ether, made alkaline with 40% sodium hydroxide solution, and the amine was extracted into ether. After drying over sodium sulfate and removal of the solvent, an oil remained, the infrared spectrum of which was identical with that of the amine obtained by method (a). The hydrochloride melted at 210–212° dec. and did not depress the melting point of the salt from method (a).

Attempts to reduce 2-phenylcyclobutanone oxime with lithium aluminum hydride or catalytically were unsuccessful.

CHARLOTTESVILLE, Va.

[CONTRIBUTION FROM UNION CARBIDE RESEARCH INSTITUTE AND THE LINDE CO. RESEARCH LABORATORY, UNION CARBIDE CORP.]

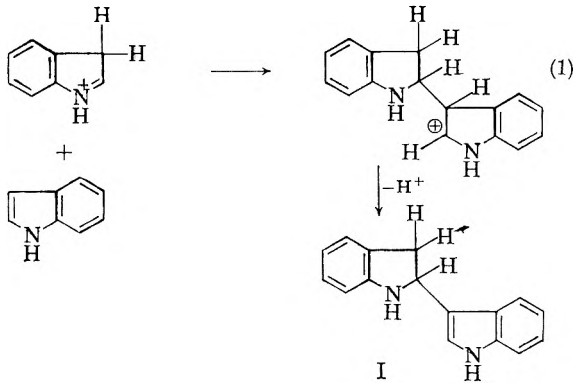
The Structure of Diskatole[1]

RICHARD L. HINMAN[2] AND E. R. SHULL[3]

Formula III has been established by NMR as the correct structure of diskatole. A crossed dimer of skatole and 2-methylindole has been prepared and its structure established as V.

It has been known for many years that indole forms crystalline dimers[4] and trimers[5] in acidic media, but it is only recently that the structures of these products have been established.[6] We became interested in the indole dimers, particularly in diskatole, in the course of studies on the relationship of the oxidation of indoles to their regulatory function in cellular growth.[7,8]

The structure of skatole dimer has not been established. The chemical evidence shows that it resembles diindole (I) in having an anilino nitrogen and an indole nitrogen, and in undergoing thermal depolymerization to the monomer.[9–11] The most recent structure proposed[11] for skatole dimer is shown in formula II. Since dimer formation involves the coupling of a protonated indole nucleus with an unprotonated one,[12] as shown for the formation of diindole (Equation 1), formation of structure II would require protonation of position-2



(1)

I

(1) Presented before the Organic Division of the American Chemical Society at the New York meeting, Sept. 9, 1960.

(2) To whom inquiries should be addressed: Union Carbide Research Institute, P.O. Box 278, Tarrytown, N.Y.

(3) (a) The Linde Co.; (b) deceased.

(4) O. Schmitz-Dumont and B. Nicolojannis, *Ber.*, **63**, 323 (1930).

(5) K. Keller, *Ber.*, **46**, 726 (1913).

(6) (a) G. F. Smith, *Chem. & Ind.*, 1451 (1954); (b) H. F. Hodson and G. F. Smith, *J. Chem. Soc.*, 3544 (1957); (c) W. E. Noland and W. C. Kuryla, *J. Org. Chem.*, **25**, 486 (1960).

(7) P. Frost and R. L. Hinman, in *Plant Growth Regulation*, R. Klein, ed., Iowa State University Press, Ames, Iowa, 1961, p. 205.

(8) S. M. Siegel, F. Porto, and P. Frost, *Physiol. Plant.*, **12**, 727 (1959).

(9) B. Oddo and G. B. Crippa, *Gazz. chim. ital.*, **54**, I, 339 (1924).

(10) B. Oddo and Q. Mingoia, *Gazz. chim. ital.*, **57**, I, 480 (1927).

(11) O. Schmitz-Dumont, K. Hamann, and K. H. Geller, *Ann.*, **504**, 1 (1933).

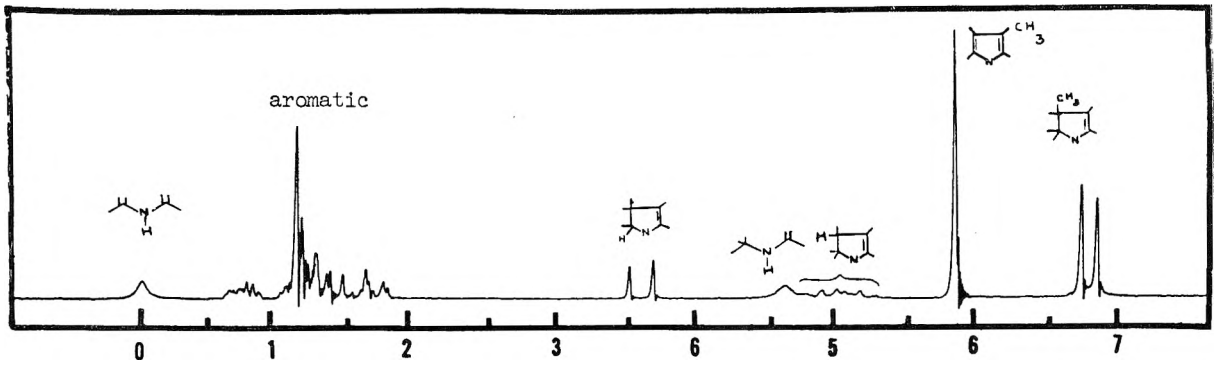
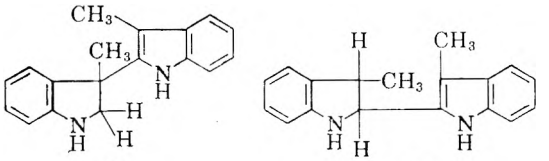


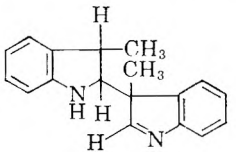
Fig. 1. NMR spectrum at 60 mc. of diskatole in carbon tetrachloride. Scale in ppm. relative to peak at lowest field

of skatole. We have recently shown, however, that protonation of indole and its simple alkyl derivatives occurs predominantly at the 3-position in solution.[13]



II

III



IV

If the 3-position were protonated, two structures could be envisioned for skatole dimer. One (III) would be formed by attack of the protonated species at position-2 of the unprotonated skatole, while the other (IV) would be formed by attack at the 3-position. As it has recently been shown[14] that substitution of skatole by large electrophilic species generally takes place at the 2-position, structure III seemed most probable.

The infrared spectrum of diskatole showed the presence of two bands at 2.90 and 2.95 μ in the NH region, indicating the presence of both anilino and indolo NH groups, similar to those reported for the dimer of 2-methylindole.[15] The ultraviolet spectrum showed the typical peaks[14] of the indole chromophore at 228, 285, and 293 mμ. The correct structure must therefore contain two NH groups and an indole ring. As structure IV contains only one NH group and the indolenine chromophore, which generally absorbs near 255 mμ,[16] it was eliminated as a possible structure of diskatole.

The two remaining structures (II and III) which differ in the positions of the hydrogens in the reduced hetero ring, could be distinguished by means of proton magnetic resonance. In the 60 mc. spectrum of diskatole (Fig. 1) the resonance lines of the methyl hydrogens are observed as a doublet at δ = + 6.7 and 6.8 ppm. (relative to the peak at lowest field strength) and a singlet at + 5.8 ppm., each of area $\sim$ 3. The doublet, which has a coupling constant of $\sim$ 8 cps. clearly indicates that one methyl is bound to a carbon bearing one other hydrogen. This structural feature (> CH—CH_3) is present only in formula III, which is therefore the correct structure of diskatole.[17]

The remainder of the spectrum is interpreted as follows. The complex multiplet (area $\sim$ 8) at δ + 1.1 ppm. is due to the aromatic ring protons. The multiplet at $\delta \sim$ + 5.0 is assigned to the hydrogen on the 3-carbon of the reduced hetero ring. The resonance of this hydrogen is split by coupling with the methyl hydrogens and with the proton at the 2-position. The doublet of area $\sim$ 1 at δ + 5.0 ppm. is due to the hydrogen at the 2-position of the reduced ring, split by coupling with the hydrogen at the 3-position. The two hydrogens attached to nitrogen are accounted for by the singlet at δ = 0 (the indole NH) and the singlet at δ + 4.6 ppm. (the reduced ring NH). The assignments of the last two peaks were made by comparison with the spectra of skatole and indoline in which the reduced ring NH appears at much higher field strength than the indole NH. The resonance line of the hydrogen bound to nitrogen

(12) That one indole nucleus must be unprotonated for successful dimerization is shown by the isolation of skatole from its solutions in 15–18M sulfuric acid, in which protonation is complete. From the reaction of skatole with dilute solutions of acid only diskatole was isolated.

(13) R. L. Hinman and J. Lang, *Tetrahedron Letters*, **21**, 12 (1960).

(14) W. E. Noland and D. N. Robinson, *Tetrahedron*, **3**, 68 (1958).

(15) B. Witkop and J. B. Patrick, *J. Am. Chem. Soc.*, **73**, 713 (1951).

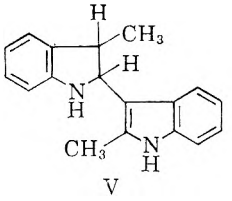
(16) B. Witkop and J. B. Patrick, *J. Am. Chem. Soc.*, **73**, 2188 (1951).

(17) It has been reported [W. E. Noland and C. F. Hammer, *J. Org. Chem.*, 25, 1525 (1960), footnote 17] that the same structure for diskatole has been proved by degradation. No details of the work have appeared.

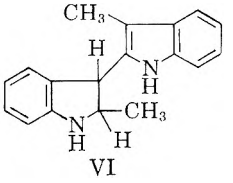
NOTE ADDED IN PROOF: After this paper had been submitted, diskatole was shown by chemical degradation to have structure III (G. Berti, A. da Settims, and D. Segnini, Tetrahedron Letters, 26, 13 (1960)).

in pyrrole is also observed at very low fields.[18] The presence of two hydrogens bound to nitrogens is further evidence against the indolenine structure (IV), as are the positions of the methyl resonances. If IV were correct the methyl resonances should appear at about the same field strengths, as both methyls are attached to saturated carbons.

The NMR spectra of two other indole dimers were also determined. The spectrum of diindole was inconclusive, but was in general agreement with the known[6b] structural features of the reduced ring. The other indole dimer examined was a "crossed" dimer formed by the reaction of skatole and 2-methylindole.[19,20] The insolubility of this dimer made it necessary to determine its NMR spectrum in acetone, which absorbs in the same region as the methyl groups of the dimer. Despite this interference, a singlet and a doublet which could be assigned to the methyl groups were clearly distinguishable in the same regions and with about the same separation as the lines due to the two methyl groups in the spectrum of diskatole. Only two structures (V and VI) can be devised which are consistent with the NMR spectrum. Of these only structure V accords with the assumption that dimerization is initiated by protonation of the 3-position of an indole, as in the formation of diskatole and diindole. (Structures of the indolenine type are ruled out because of the indole chromophore in the ultraviolet and two bands in the NH region of the infrared.)



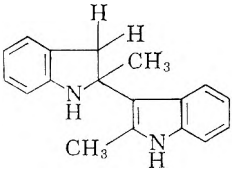
V



VI

In the course of this work we determined the 40 mc. NMR spectra of a number of simple indoles. In general our results agree with the 60 mc. spectra reported recently.[21] In addition to the previously reported observations we found evidence of coupling between the α- or β-ring protons and the hydrogens of alkyl groups at adjacent carbons on the hetero ring. Thus, the methyl resonances of skatole and of 2-methylindole in chloroform, carbon tetrachloride, benzene, or acetone, appeared as doublets with a coupling constant of ~ 1 cps. The resonance of the methylene hydrogens of indole-3-acetic acid in acetone showed similar splitting. In these cases the peaks of the ring protons were more complex than would be expected by coupling with the hydrogen on the pyrrole nitrogen only. In a 60-mc. scan of 1,2-dimethylindole in carbon tetrachloride the coupling between the β-proton and the hydrogens of the 2-methyl group was 0.7 ± 0.2 cps.[22] This splitting affords an additional method[21] for determining the presence of a proton on an adjacent ring carbon.

The major product from the reaction of skatole and 2-methylindole was diskatole. Steric effects and the relative basicities of the monomers favor the formation of this product rather than the "crossed" dimer (V). Molecular models show that the hindrance about the interannular bond in V is much greater than in diskatole. In the dimer (VII) of 2-methylindole,[15] hindrance about the interannular bond is so great that the rings are essentially locked in place. It is this effect which prevents dimerization, since the first step, protonation of 2-methylindole, occurs readily.[13,23]



VII

The formation of the "crossed" dimer (V) requires the reaction of a protonated skatole molecule with an unprotonated 2-methylindole. In other studies under way in this laboratory we have determined that the pK_a of 2-methylindole is -0.3 while that of skatole is -4.3. The more basic 2-methylindole would therefore be protonated first, making it unavailable for reaction with the protonated skatole.[24]

(18) J. D. Roberts, *Nuclear Magnetic Resonance*, McGraw-Hill, New York, 1956, p. 65. It is interesting that the hydrogen on the pyrrole nitrogen of diskatole (and diindole) gives rise to fairly sharp peaks in chloroform whereas the spectra of skatole and other simple indoles show very broad resonance lines or none at all. It has been suggested by Dr. Earl Whipple that the line sharpening in the dimers may be explained by the increase in the effective volume which would increase the correlation time for quadrupole relaxation of the N^{14} spin polarization.

(19) Although 2-substituted indoles, such as 2-methylindole, do not form dimers by treatment with acid [O. Schmitz-Dumont and K. H. Geller, *Ber.*, **66**, 766 (1933)], it seemed likely that "crossed" dimers might be formed by reaction of a 2-substituted indole with a protonated 3-substituted indole.

(20) Shortly after completion of this work, Dr. W. E. Noland informed us of his work on "crossed" dimers, including the dimer from skatole and 2-methylindole, which was not isolated as the free dimer but as the maleyl derivative. We are indebted to Dr. Noland for a copy of this paper[17] prior to its publication.

(21) L. A. Cohen, J. W. Daly, H. Kny, and B. Witkop, *J. Am. Chem. Soc.*, 82, 2184 (1960).

(22) Spectrum obtained by Dr. Earl B. Whipple of the Union Carbide Research Institute.

(23) The proposed structure of this dimer is based on the assumption that it would be formed by 3-protonation. A dimer of 2-methylindole with a 3-3′ interannular bond has been prepared by an indirect route.[15]

(24) As Noland has pointed out,[17] 2-methylindole should be more susceptible than skatole to attack by a protonated skatole. It may be this fact alone which enables the reaction to proceed at all.

The proof of structure of diskatole and the related work on indole dimerization reported in this paper illustrate an important point in indole chemistry. Substitution of indoles by electrophilic species takes place at the 3-position if that position is not occupied. When the 3-position bears a substituent, as in skatole, *small* electrophilic species will still attack the 3-position. Thus, the proton, bromonium ion,[25] and certain electrophilic oxidizing agents[26] attack the 3-position of skatole and its derivatives. If the electrophilic species is large, such as a protonated indole, or in the cases reported by Noland,[14] the electrophile may enter the 2-position.

Finally, attention is called to the similarity of indoles to simple vinylamines in their mode of protonation. The similarity extends to dimerization, since a number of typical vinylamines, particularly the Δ^2-tetrahydropyridines[27a] and Δ^2-pyrrolines,[27b] undergo dimerization through intermediates similar to those of the protonated indoles.

EXPERIMENTAL[28]

Diskatole. Prepared by passing dry hydrogen chloride into a rapidly stirred solution of skatole in dry thiophene-free benzene. The work-up was carried out as described previously,[9] yielding short white needles, m.p. 125–127° (reported[9] m.p. 125–127°). The sample used for spectral studies had an analysis in close agreement with theory. Ultraviolet spectrum (95% ethanol): λ_{max} 228, 285, 293 mμ; ϵ_{max} 39,400, 12,200, 11,500.

2-(2′-Methylindoyl)-3-methylindoline ("crossed" dimer). The reaction was carried out under the conditions described for the preparation of diskatole, using 0.005 mole each of 2-methylindole and skatole. After about 15 min. of reaction a red gelatinous mass was deposited which prevented effective stirring. Introduction of hydrogen chloride was continued with occasional stirring for an additional 45 min. The solvent was removed by distillation *in vacuo*, and the residue was dried overnight in a vacuum desiccator. The red powder which was obtained in this way was triturated with hot 10% sodium hydroxide and extracted with benzene. The combined extracts were dried over sodium sulfate, concentrated to about 50 ml, and heated to boiling. *n*-Hexane was added until the hot solution was turbid, when the solution was allowed to cool to room temperature and was then placed in the refrigerator overnight. The oil which was deposited partially solidified on scratching, and the whole mass was filtered. The semisolid residue was again subjected to the benzene-hexane conditions for crystallization and a small quantity of white powder, m.p. 209–213° dec. was obtained. Recrystallization of this material from 95% ethanol and finally from absolute ethanol (25 ml. for 0.5 g. of solid) produced a white powder, m.p. 214–215° dec.

Anal. Calcd. for C_9H_9N: C, 82.40; H, 6.91; N, 10.68. Found: C, 82.52; H, 7.18; N, 10.78. Ultraviolet spectrum (95% ethanol): λ_{max} 227, 285, 291; ϵ_{max} 48,000, 13,500, 12,500. Infrared spectrum (KBr): 3.00, 3.07 μ (NH bands). The "crossed" dimer was much less soluble in all solvents than diskatole and did not show the latter's sensitivity to air and light.

The principal product from this reaction was diskatole, isolated by concentrating the various mother liquors from the crystallizations. Some 2-methylindole was also recovered. Attempts to improve the yield of the "crossed" dimer by using a 3:1 molar ratio of 2-methylindole to skatole, or by adding a solution of skatole dropwise to the stirred solution of 2-methylindole and hydrogen chloride were unsuccessful. No "crossed" dimer was obtained.

NMR studies. The NMR spectra were obtained by E. R. Shull at the Linde Laboratories using a Varian V-4300 B 40 mc. high-resolution NMR spectrometer equipped with a 12 inch electromagnet and super stabilizer. The NMR patterns of the compounds in solution were inserted during continuous scans between the CHO and CH_3 peaks of acetaldehyde, as a means of approximating the chemical shifts. The areas under the NMR peaks were obtained using an Ott planimeter.

Acknowledgment. The authors are indebted to Dr. Earl Whipple of the Union Carbide Research Institute for many helpful discussions of the NMR spectra and their interpretation.

TARRYTOWN, N. Y.

(25) A. Patchornick, W. B. Lawson, and B. Witkop, *J. Am. Chem. Soc.*, **80**, 4748 (1958).

(26)(a) B. Witkop, *J. Am. Chem. Soc.*, **72**, 2311 (1950); (b) K. Freter, J. Axelrod, and B. Witkop, *J. Am. Chem. Soc.*, **79**, 3191 (1957).

(27)(a) N. J. Leonard and F. P. Hauck, Jr., *J. Am. Chem. Soc.*, **79**, 5279 (1957); (b) N. J. Leonard and A. G. Cook, *J. Am. Chem. Soc.*, **81**, 5627 (1959).

(28) Melting points are uncorrected. Ultraviolet spectra were determined with a Beckman DK-2 recording spectrophotometer and infrared spectra with a Perkin-Elmer 21 instrument equipped with sodium chloride optics.

[CONTRIBUTION FROM THE ORGANIC RESEARCH DIVISION, U. S. VITAMIN & PHARMACEUTICAL CORPORATION]

Hydantoic Acid Esters and Amides

SEYMOUR L. SHAPIRO, IRA M. ROSE, ERIC ROSKIN, AND LOUIS FREEDMAN

Received May 27, 1960

A series of hydantoic acid amides and δ-substituted hydantoic acid esters and amides has been synthesized and examined for pharmacological effects. Selected compounds afforded good anticonvulsant and antiinflammatory activity.

Many investigations of substituted hydantoins have yielded important pharmacological activity,[1] and other workers[2] have evaluated open chain analogs of such physiologically active ring systems. Herein, such analogs of hydantoin (Table) have been examined for pharmacological activity, particularly as anti-inflammatory agents,[3] anticonvulsants,[1] and antibacterial agents.[4]

The reaction of ethyl hydantoate with primary amines proceeded readily in methanol to give the corresponding amides of hydantoic acid (compounds 46–60), and with α,ω-diamines, the diamides[5,6] were obtained (compounds 61–68). While the reaction was readily effected with substituted alkylamines (compounds 48, 58, 59), it was unsuccessful with secondary amines (*N*-methylbenzylamine), or with amines having substituents on the α-carbon atom (*d*-α-methylphenethylamine, α-phenethylamine, isopropylamine, benzhydrylamine).

Bachmann[7] found water was an acceptable solvent using methylamine, but the sterically hindered α-phenethylamine could not be induced to react in methanol, in methanol under sodium methoxide catalysis, or in water. Instead, the reaction with this amine, as well as with *N*-methylbenzylamine, yielded hydantoin.

With the amines successfully employed, ethyl hydantoate is converted and does not cyclize to hydantoin. Alternatively, with steric hindrance in the amine,[8,9] cyclization to hydantoin occurs. It was of interest that the benzylamine failed to give the corresponding amide when acetonitrile was substituted for methanol as the solvent. Aromatic amines such as aniline,[10] did not react, nor did sodium *p*-aminobenzoate.[11]

The reactions of amines with carbethoxymethyl isocyanate[12,13] gave the corresponding ethyl α-substituted hydantoates (compounds 1–17). These were readily isolable crystalline solids except in the instance of the esters from the *N*-methyldialkylaminoalkylamines which were obtained as liquids. In the reaction with dimethylaminopropylamine, a waxy product was obtained which, in the course of purification by distillation, cyclized to 3-dimethylaminopropylhydantoin (I).

The ethyl δ-substituted hydantoates were converted by treatment with ammonia to the hydantoamides (compounds 18–33), and with benzylamine to the corresponding *N*-benzyl δ-substituted hydantoamides (compounds 34–45).

Compound 9 which has an aliphatic and aromatic carbethoxy group gave but a single product with each amine (compounds 26 and 40) with attack presumably involving displacement at the more reactive aliphatic ester site.[14]

(1) (a) J. J. Spurlock, *J. Am. Chem. Soc.*, **75**, 1115 (1953); (b) P. C. Teague, A. R. Ballentine, and G. L. Rushton, *J. Am. Chem. Soc.*, **75**, 3429 (1953); (c) E. Ware, *Chem. Revs.*, **46**, 403 (1953); (d) R. E. Nitz, W. Persch, and A. Schmidt, *Arzneimittel-Forsch.*, **5**, 357 (1955); (e) C. L. Mitchell, H. H. Keasling, and E. G. Gross, *J. Am. Pharm. Assoc., Sci. Ed.*, **48**, 122 (1959); (f) W. Perkow, *Arzneimittel-Forsch.*, **10**, 284 (1960); (g) B. Lustig and W. Persch, *Arzneimittel-Forsch.*, **4**, 733 (1954); (h) G. Stille and I. Brunckow, *Arzneimittel-Forsch.*, **4**, 723 (1954).

(2) (a) J. H. Billman and P. H. Hidy, *J. Am. Chem. Soc.*, **65**, 760 (1943); (b) S. D. Upham and O. C. Dermer, *J. Org. Chem.*, **22**, 799 (1957); (c) S. L. Shapiro, I. M. Rose, F. C. Testa, E. Roskin, and L. Freedman, *J. Am. Chem. Soc.*, **81**, 6498 (1959).

(3) (a) L. A. Cohen and E. M. Fry, *J. Am. Chem. Soc.*, **78**, 5863 (1956); (b) B. K. Forscher and H. C. Cecil, *J. Dental Research*, **36**, 927 (1957).

(4) (a) R. L. Dennis, W. J. Plant, C. G. Skinner, G. L. Sutherland, and W. Shive, *J. Am. Chem. Soc.*, **77**, 2362 (1955); (b) E. Froelich, A. Fruehan, M. Jackman, F. K. Kirchner, E. J. Alexander, and S. Archer, *J. Am. Chem. Soc.*, **76**, 3099 (1954).

(5) C. L. Agre, C. Dinga, and R. Pflaum, *J. Org. Chem.*, **21**, 561 (1956).

(6) O. Stoutland, L. Heglen, and C. L. Agre, *J. Org. Chem.*, **24**, 818 (1959).

(7) W. E. Bachmann and C. E. Maxwell III, *J. Am. Chem. Soc.*, **72**, 2880 (1950).

(8) S. L. Shapiro, I. M. Rose, and L. Freedman, *J. Am. Chem. Soc.*, **80**, 6065 (1958).

(9) For similar dependence of steric factors on reactivity in a related series, see E. J. Tarlton, S. Gelblum, M. A. Mosley, and A. F. McKay, *J. Org. Chem.*, **23**, 1973 (1958).

(10) In ref. 7, reaction of aniline with ethyl δ-nitrohydantoate gave ethyl δ-phenylhydantoate, m.p. 109.5–110° (see Table I, compound 8) with no attack at the ester group.

(11) S. L. Shapiro, I. M. Rose, and L. Freedman, *J. Am. Chem. Soc.*, **81**, 6322 (1959).

(12) R. G. Arnold, J. A. Nelson, and J. J. Verbanc, *Chem. Revs.*, **57**, 47 (1957).

(13) D. A Smith and C. C. Unruh, *J. Org. Chem.*, **23**, 301 (1958).

(14) (a) L. L. Herbst, Jr., and M. E. Jacox, *J. Am. Chem. Soc.*, **74**, 3004 (1952); (b) C. C. Price and W. J. Belanger, *J. Am. Chem. Soc.*, **76**, 2682 (1954); (c) B. Jones and J. G. Watkinson, *J. Chem. Soc.*, 4064 (1958); (d) H. M. Humphreys and L. P. Hammett, *J. Am. Chem. Soc.*, **78**, 521 (1956).

TABLE I

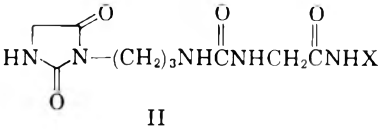
No.	R	M.P.,[b] or B.P., (Mm.)[c]	S[d]	Yield,[e] %	Formula	Analyses, %[f] Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
					RR_1—N—CO—$NHCH_2COOC_2H_5$[a]						
1[g]	$HOCH_2CH_2$—	74–77	A	83	$C_7H_{14}N_2O_4$	44.2	44.0	7.4	7.1		
2	C_3H_5—[h]	82–83	A	90	$C_8H_{14}N_2O_3$					15.0	15.4
3	i-C_5H_{11}—	77–78	B	78	$C_{10}H_{20}N_2O_3$	55.5	55.8	9.3	9.3	13.0	12.6
4	n-C_7H_{15}—	64–65	A	96	$C_{12}H_{24}N_2O_3$					11.5	11.2
5	[i]	109–114	B	89	$C_{13}H_{22}N_2O_3$	61.4	61.1	8.7	8.8	11.0	10.6
6	$C_6H_5CH_2CHCH_3$—[j]	73–76	B	50	$C_{14}H_{20}N_2O_3$	63.6	63.4	7.6	7.7	10.6	10.5
7	$(C_6H_5)_2CH$—	154–155	C	57	$C_{18}H_{20}N_2O_3$	69.2	69.3	6.5	6.3	9.0	9.5
8[k]	C_6H_5—	111–113	B	74	$C_{11}H_{14}N_2O_3$						
9	p-$C_2H_5OOCC_6H_4$—	139–140	C	81	$C_{14}H_{18}N_2O_5$	57.1	57.1	6.2	6.2		
10	$(CH_3)_2N(CH_2)_2$—[a1]	122–126 (0.10)		76	$C_{10}H_{21}N_3O_3$	51.9	51.8	9.2	9.2	18.2	17.8
11	$(C_2H_5)_2N(CH_2)_2$—[a1]	123 (0.10)		86	$C_{12}H_{25}N_3O_3$	55.6	55.1	9.7	9.9	16.2	16.4
12	$(CH_3)_2N(CH_2)_3$—[a1]	128–130 (0.12)		82	$C_{11}H_{23}N_3O_3$	53.9	53.1	9.5	9.5		
13	[l]	65–66	B	45	$C_{10}H_{19}N_3O_3$	52.4	52.8	8.4	8.4	18.3	18.5
					$C_2H_5OOCCH_2NHCONH$—X—$NHCONHCH_2COOC_2H_5$[m]						
14	—$(CH_2)_3$—	157–159	D	78	$C_{13}H_{24}N_4O_6$	47.0	47.3	7.3	7.4		
15	—$(CH_2)_4$—	169–172	E	85	$C_{16}H_{30}N_4O_6$	48.5	48.5	7.6	7.5	16.2	16.1
16	—$(CH_2)_6$—	170–174	E	91	$C_{16}H_{30}N_4O_6$	51.3	51.7	8.1	8.0	15.0	15.3
17	[n]	207–208	D	79	$C_{14}H_{24}N_4O_6$	48.8	49.3	7.0	7.0	16.3	16.3
					$RR_1NCONHCH_2CONH_2$[a]						
18	$HOCH_2CH_2$—	159–161	E	19	$C_5H_{11}N_3O_3$	37.3	37.8	6.9	6.8	26.1	26.4
19	C_3H_5—[h]	197–198	A	47	$C_6H_{11}N_3O_2$	45.9	46.2	7.1	6.9	26.7	26.4
20	i-C_5H_{11}—	158–161	F	23	$C_9H_{17}N_3O_2$	51.3	51.7	9.2	9.1	22.4	22.6
21	n-C_7H_{15}—	194–195	A	77	$C_{10}H_{21}N_3O_2$	55.8	55.9	9.8	9.5		
22	[i]	118–121	D	47	$C_{11}H_{19}N_3O_2$	58.6	58.8	8.5	8.3	18.7	19.2
23	$C_6H_5CH_2CHCH_3$—[j]	171–173	A	47	$C_{12}H_{17}N_3O_2$	61.3	61.1	7.3	7.5	17.9	17.8
24	$(C_6H_5)_2CH$—	225–229	E	50	$C_{16}H_{17}N_3O_2$	67.8	68.1	6.1	6.2		
25	C_6H_5—	195–197	A	76	$C_9H_{11}N_3O_2$	56.0	56.5	5.7	5.7	21.8	22.1
26	p-$C_2H_5OOCC_6H_4$—	204–205	A	74	$C_{12}H_{15}N_3O_4$	54.3	54.5	5.7	5.8		
27	$(CH_3)_2N(CH_2)_2$—[a1]	97–100	A	94	$C_8H_{18}N_4O_2$	47.5	47.7	9.0	9.2	27.7	28.2
28	$(C_2H_5)_2N(CH_2)_2$—[a1]	84–85	A	83	$C_{10}H_{22}N_4O_2$	52.2	52.2	9.6	10.1	24.3	24.1
29	$(CH_3)_2N(CH_2)_3$—[a1]	95–97	A	97	$C_9H_{20}N_4O_2$	50.0	50.0	9.3	9.2	25.9	25.4
30	[o]	202–204	A	95	$C_7H_{13}N_3O_2$	49.1	49.0	7.7	7.2	24.6	24.4
31	[l]	180–185	A	84	$C_9H_{15}N_4O_4$	48.0	48.2	8.1	7.8	28.0	27.7
					$NH_2COCH_2NHCONH$—X—$NHCONHCH_2CONH_2$[m]						
32	—$(CH_2)_3$—	224–225	F	24	$C_9H_{18}N_6O_4$	39.4	39.4	6.6	7.1	30.6	30.6
33	[n]	228 dec.	F	97	$C_{10}H_{22}N_6O_6$[p]	37.3	38.0	6.9	7.1	26.1	26.7
					$RR_1NCONHCH_2CONHCH_2C_6H_5$[a]						
34	C_3H_5—[h]	186–188	A	38	$C_{13}H_{17}N_3O_2$	63.1	63.0	6.9	7.1	17.0	16.7
35	i-C_5H_{11}—	174–177	C	50	$C_{15}H_{23}N_3O_2$	65.0	65.4	8.4	8.3	15.2	15.4

TABLE I (*Continued*)

No.	R	M.P.,[b] or B.P., (Mm.)[c]	S[d]	Yield,[e] %	Formula	Analyses, %[f] Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
36	*n*-C_7H_{15}—	160–162	A	34	$C_{17}H_{27}N_3O_2$					13.8	14.0
37	[i]	178–179	D	47	$C_{18}H_{25}N_3O_2$	68.5	68.4	8.0	7.8	13.3	13.6
38	$(C_6H_5)_2CH$—	225–230	E	42	$C_{12}H_{23}N_3O_2$	74.0	74.6	6.2	6.1	11.3	11.1
39	C_6H_5—	210–211	A	71	$C_{16}H_{17}N_3O_2$	67.8	68.3	6.1	6.5	14.8	15.1
40	*p*-$C_2H_5OOCC_6H_4$—	211–212	G	31	$C_{19}H_{21}N_3O_4$	64.2	64.0	6.0	6.1		
41	$(CH_3)_2N(CH_2)_2$—[a1]	93	H	32	$C_{15}H_{24}N_4O_2$	61.6	61.6	8.3	8.2	19.2	19.5
42	$(CH_3)_2N(CH_2)_3$—	136–137	C	34	$C_{15}H_{24}N_4O_2$	61.6	61.2	8.3	8.2	19.2	19.5
43	[j]	145–150	C	35	$C_{14}H_{19}N_3O_2$					16.1	16.2
44	[k]	180–183	A	51	$C_{15}H_{22}N_4O_2$	62.0	62.4	7.6	7.6	19.3	19.4
45	[q]	197–203	E	58	$C_{24}H_{30}N_6O_4$	61.8	61.2	6.5	6.6	18.0	17.3
					$NH_2CONHCH_2CONHR$						
46[r]	H	198–200	A	79							
47[s]	CH_3—	181–183	E	76							
48	$HOCH_2CH_2$—	133–134	I	63	$C_5H_{11}N_3O_3$	37.3	37.3	6.9	6.6	26.1	26.0
49	C_3H_5—[h]	177–178	I	33	$C_6H_{11}N_3O_3$	45.9	45.9	7.1	7.1	26.7	26.8
50	*i*-C_5H_{11}—	201–202	J	35	$C_8H_{17}N_3O_2$	51.3	51.4	9.2	9.3	22.4	22.3
51	*n*-C_5H_{11}—	183–185	J	57	$C_8H_{17}N_3O_2$	51.3	51.0	9.2	9.1	22.4	22.5
52	*n*-C_7H_{15}—	182–185	J	63	$C_{10}H_{21}N_3O_2$					19.5	19.2
53	[i]	209–211	J	61	$C_{11}H_{19}N_3O_2$	58.6	58.3	8.6	8.1		
54	[k]	175–177	J	22	$C_8H_{11}N_3O_3$	48.7	48.8	5.6	5.7		
55	$C_6H_5CH_2$—	198–200	J	36	$C_{10}H_{13}N_3O_2$	58.0	58.2	6.3	6.7	20.3	20.0
56	*p*-$ClC_6H_4CH_2$—	197–198	F	58	$C_{10}H_{12}ClN_3O_2$	49.7	50.0	5.0	5.4	17.4	17.4
57	$C_6H_5CH_2CH_2$—	175–177	J	49	$C_{11}H_{15}N_3O_2$	59.7	60.0	6.8	6.6	19.0	18.6
58	$(C_2H_5)_2N(CH_2)_2$—	145–147	D	58	$C_9H_{20}N_4O_2$	50.0	50.1	9.3	8.9	25.9	26.3
59	$(CH_3)_2N(CH_2)_3$—	163–167	D	47	$C_8H_{18}N_4O_2$	47.5	47.6	9.0	8.9	27.7	27.4
60	[u]	205–206	D	57	$C_9H_{21}IN_4O_2$	31.4	31.4	6.2	6.0		
					$NH_2CONHCH_2CONH$—X—$NHCOCH_2NHCONH_2$[m]						
61	—$(CH_2)_2$—	233–234	G	62	$C_8H_{16}N_6O_4$	36.9	36.8	6.2	6.1	32.3	32.4
62	—$(CH_2)_3$—	226–228	G	68	$C_9H_{18}N_6O_4$	39.4	39.3	6.6	6.5		
63	—$(CH_2)_4$—	242–244	G	45	$C_{10}H_{20}N_6O_4$	41.7	41.8	7.0	7.1		
64	—$(CH_2)_5$—	246	G	49	$C_{11}H_{22}N_6O_4$	43.7	43.4	7.3	6.7	27.8	27.9
65	—$(CH_2)_6$	221–222	G	50	$C_{12}H_{24}N_6O_4$	45.6	45.8	7.7	7.7	26.6	26.6
66	—$(CH_2)_7$—	230	G	35	$C_{13}H_{26}N_6O_4$	47.3	47.2	7.9	7.8	25.4	25.3
67	*m*-$CH_2C_6H_4CH_2$—	220–222	G	45	$C_{14}H_{20}N_6O_4$	50.0	49.8	6.0	6.0	25.0	25.0
68	—$(CH_2)_3NCH_3(CH_2)_3$—	182–183	G	49	$C_{13}H_{27}N_7O_4$	45.2	44.9	7.9	7.9	28.4	27.9

[a] R_1 is hydrogen unless otherwise shown; [a1] $R_1 = CH_3$. [b] Melting points were determined on a Fisher-Johns melting point block and are not corrected. [c] Compound no. (n_D^{20}) — 10(1.4715); 11(1.4694); 12(1.4704). [d] S = recrystallizing solvent; A = crystallized from reaction mixture; B = ethyl acetate—hexane; C = ethyl acetate; D = ethyl acetate—ethanol; E = ethanol; F = water; G = ethanol-water; H = ethyl acetate–ether; I = ethyl acetate–methanol; J = butanol–ethyl acetate. [e] Yields are indicated for analytically pure product. [f] Analyses by Weiler and Strauss, Oxford, England. [g] Reported, A. C. Smith, Jr., and C. C. Unruh, *J. Org. Chem.*, **22**, 442 (1957). [h] C_3H_5 = allyl. [i] R = 2,5 endo methylenecyclohexylmethyl—. [j] Derived from *d*-α-methylphenethylamine. [k] Reported, W. Siefkin, *Ann.*, **562**, 75 (1949), m.p. 111°. [l] RR_4N derived from *N*-methylpiperazine. [m] X shown under R column as —$(CH_2)_n$—. [n] HN—X—NH replaced by derivative from piperazine. [o] RR_4N is pyrrolidyl; compound obtained from corresponding ethyl ester, m.p. 112–113°. [p] Analyses calculated for dihydrate. [q] Compound is bis-*N*-benzyl derivative of compound 33. [r] Reported, Beilstein IV, p. 362, m.p. 204°. [s] Reported, W. E. Bachmann and C. E. Maxwell, III, *J. Am. Chem. Soc.*, **72**, 2880 (1950), m.p. 180–180.5°. [t] R = furfuryl. [u] Methiodide of compound 59.

Ammonia or benzylamine gave the desired amides with compounds 1 and 2 as well as the unanticipated[15] by-products, 3-hydroxyethylhydantoin and 3-allylhydantoin, respectively. The diester, compound 14, similarly reacted gave amides as well as a by-product, indicative of cyclization coupled with amidation, II.



II

X = H
$C_6H_5CH_2$—

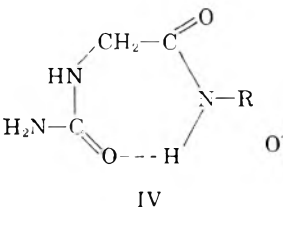
In the anticonvulsant test[16] the principal effects were noted with the δ,δ^1-polymethylenebishydantoamides (compounds 61–67). Interestingly, compound 61 potentiated metrazole convulsions, whereas compounds 63 and 66 gave 3+ anticonvulsant activity. The hexamethylene derivative (compound 65) gave the peak effect with 4+ activity.

The *m*-xylylene derivative in this group (compound 67) was without anticonvulsant action (as was compound 68), but showed good central nervous system (CNS) depressant effects[17] (LD_{min} = 500 mg./kg.), per cent reduction in activity = 23% at 20 mg./kg. Compounds 26 and 58 also showed good CNS depressant effects.

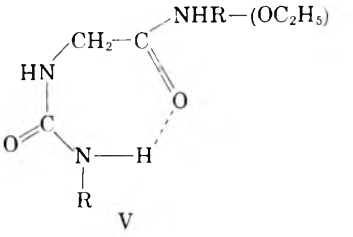
Good anti-inflammatory activity[18] was noted as follows: Compound No./LD_{min} mg./kg./units per gram: 55/100/80; 58/>1000/9; 45/200/22; 53/-300/20; 18/750/15; 23/450/10; 57/200/10; 51/-1000/7.5. Other compounds with lesser activity (< 10 units per gram) were compounds 3, 6–9, 13, 14, 16, 19, 21, 22 and 30.

Other noteworthy responses were hypotension with compounds 39 and 42, hypertension with compound 3, ganglionic block with compound 42, adrenergic block with compound 48, and bronchodilation with compounds 12 and 27. Antibacterial evaluation of selected compounds will be reported elsewhere.

The proven hydrogen-bonded cyclic structure for biurets[19] would suggest consideration of similar structures for compounds of this series as typified by IV and V.



IV



V

EXPERIMENTAL[20]

p-Chlorobenzylamide of hydantoic acid (Compound 56). A solution of 3.65 g. (0.025 mole) of ethyl hydantoate and 3.89 g. (0.028 mole) of *p*-chlorobenzylamine in 35 ml. of methanol, after standing 14 days, gave 3.99 g. (66%) of product, m.p. 195–196°.

Titrations in other runs with selected amines and ethyl hydantoate indicated: compound 49, 67% reaction in 3 days and 77% after 5 days; compound 50, 82% reaction after 9 days. In general, for compounds 46–68, the reaction mixture was stored 10–15 days at 20° before work-up.

Using 3-bis(hydroxyethyl)aminopropylamine, titration indicated complete reaction after 12 days although no pure compound was isolated. Similarly, with 1,2-propanediamine, titration indicated reaction of one equivalent of amino group with no pure compound isolated.

Using α-phenethylamine as the reactant amine, titration indicated less than 10% reaction after 8 days, and after an 8-hr. reflux period, hydantoin (19%) was isolated, m.p. 220°. This reaction failed when similarly conducted under sodium methoxide catalysis, or in water. The following sterically hindered amines also failed to give products: *d*-α-methylphenethylamine, isopropylamine, benzhydrylamine, and *N*-methylbenzylamine.

When aniline was heated with ethyl hydantoate at 159° in the absence of solvent, a rapid evolution of ammonia initiated, and 50% of reactant ester was recovered. The use of butanol as a solvent resulted in similar evolution of ammonia, and 69% recovery of ethyl hydantoate.

Sodium *p*-aminobenzoate did not react after 8 days in methanol.

Ethyl δ-p-carbethoxyphenyl hydantoate (Compound 9). A solution of 2.5 g. (0.019 mole) of carbethoxymethyl isocyanate in 50 ml. of ether was treated portion-wise with 3.5 g. (0.021 mole) of ethyl *p*-aminobenzoate, with rapid formation of product, 5.3 g. (93%), m.p. 135°.

3-Dimethylaminopropylhydantoin. A solution of 9.7 g. (0.08 mole) of carbethoxymethyl isocyanate in 100 ml. of ether was maintained at 0–20° during the addition of 8.4 g. (0.08 mole) of dimethylaminopropylamine. Evaporation of the ether afforded a gelatinous residue which on distillation, b.p. 146–150° (0.2 mm.) gave 1.65 g. of an oil which crystallized. Recrystallization (ethyl acetate–hexane) afforded the product (9%), m.p. 86–87°.

Anal. Calcd. for $C_8H_{15}N_3O_2$: C, 51.9; H, 8.2; N, 22.7. Found: C, 52.3; H, 8.2; N, 22.4.

N^1-[(N-Carbethoxymethyl)carbamido]-N^4-methylpiperazine (Compound 13). A solution of 9.7 g. (0.075 mole) of carbethoxymethyl isocyanate in 50 ml. of ethyl acetate was maintained at 0° during the addition of 7.62 g. (0.075 mole) of *N*-methylpiperazine. After 3 days, 1.65 g. of crystals were separated (solid A) and the filtrate concentrated to an oily residue which after trituration with ether gave 0.65 g. (solid B). Evaporation of the ether filtrate gave an oil which was extracted repeatedly with hexane (total 1.2 l.), and which on standing and clearing with ethyl acetate gave 7.7 g. (45%) of product, m.p. 65–66°.

(15) L. L. McKinney, U. S. Pat. 2,829,157 (Apr. 1, 1958), indicates the δ-substituted hydantoic acid esters cyclize to hydantoins under the influence of heat or acid, with reversal of this reaction under alkaline conditions.

(16) For method of testing see S. L. Shapiro, V. A. Parrino, and L. Freedman, *J. Am. Chem. Soc.*, 81, 3996 (1959).

(17) For method of testing see S. L. Shapiro, I. M. Rose, E. Roskin, and L. Freedman, *J. Am. Chem. Soc.*, 80, 1648 (1958).

(18) For method of testing see S. L. Shapiro, H. Soloway, and L. Freedman, *J. Am. Pharm. Assoc., Sci. Ed.*, 46, 333 (1957).

(19) (a) W. D. Kumler and C. M. Lee, American Chemical Society, Cleveland Meeting, 1960, p. 35N; (b) I. C. Kogon, *J. Am. Chem. Soc.*, 79, 2253 (1957); (c) M. Nardelli and I. Chierici, *J. Chem. Soc.*, 1952 (1960).

(20) Descriptive data shown in the table are not reproduced in the Experimental. Typical examples of the synthesis are given.

Solid A, recrystallized (ethyl acetate–ethanol) gave 0.65 g., m.p. 207–208°, identical with compound 17.[21]

Solid B, recrystallized (ethyl acetate–hexane) gave 0.37 g., m.p. 140–144° of unproved structure[22] which fits the following empirical formula.

Anal. Calcd. for $C_9H_{16}N_2O_5$: C, 46.6; H, 6.9; N, 12.1. Found: C, 47.2; H, 6.8; N, 12.2.

δ-p-Carbethoxyphenylhydantoamide (Compound 26). A solution of 2.42 g. (0.008 mole) of compound 9 in 30 ml. of methanol was maintained below 35° while saturated with ammonia and stoppered. After 3 days at 20°, 1.6 g. of product separated, m.p. 204–205°. The filtrate on standing gave an additional 0.35 g., m.p. 204–205° (total yield 90%).

N-Benzyl-δ-hydroxyethylhydantoamide. A solution of 3.2 g. (0.016 mole) of compound 1 in 20 ml. of methanol was treated with 1.9 g. (0.018 mole) of benzylamine. After 3 days, 100 ml. of ether was added. On standing, 1.17 g. of crystals was obtained, m.p. 90–95°. The filtrate was evaporated and on solution in 40 ml. of ethyl acetate and seeding yielded 0.8 g. of crystals. Repetition of this process gave 0.32 g. of the above, total 2.29 g. This was dissolved in a mixture of 3 ml. of ethanol and 55 ml. of ethyl acetate. The initial crop of crystals was separated (0.25 g.), m.p. 135–141°, and recrystallized (ethanol–ethyl acetate) to give 0.1 g. of product, m.p. 140–141°.

Anal. Calcd. for $C_{12}H_{17}N_3O_3$: C, 57.4; H, 6.8; N, 16.7. Found: C, 57.4; H, 6.6; N, 17.1.

The filtrate on further standing gave a different solid which recrystallized (ethanol-hexane), m.p. 103.5–104°, proved to be 3-hydroxyethylhydantoin.[23]

Anal. Calcd. for $C_5H_8N_2O_3$: C, 41.7; H, 5.6. Found: C, 41.7; H, 5.4.

δ-Hydroxyethylhydantoamide (Compound 18). A solution of 4.0 g. (0.02 mole) of compound 1 in 20 ml. of methanol was saturated with ammonia. After storage for 3 days at 20° and seeding, 1.65 g. of crude product was obtained. The filtrate on dilution with 200 ml. of ether gave 0.85 g. of crude 3-hydroxyethylhydantoin, m.p. 90–96°.

N-Benzyl-δ-allylhydantoamide (Compound 34). A solution of 3.0 g. (0.016 mole) of compound 2 in 30 ml. of methanol was treated with 1.9 g. (0.018 mole) of benzylamine. After 3 days, upon seeding and cooling at 10° for 4 hr., 0.9 g. of product was obtained, m.p. 186–188°. Concentration of the filtrate and trituration with ethyl acetate gave an additional 0.6 g. of product, m.p. 186–187°; total yield 38%. The ethyl acetate was removed from the filtrate and the residue triturated with hexane gave 1.35 g. (60%) of crystals of 3-allylhydantoin,[24] m.p. 75°; recrystallized (ethyl acetate–hexane) m.p. 78°.

Anal. Calcd. for $C_6H_8N_2O_2$: C, 51.4; H, 5.8; N, 20.0. Found: C, 50.8; H, 5.8; N, 20.1.

Under similar conditions, employing ammonia and compound 2, *δ-allyl-hydantoamide* (compound 19) was obtained in 47% yield, and *3-allylhydantoin* (m.p. 78°) was obtained in 19% yield.

δ,δ¹-Trimethylenebishydantoamide (Compound 32). A solution of 4.0 g. (0.012 mole) of compound 14 in 45 ml. of methanol was maintained below 30° while saturated with ammonia. After 24 hr., 2.57 g. of crystals were obtained and dissolved in 60 ml. of water, yielding 0.8 g. (24%), m.p. 224–225°. The aqueous filtrate was concentrated to 10 ml. to give 0.85 g. (24%) of crystals, m.p. 180–184°, which analysis indicated to be the hydantoin II, X = H.

Anal. Calcd. for $C_9H_{15}N_5O_4$: C, 42.0; H, 5.9. Found: C, 41.5; H, 6.2.

δ,δ¹-Trimethylene(bis-N-benzylhydantoamide). A solution of 3.3 g. (0.01 mole) of compound 14 in 30 ml. of methanol was treated with 4.28 g. (0.04 mole) of benzylamine. After 4 days the formed solid (1.6 g.) was separated, m.p. 160–190°, and recrystallized (dimethylformamide) to give 0.52 g. (12%) of product, m.p. 195–207°.

Anal. Calcd. for $C_{22}H_{30}N_6C_4$: N, 18.5. Found N, 18.1.

Evaporation of the filtrate and trituration with ether gave 1.4 g. of white solid, recrystallized from water to give 0.7 g. (20%) of crystals which analysis indicated to be the hydantoin II, X = $C_6H_5CH_2$—.

Anal. Calcd. for $C_{16}H_{21}N_5O_4$: C, 55.3; H, 6.1; N, 20.2. Found: C, 55.3; H, 5.6; N, 20.3.

Acknowledgment. The authors wish to thank Dr. G. Ungar and his staff for the pharmacological results of the screening of the compounds, and F. Testa for his technical assistance.

YONKERS 1, N. Y.

(21) This may have resulted from the presence of piperazine as an impurity in the *N*-methylpiperazine.

(22) E. Fischer, *Ber.*, **34**, 440 (1901), reports carbonyldiglycindiethyl ester, m.p. 146°, prepared from phosgene and glycine diethyl ester.

(23) A. C. Smith, Jr., and C. C. Unruh, *J. Org. Chem.*, **22**, 442 (1957), report m.p. 98–101°.

(24) Beilstein, XXIV, p. 250, reports m.p. 78°.

[CONTRIBUTION FROM THE PFISTER CHEMICAL WORKS, INC.]

Amino Acid Analogs. I. Analogs of the Glutamic Acid, Proline Interconversion. Part I. ω-Methyl- and ω-Phenylketoglutamic Acids and 5-Methyl- and 5-Phenylprolines

HERMAN GERSHON AND ALFRED SCALA

Received September 29, 1960

Some analogs of glutamic acid, Δ′-pyrroline-5-carboxylic acid and proline were synthesized.

The interconversion of glutamic acid and proline in both animal tissues and microorganisms has been reviewed by Stetten[1] and Vogel.[2] This relationship consists essentially of the following series of reversible transformations: glutamic acid ⇌ glutamic-γ-semialdehyde ⇌ Δ′-pyrroline-5-carboxylic

(1) M. R. Stetten, *Amino Acid Metabolism*, W. D. McElroy and H. B. Glass, eds., Johns Hopkins Press, Baltimore, Md., 1955, p. 277.

(2) H. J. Vogel, *Amino Acid Metabolism*, W. D. McElroy and H. B. Glass, eds., Johns Hopkins Press, Baltimore, Md., 1955, p. 335.

acid ⇌ proline. Since this sequence seems to be a major metabolic pathway for both glutamic acid and proline, it was of interest to prepare analogs of these compounds and their respective intermediates in order to determine whether, by this means, metabolic inhibition could be achieved.

It was reported by Ginsburg, Lovett, and Dunn[3] that the strain of tuberculosis bacteria, which infects humans, has on the average 50% more glutamic acid than noninfectious strains. Glutamic acid and proline have also been implicated in cancer[4-7] studies. It is evident that glutamic acid and proline analogs should be of interest in studies of these diseases.

Among the structural alterations which can be employed for forming antimetabolites is the substitution of a methyl or phenyl ketone for a carboxyl group. Several successful antimetabolites have thus been prepared. Woolley,[8] *et al.* found that β-acetylpyridine was a nicotinic acid antagonist. Upon replacing the carboxyl group in pantothenic acid by a phenyl ketone, Woolley[9] and Collyer produced a potent pantothenic acid antagonist. Employing the same structural alteration, Dittmer[10] reported that α-aminolevulinic acid and aspartophenone were aspartic acid antagonists.

The substitution of a methyl group for a hydrogen atom has also led to successful antagonists. Examples of this replacement include α-methylaspartic acid,[11] ethionine,[12] methyltryptophans,[13,14] and many others.

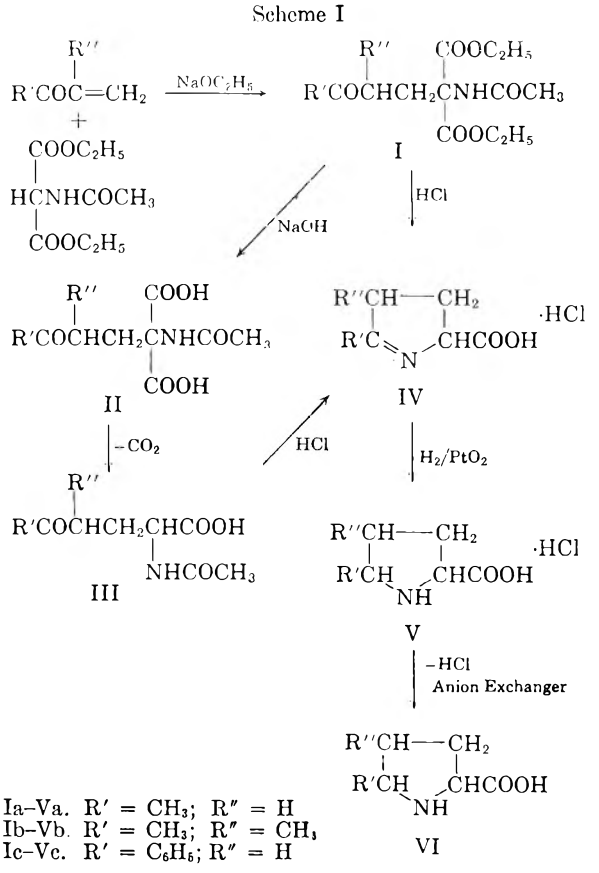
Scheme I indicates the approach to the preparation of the analogs of each of the intermediates of the glutamic acid to proline interconversion.

The synthetic methods with some modifications were modeled after the condensation of acrolein with ethyl acetamidomalonate by Moe and Warner[15] and the hydrolysis and hydrogenation procedures of Vogel and Davis.[16] Methyl vinyl ketone and methyl isopropenyl ketone were condensed with acetamidomalonate according to the conditions of the Michael condensation, and β-bromopropiophenone was condensed with ethyl acetamidomalonate in the presence of sodium ethylate, slightly in excess of one molecular proportion. When the intermediates were hydrolyzed by alkali, malonic acids were obtained which, on decarboxylation, yielded the corresponding acetylated glutamic acid analogs. These analogs, and the ethyl acetamidomalonate condensation products, were acid hydrolyzed to yield 2- and 2,3-substituted Δ′-pyrroline-5-carboxylic acids which, in turn, were hydrogenated over Adams' catalyst at three to four atmospheres of hydrogen to 5- and 4,5-substituted prolines.

The substituted prolines, Va–c, the pyrroline, IV-b and the methyl ketone, III-b can exist as diastereoisomeric racemates. The stereochemistry of these compounds has not been determined.

After completion of this work, the current literature revealed the preparation of ethyl acetamido-3-oxobutylmalonate by Sanno[17] and its hydrolysis to Δ′-2-methylpyrroline-5-carboxylic acid hydrochloride. The hydrogen of this pyrroline to 5-methylproline hydrochloride was also reported by Sanno[18] *et al.*

Scheme I



Ia–Va. R′ = CH_3; R″ = H
Ib–Vb. R′ = CH_3; R″ = CH_3
Ic–Vc. R′ = C_6H_5; R″ = H

(3) B. Ginsburg, S. L. Lovett, and M. S. Dunn, *Arch. Biochem. Biophys.*, 60, 164 (1956).

(4) S. Kit and J. Awapara, *Cancer Research*, 13, 694 (1953).

(5) F. S. Hammett, *Proc. Soc. Exptl. Biol. Med.*, 45, 601 (1940).

(6) J. M. White, G. Ozawa, G. A. L. Ross, and E. W. McHenry, *Cancer Research*, 14, 508 (1954).

(7) J. R. Beaton, W. J. McGanity, and E. W. McHenry, *Can. Med. Assoc. J.*, 65, 219 (1951).

(8) D. W. Woolley, F. M. Strong, R. J. Madden, and C. A. Elvehjem, *J. Biol. Chem.*, 124, 715 (1938).

(9) D. W. Woolley and M. L. Collyer, *J. Biol. Chem.*, 159, 263 (1945).

(10) K. Dittmer, *Antimetabolites*, R. W. Miner, ed., *Annals N. Y. Acad. Sci.*, 52, 1274 (1950).

(11) E. Roberts and P. F. Hunter, *Proc. Soc. Exptl. Biol. Med.*, 83, 720 (1953).

(12) H. M. Dyer, *J. Biol. Chem.*, 124, 519 (1938).

(13) T. F. Anderson, *Science*, 101, 565 (1945).

(14) P. Fildes and H. M. Rydon, *Brit. J. Exptl. Pathol.*, 28, 211 (1947).

(15) O. A. Moe and D. T. Warner, *J. Am. Chem. Soc.*, 70, 2763 (1948).

(16) H. J. Vogel and B. D. Davis, *J. Am. Chem. Soc.*, 74, 109 (1952).

(17) Y. Sanno, *Yakugaku Zasshi*, 78, 1113 (1958); *Chem. Abstr.*, 53, 5238 (1959).

Seven of these compounds, III-a and b; IV-a, b, and c; and V-a and b were screened for antitubercular activity in mice by Dr. Crowle[19] according to his method, and were found to be ineffective.

All of the malonic acids, glutamic acid analogs, pyrrolines, and prolines were screened by the Cancer Chemotherapy National Service Center against Sarcoma-180, Carcinoma-755, and Leukemia-1210 in mice. The results were generally negative.

Work with proline requiring mutants of *Escherichia coli* is now in progress and will be reported on at a later date.

EXPERIMENTAL

Ethyl 2-acetamido-2-carbethoxy-5-oxohexanoate (I-a). To 200 ml. of absolute ethanol in which 1.25 g. (0.054 g.-atom) of sodium had been dissolved, was added 217 g. (1.0 mole) of ethyl acetamidomalonate. Keeping the temperature below 25°, 90 g. (1.29 moles) of methyl vinyl ketone[20] was added dropwise with agitation. Stirring was continued overnight, and then the sodium ethylate was neutralized with glacial acetic acid and the crystalline product filtered and washed with ether. The yield was 214 g., m.p. 80–85°. The mother liquor was diluted with an equal volume of ether and cooled in the freezer overnight. An additional yield of 47 g. was obtained, m.p. 76–85°. The combined crude yield was 94%. An analytical sample was prepared by recrystallization from water, m.p. 87°, lit.,[17] m.p. 89–90°.

Anal. Calcd. for $C_{13}H_{21}NO_6$: C, 54.36; H, 7.32; N, 4.88. Found: C, 54.89; H, 7.20; N, 4.87.

Ethyl 2-acetamido-2-carbethoxy-4-methyl-5-oxohexanoate (I-b). To 180 ml. of absolute ethanol, in which 1.25 g. (0.054 g.-atom) of sodium had been dissolved, was added 217 g. (1.0 mole) of ethyl acetamidomalonate, and 110 g. (1.29 moles) of methyl isopropenyl ketone[21] was added dropwise with agitation at 12–15°. The mixture was stirred for 4 hr. and let stand overnight. After neutralization of the base with glacial acetic acid, the alcohol was removed under vacuum, and the residue was taken up in 200 ml. of methylene chloride and washed with 100 ml. of water, which was back extracted with methylene chloride. Upon evaporation of the methylene chloride, 282 g. of a sirupy residue remained, which could not be crystallized. The yield was 93% and the product was sufficiently pure for further work.

Ethyl 2-acetamido-4-benzoyl-2-carbethoxybutyrate (I-c). In 840 ml. of absolute ethanol was dissolved 23.4 g. (1.02 g.-atoms) of sodium and 217 g. (1.0 mole) of ethyl acetamidomalonate was added. To the clear solution was added, dropwise with agitation, 213 g. (1.0 mole) of β-bromopropiophenone, prepared according to Foreman and McElvain.[22] The mixture was agitated and kept under reflux overnight. On cooling, the sodium bromide was filtered off and washed with alcohol. The combined filtrates were evaporated under vacuum and the residue was taken up in methylene chloride, washed with water, and the methylene chloride evaporated. The residue was dissolved in isopropyl alcohol, cooled in the freezer, and the crystals were collected and washed with ether. The yield was 261 g., 75%, m.p. 110–112°. An analytical sample was prepared from 50% aqueous isopropyl alcohol, m.p. 113–114°.

Anal. Calcd. for $C_{18}H_{23}NO_6$: C, 61.89; H, 6.59; N, 4.01. Found: C, 61.55; H, 6.45; N, 3.92.

Acetamido(3-oxobutyl)malonic acid (II-a). To a solution of 20 g. (0.5 mole) of sodium hydroxide in 200 ml. of water was added 57.4 g. (0.2 mole) of ethyl 2-acetamido-2-carbethoxy-5-oxohexanoate. The mixture was allowed to stand overnight. The solution was treated with decolorizing carbon and passed through a column of Amberlite IR-120 (H^+) to remove the alkali. The eluate was decolorized with charcoal and evaporated under vacuum below 40°. The crude yield was 17.7 g. of product, 60% m.p. 92–95° dec. An analytical sample was prepared from isopropyl alcohol, keeping the temperature below 50°, m.p. 97–98° dec.

Anal. Calcd. for $C_9H_{13}NO_6$: C, 46.75; H, 5.63; N, 6.06. Found: C, 46.97; H, 5.51; N, 5.66.

DL-*2-Acetamido-5-oxohexanoic acid* (III-a). A solution was made of 46.2 g. (0.2 mole) of the malonic acid in water and boiled for 1 hr. till gas evolution ceased. The solution was decolorized with charcoal and evaporated to dryness under vacuum. The sirupy residue was taken up in 150 ml. of isopropyl alcohol, decolorized with charcoal, and 20 ml. of ether was added. After cooling to −20° with occasional stirring, the solution was allowed to remain in the freezer 1–2 days. A crude product weighing 35.5 g. (95% yield) was obtained, m.p. 96–98°. An analytical sample was prepared by recrystallization from 2:1 methanol-ether, m.p. 102–103°.

Anal. Calcd. for $C_8H_{13}NO_4$: C, 51.34; H, 6.95; N, 7.49. Found: C, 51.69; H, 7.15; N, 7.48.

Acetamido(2-methyl-3-oxobutyl)malonic acid (II-b). The procedure was the same as for the previous malonic acid. The yield was 54% and the product decomposed at 100–102°. An analytical sample was prepared from isopropyl alcohol, which melted with gas evolution at 106°.

Anal. Calcd. for $C_{10}H_{15}NO_6$: C, 48.98; H, 6.12; N, 5.71. Found: C, 49.12; H, 6.01; N, 5.46.

2-Acetamido-4-methyl-5-oxohexanoic acid (III-b). The procedure was the same as for the previous hexanoic acid, and the yield was 92%. The product melted at 118–122°. An analytical sample was prepared from isopropyl alcohol, m.p. 128–129°.

Anal. Calcd. for $C_9H_{15}NO_4$: C, 53.73; H, 7.46; N, 6.97. Found: C, 53.57; H, 7.60; N, 7.11.

Acetamido(2-benzoylethyl)malonic acid (IV-c). To a solution of 20 g. (0.5 mole) of sodium hydroxide in 400 ml. of 50% ethanol was added 69.8 g. (0.2 mole) of ethyl 2-acetamido-4-benzoyl-2-carbethoxybutyrate. On standing overnight, the sodium salt of the malonic acid crystallized. The product was brought into solution by the addition of 1000 ml. of water, decolorized with charcoal, and acidified with concentrated hydrochloric acid. The malonic acid was filtered off, washed free of chloride, and dried at 50°, m.p. 189–192° with gas evolution. The crude yield was 55.7 g. 95%. An analytical sample was prepared by recrystallization from isopropyl alcohol, m.p. 192–193° dec.

Anal. Calcd. for $C_{14}H_{15}NO_6$: C, 57.33; H, 5.12; N, 4.78. Found: C, 57.31; H, 4.31; N, 4.48.

DL-*2-Acetamido-4-benzoylbutyric acid* (III-C). The decarboxylation of acetamido(2-benzoylethyl)malonic acid was carried out by boiling 58.6 g. (0.2 mole) in 1000 ml. of water for 2 hr. The mixture was cooled in the refrigerator overnight, filtered, and washed with water. The yield of crude product was 38.5 g., 77%, m.p. 195–196°. An analytical sample was prepared from isopropyl alcohol, m.p. 195–196°.

Anal. Calcd. for $C_{12}H_{13}NO_4$: C, 62.65; H, 6.02; N, 5.62. Found: C, 62.95; H, 6.07; N, 5.48.

Δ'-*2-Methylpyrroline-5-carboxylic acid hydrochloride* (IV-a). Eighty-six and one-tenth grams (0.3 mole) of ethyl-2-acetamido-2-carbethoxy-5-oxohexanoate was heated under reflux with 500 ml. of concd. hydrochloric acid overnight. The excess acid was removed under vacuum in a flash evaporator. The residue was taken up in water, decolorized with

(18) S. Tatsuoka, K. Tanaka, Y. Ueno, and Y. Sanno, Japan. 9977 (1958), Nov. 19; *Chem. Abstr.*, **54**, 5696 (1960).

(19) A. J. Crowle, *Tubercle*, **39**, 41 (1958).

(20) Methyl vinyl ketone was purchased from Charles Pfizer and Co., Inc., Brooklyn, N. Y.

(21) Methyl isopropenyl ketone was generously supplied by Celanese Corporation of America, New York 16, N. Y.

(22) E. L. Foreman and S. M. McElvain, *J. Am. Chem. Soc.*, **62**, 1435 (1940).

charcoal, and evaporated to dryness in the evaporator. The product was taken up in 150 ml. of methanol and cooled for several days in the freezer. The crystals were filtered, washed with acetone and dried, yielding 29.8 g. of crude material, 61%, m.p. 186–189° dec. An analytical sample was prepared from 1:1 methanol ether, m.p. 189–190° dec., lit.,[17] m.p. 193° dec.

Anal. Calcd. for $C_6H_{10}ClNO_2$: C, 44.17; H, 6.12; N, 8.56. Found: C, 43.97; H, 6.29; N, 8.49.

5-Methylproline hydrochloride (V-a). A solution of 16.4 g. (0.1 mole) of Δ′-2-methylpyrroline-5-carboxylic acid hydrochloride in 150 ml. of methanol was made and 50 mg. of platinum oxide was added. The mixture was hydrogenated in the Parr hydrogenator under 3 atm. of pressure for 0.5 hr., at which time the theoretical uptake of hydrogen was completed. The catalyst was filtered off and the solvent evaporated under a stream of air. A quantitative yield of 5-methylproline hydrochloride was obtained, m.p. 184–188°. An analytical sample was obtained from methanol, m.p. 191–192°, lit.,[19] m.p. 186–187°.

Anal. Calcd. for $C_6H_{12}ClNO_2$: C, 43.50; H, 7.25; N, 8.46. Found: C, 43.66; H, 7.27; N, 8.50.

5-Methylproline (VI-a). The free amino acid was obtained from the hydrochloride by passing an aqueous solution through a column of Amberlite IR-45 in the acetate cycle. The effluent was taken to dryness under vacuum and the residue was recrystallized from isopropyl alcohol, m.p. 188–189°.

Anal. Calcd. for $C_6H_{11}NO_2$: C, 55.81; H, 8.53; N, 10.85. Found: C, 56.22; H, 8.72; N, 10.60.

Δ′-2,3-Dimethylpyrroline-5-carboxylic acid hydrochloride (IV-b). The title compound was prepared from ethyl 2-acetamido-2-carbethoxy-4-methyl-5-oxohexanoate in the same manner as Δ′-2-methylpyrroline-5-carboxylic acid hydrochloride. The yield was 61%, m.p. 148–150°. An analytical sample was prepared from methanol mixed with ether, m.p. 153–154°.

Anal. Calcd. for $C_7H_{12}ClNO_2$: C, 47.32; H, 6.76; N, 7.89. Found: C, 47.45; H, 6.78; N, 8.01.

4,5-Dimethylproline hydrochloride (V-b). This compound was prepared by hydrogenation in the same manner as 5-methylproline hydrochloride. The yield was quantitative, m.p. 128–130°. An analytical sample was prepared from methanol, m.p. 131.5–133.0°.

Anal. Calcd. for $C_7H_{14}ClNO_2$: C, 46.92; H, 8.35; N, 7.80. Found: C, 46.52; H, 8.30; N, 7.90.

4,5-Dimethylproline (VI-b). The method of preparation was the same as for 5-methylproline. An analytical sample was prepared from isopropyl alcohol, m.p. 196.5–197.5°.

Anal. Calcd. for $C_7H_{13}NO_2$: C, 58.74; H, 9.09; N, 9.79. Found: C, 58.36; H, 8.86; N, 9.33.

Δ′-2-Phenylpyrroline-5-carboxylic acid hydrochloride (IV-c). The title compound was prepared from ethyl 2-acetamido-4-benzoyl-2-carbethoxybutyrate by the same method as Δ′-2-methylpyrroline-5-carboxylic acid hydrochloride. The yield was 55%, m.p. 169–173°. An analytical sample was prepared from a 1:2 methanol-ether mixture, m.p. 172–173°.

Anal. Calcd. for $C_{11}H_{12}ClNO_2$: C, 58.54; H, 5.76; N, 6.29. Found: C, 58.43; H, 5.50; N, 6.20.

5-Phenylproline hydrochloride (V-c). The method of preparation was the same as for 5-methylproline hydrochloride; however, the product crystallized only once after standing in the freezer for 2 years. It could not be recrystallized. The yield was 62% and the product was analyzed without further purification, m.p. 115–117°.

Anal. Calcd. for $C_{11}H_{14}ClNO_2$: C, 58.02; H, 6.15; N, 6.15. Found: C, 58.38; H, 6.37; N, 6.17.

5-Phenylproline (VI-c). The method of preparation was the same as for 5-methylproline. An analytical sample was prepared from isopropyl alcohol, m.p. 213–214°.

Anal. Calcd. for $C_{11}H_{13}NO_2$: C, 69.10; H, 6.81; N, 7.33. Found: C, 69.57; H, 7.28; N, 7.23.

RIDGEFIELD, N. J.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, TENNESSEE EASTMAN CO., DIVISION OF EASTMAN KODAK CO.]

Addition of 2-Aminopyridines to Methyl Propiolate

GERALD R. LAPPIN

Received September 15, 1960

The reaction of 2-aminopyridine with methyl propiolate gave not only the expected 2H-pyrido[1,2-a]pyrimidin-2-one, but also a noncyclic adduct of one mole of the aminopyridine and two moles of ester, methyl 2-(2-methoxycarbonylvinylimino)-1(2H)-pyridineacrylate. The various methyl-2-aminopyridines reacted similarly to form methyl-2H-pyrido[1,2-a]-pyrimidin-2-ones. Unexpectedly, 6-methyl-2-aminopyridine gave only this type of product. The other methyl-2-aminopyridines gave, in addition, homologs of the 1:2 adduct above noted. A 1:1 adduct, a methyl 2-imino-3(or 4)-methyl-1(2H)-pyridineacrylate, could also be obtained in the reaction with 3-methyl-2-aminopyridine and 4-methyl-2-aminopyridine

The addition of amines to α,β-acetylenic esters has been reported to give β-amino-α,β-ethylenic esters.[1] The addition of 2-aminopyridines to an α,β-acetylenic ester has not been reported. However, this amine adds to methyl acrylate to give not only a noncyclic product derived from the amino tautomer[2] but also a cyclic product derived from the imino tautomer of the aminopyridine.[2,3] It appeared of interest to investigate the effect of the 2-aminopyridine tautomerism on its addition to an α,β-acetylenic ester such as methyl propiolate.

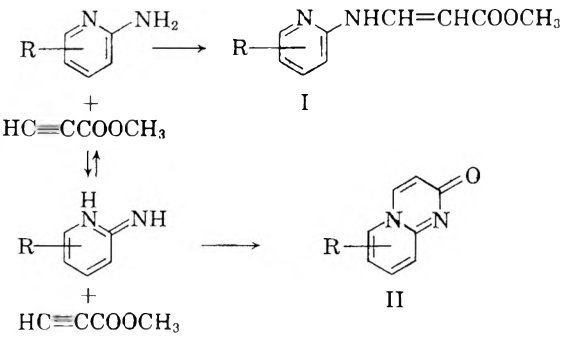
By analogy with the reported reaction with methyl acrylate, the addition of 2-aminopyridine to methyl propiolate might be expected to give two products, methyl 2-(2-pyridylamino)acrylate (I. R = H) and 2H-pyrido[1,2-a]pyrimidin-2-one (II. R = H).

Compounds having both types of structures are known. The acid produced by hydrolysis of I, 2-(2-pyridylamino)acrylic acid, can be prepared by hydrolysis of diethyl (2-pyridylaminomethylene)

(1) C. Moureu and I. Lazennac, *Bull. Soc. Chim.*, **35**, 1190 (1906).

(2) R. Adams and I. Pachter, *J. Am. Chem. Soc.*, **74**, 5491 (1952).

(3) G. R. Lappin, *J. Org. Chem.*, **23**, 1358 (1958).



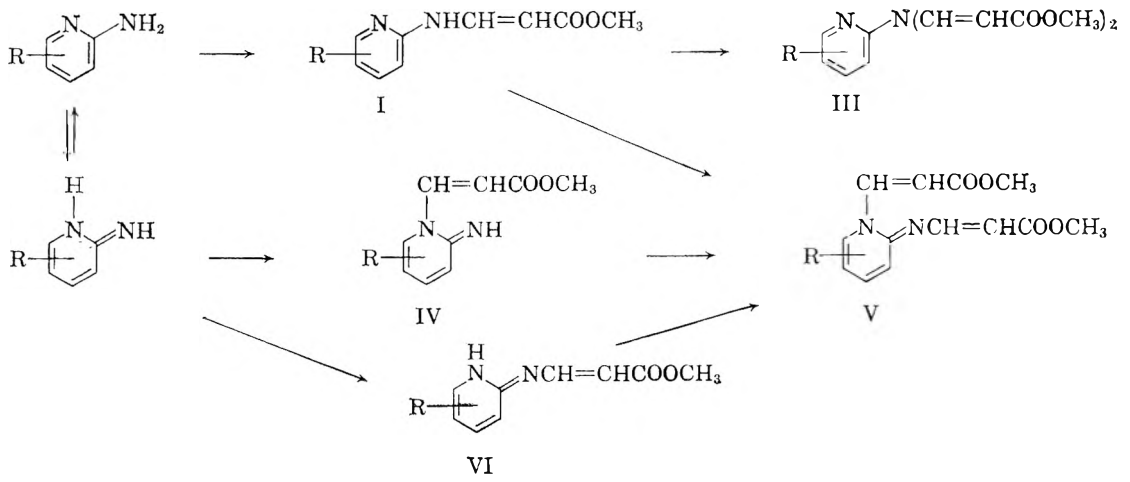
malonate,[4] while II can be prepared by the reaction of 2-aminopyridine with 2-bromoacrylic acid.[2]

When 2-aminopyridine was mixed with methyl propiolate, a violently exothermic reaction occurred. The product was a red tar from which no identifiable substance could be obtained. However, if the reaction was carried out in ether solution at 10–20° using equimolar quantities of the two reactants, a solid product slowly precipitated from the solution. Visual examination of this product showed that it consisted of a mixture of white crystals and orange crystals. These two substances could be cleanly separated by continuous ether extraction. The white, completely insoluble product was shown to be 2H-pyrido[1,2-a]pyrimidin-2-one (II. R = H) by comparison of its infrared spectrum with that of an authentic specimen. The slightly soluble, orange, crystalline product, m.p. 134–135°, had the correct analysis for $C_{13}H_{14}N_2O_4$, an adduct of one mole of 2-aminopyridine with two moles of methyl propiolate. This type of product will hereafter be called a diadduct. The use of an excess of 2-aminopyridine did not alter the nature of the products obtained.

When this reaction was applied to the various methyl-2-aminopyridines, the results were similar. All except 6-methyl-2-aminopyridine gave a mixture of an ether-insoluble, high-melting, colorless product in 7–34% yield and a lower melting yellow or orange product which was slightly ether-soluble in 29–63% yield. Only one product was obtained with 6-methyl-2-aminopyridine, a 77% yield of a high-melting, ether-insoluble, colorless solid. In each case, ether extraction gave a clean separation of the two types of products. All of the high-melting, insoluble products were shown to be methyl - 2H - pyrido[1,2 - a]pyrimidin - 2 - ones (II. R = CH_3) by analysis and comparison of their infrared spectra with that of 2H-pyrido[1,2-a]-pyrimidin-2-one. Because 6-methyl-2-amino-pyridine had previously given only 1,8-naphthyridine derivatives in cyclization reactions[5] and gave no cyclic product with methyl acrylate,[3] the high yield of 5-methyl-2H-pyrido[1,2-a]pyrimidin-2-one was completely unexpected. To further confirm the structure of this product, it was subjected to alkaline hydrolysis. A good yield of 6-methyl-2-aminopyridine was obtained, showing that the compound did indeed have the pyridopyrimidinone structure. The isomeric 1,8-naphthyridin-4-ol would have survived this hydrolysis unchanged.

Analysis of the colored, lower melting products showed that only the one from 5-methyl-2-aminopyridine was a diadduct of the type given by 2-aminopyridine. Both 3-methyl-2-aminopyridine and 4-methyl-2-aminopyridine gave a monoadduct; that is, a 1:1 adduct of the amine and methyl propiolate. These monoadducts, however, could be converted to diadducts by reaction with more methyl propiolate. In the case of 4-methyl-2-aminopyridine, using an excess of methyl propiolate gave a low yield of monoadduct in the insoluble product, but also a higher yield of the more soluble diadduct in the ether solution. Neither 2-aminopyridine nor 5-methyl-2-aminopyridine could be made to give a monoadduct, however. It appears that the type of adduct formed is largely dependent on the relative insolubility of the monoadduct and diadduct of a given 2-aminopyridine in ether.

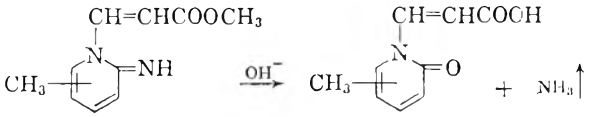
The structures considered for the adducts were



as follows. If the initial attack was at the amino nitrogen, the monoadduct would have the 2-(2-pyridylamino)acrylate structure, I. The addition of the second mole of methyl propiolate could then

(4) G. R. Lappin, *J. Am. Chem. Soc.*, **71**, 3258 (1949).
(5) G. R. Lappin, *J. Am. Chem. Soc.*, **70**, 3348 (1948).

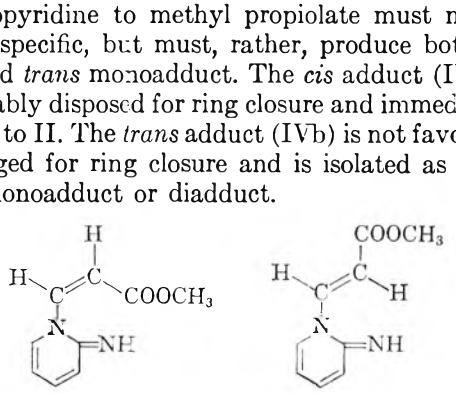
occur either at the amino nitrogen or the ring nitrogen to give either III or V. If the initial attack occurred at the ring nitrogen, the monoadduct would be a 2-imino-1(2H)-pyridineacrylate (IV) and the second mole of methyl propiolate could react only at the imino nitrogen to give a 2-(2-methoxycarbonylvinylimino) - 1(2H) - pyridineacrylate (V). Another, but less likely, structure for the monoadduct is VI, which would also give V as the diadduct. The fact that the monoadducts and diadducts were colored seemed to eliminate I and III from consideration. The structure of the monoadducts was positively established as IV by their easy alkaline hydrolysis to ammonia and a methyl-2-oxo-1(2H) - pyridineacrylic acid (VII). Neither I nor VI could give these products.



VII

With the structure IV established for the monoadduct, the diadduct could only be V.

Attempts to cyclize the monoadduct to II were unsuccessful; therefore, the addition of the 2-aminopyridine to methyl propiolate must not be stereospecific, but must, rather, produce both the *cis* and *trans* monoadduct. The *cis* adduct (IVa) is favorably disposed for ring closure and immediately closes to II. The *trans* adduct (IVb) is not favorably arranged for ring closure and is isolated as either the monoadduct or diadduct.



IVa IVb

The reaction of 2-aminopyridine and the methyl-aminopyridines has produced two unexpected and, at present, unexplained results. First, 6-methyl-2-aminopyridine gave a good yield of pyridopyrimidinone, although in all previously reported reactions of this compound only noncyclic products or 1,8-naphthyridines have been produced. Second, noncyclic, nonresonance-stabilized, imino-form adducts have been isolated for the first time. Previously reported 2-aminopyridine derivatives substituted on the ring nitrogen have been either a quaternary salt such as 1-methyl-2-aminopyridinium iodide, in which the pyridine ring is in its normal resonance-stabilized form rather than the imino form or a cyclic derivative of the imino form such as II.

EXPERIMENTAL

Addition of 2-aminopyridine to methyl propiolate. To a cold solution of 9.4 g. (0.1 mole) of 2-aminopyridine in 50 ml. of ether, a solution of 8.4 g. (0.1 mole) of methyl propiolate in 10 ml. of ether was added. A solid precipitate appeared after 30 min. and appeared to continue to increase in amount for 48 hr. After this time, the product was collected by filtration and was then extracted with dry ether in a Soxhlet extractor until the effluent from the extraction was colorless. There remained undissolved 3.4 g. (24%) of off-white crystals, m.p. 248–250°. This material was shown to be 2H-pyrido[1,2-a]pyrimidin-2-one (II. R = H) by comparison of its infrared spectrum with that of an authentic specimen.

The ether solution from the extraction was evaporated to dryness to give 8.0 g. (29%) of yellow-orange crystals (V. R = H), m.p. 134–135° after recrystallization from ethyl alcohol.

Anal. Calcd. for $C_{13}H_{14}N_2O_4$: C, 59.5; H, 5.35; N, 10.7. Found: C, 59 8; H, 5.47; N, 10.5.

When this experiment was repeated using 18.8 g. (0.2 mole) of 2-aminopyridine and 8.4 g. (0.1 mole) of methyl propiolate, there was obtained 3.8 g. of II, R = H, and 6.8 g. of V, R = H.

A third experiment carried out in the same manner, except that 9.4 g. (0.1 mole) of 2-aminopyridine and 16.8 g. (0.2 mole) of methyl propiolate were used, gave 2.3 g. of II, R = H, and 10.5 g. of V, R = H.

Addition of 3-methyl-2-aminopyridine to methyl propiolate. To a cold solution of 11.0 g. (0.1 mole) of 3-methyl-2-aminopyridine in 50 ml. of ether, a solution of 8.4 g. (0.1 mole) of methyl propiolate in 10 ml. of ether was added. The reaction was quite exothermic and cooling was required to prevent the solution from boiling. After 24 hr. at 5–10°, the product was collected and extracted with dry ether in a Soxhlet extractor, as in the reaction with 2-aminopyridine. The insoluble, white crystalline product (II. R = 8 − CH_3) m.p. 226–228°, weighed 6.0 g. (37%).

Anal. Calcd. for $C_9H_8N_2O$: C, 67.5; H, 5.00; N, 17.5. Found: C, 67.3; H, 5.13; N, 17.2.

By evaporation of the ether solution there was obtained 8.5 g. (44%) of IV, R = 3 − CH_3, as golden yellow crystals, m.p. 114–115°.

Anal. Calcd. for $C_{10}H_{12}N_2O_2$: C, 62.5; H, 6.25; N, 14.59. Found: C, 62.1; H, 6.44; N, 14.60.

Addition of 4-methyl-2-aminopyridine to methyl propiolate. To a solution of 11.0 g. (0.1 mole) of 4-methyl-2-aminopyridine in 200 ml. of ether was added 8.4 g. (0.1 mole) of methyl propiolate. After 1 week the product was collected and extracted as before. There was obtained 1.1 g. (7%) of II R = 7 − CH_3; m.p. 255–260° dec.

Anal. Calcd. for $C_9H_8N_2O$: C, 67.5; H, 5.00; N, 17.5. Found: C, 67.4; H, 5.12; N, 17.3.

The soluble product (IV. R = 4 − CH_3) was obtained as golden yellow crystals from ethyl alcohol–ether, m.p. 101–102°, weight, 12.0 g. (63%).

Anal. Calcd. for $C_{10}H_{12}N_2O_2$: C, 62.5; H, 6.25; N, 14.59. Found: C, 62.4; H, 6.44; N, 14.38.

When 11.0 g. (0.1 mole) of 4-methyl-2-aminopyridine was treated in exactly the same manner with 16.8 g. (0.2 mole) of methyl propiolate, the insoluble product gave, after extraction, 1.2 g. of the pyridopyrimidinone (II. R = 7 − CH_3) and 5.6 g. of the monoadduct (IV. R = 4 − CH_3). Evaporation of the filtrate from the reaction mixture, followed by recrystallization of the residue from ethyl alcohol, gave 9.1 g. of pinkish buff crystals (V. R = 4 − CH_3) m.p. 140–141°.

Anal. Calcd. for $C_{14}H_{16}N_2O_4$: C, 60.8; H, 5.80; N, 10.15. Found: C, 60.7; H, 5.63; N, 10.02.

Addition of 5-methyl-2-aminopyridine to methyl propiolate. A solution of 11.0 g. (0.1 mole) of 5-methyl-2-aminopyridine and 8.4 g. (0.1 mole) of methyl propiolate in 50 ml. of ether was held at room temperature for 4 days. The product was collected and extracted as before. There was obtained 2.3 g. (15%) of II, R = 6 − CH_3, m.p. 226–228°.

Anal. Calcd. for $C_9H_8N_2O$: C, 67.5; H, 5.00; N, 17.5. Found: C, 67.4; H, 5.05; N, 17.1.

There was also obtained 11.3 g. (41%) of V, R = 5 − CH_3, as yellow crystals, m.p. 152–153°, after recrystallization from alcohol.

Anal. Calcd. for $C_{14}H_{16}N_2O_4$: C, 60.8; H, 5.80; N, 10.15. Found: C, 61.1; H, 6.10; N, 10.25.

Addition of 6-methyl-2-aminopyridine to methyl propiolate. A solution of 11.0 g. (0.1 mole) of 6-methyl-6-aminopyridine and 8.4 g. (0.1 mole) of methyl propiolate in 50 ml. of dry ether was held at room temperature for 5 days. Filtration of the mixture gave 12.3 g. (77%) of II, R = 5 − CH_3, m.p. 194–195°.

Anal. Calcd. for $C_9H_8N_2O$: C, 67.5; H, 5.00; N, 17.5. Found: C, 67.2; H, 5.21; N, 17.6.

This substance rapidly absorbed water from the air to give a dihydrate which dehydrated to the anhydrous form when heated to about 150°.

Anal. Calcd. for $C_9H_{12}N_2O_3$: C, 55.1; H, 6.10; N, 14.30. Found: C, 55.3; H, 6.05; N, 14.32.

Evaporation of the filtrate from the isolation of the above product gave a red tar, from which was obtained by distillation 1.3 g. of recovered 6-methyl-2-aminopyridine.

Hydrolysis of 5-methyl-2H-pyrido[1,2-a]pyrimidin-2-one (II. R = 5 −CH_3). This substance (4.8 g., 0.03 mole) was refluxed with 10 ml. of 10% aqueous sodum hydroxide for 10 hr. After being cooled, the solution was extracted with ether in a continuous extractor. Evaporation of the extract gave 2.9 g. (88%) of 6-methyl-2-aminopyridine.

Conversion of monoadduct to diadduct by reaction with methyl propiolate. A solution of 1.9 g. (0.10 mole) of the monoadduct (IV) and 1.0 g. (0.12 mole) of methyl propiolate in 25 ml. of chloroform and 25 ml. of dry ether was refluxed for 4 hr. The solution was then evaporated to dryness *in vacuo* and the residue was recrystallized from ethyl alcohol. In this way the following compounds were obtained.

Methyl 2-(2-methoxycarbonylvinylimino)-4-methylpyridineacrylate (V. R = 4 − CH_3). The yield of brick colored crystals m.p. 140–141°, was 2.1 g. (70%). This compound was shown by a mixture melting point to be identical with the product previously obtained from the reaction of 2 moles of methyl propiolate with 1 mole of 4-methyl-2-aminopyridine.

Methyl 2-methoxycarbonylvinylimino)-3-methylpyridineacrylate (V. R = 3 − CH_3). The yield of yellow crystals, m.p. 151–152°, was 1.8 g. (65%).

Anal. Calcd. for $C_{14}H_{16}N_2O_4$: C, 60.8; H, 5.80; N, 10.15. Found: C, 60.6; H, 5.71; N, 9.96.

Hydrolysis of IV. R = 3 − CH_3. Three grams of this adduct was refluxed for 30 min. with 30 ml. of 10% aqueous sodium hydroxide. Ammonia was evolved during this heating. The solution was cooled and acidified with dilute hydrochloric acid to give, after drying in a vacuum oven, 2.1 g. (70%) of 3-methyl-2-oxo-1(2H)-pyridineacrylic acid, m.p. 238–240°.

Anal. Calcd. for $C_9H_9NO_3$: C, 60.4; H, 5.03; N, 7.82. Found: C, 60.3; H, 5.14; N, 7.65.

Hydrolysis of IV. R = 4 − CH_3. This adduct was hydrolyzed as previously described for IV, R = 3 − CH_3, to give a 62% yield of 4-methyl-2-oxo-1(2H)-pyridineacrylic acid, m.p. 229–230°.

Anal. Calcd. for $C_9H_9NO_3$: C, 60.4; H, 5.03; N, 7.82. Found: C, 60.2; H, 5.30; N, 7.68.

KINGSPORT, TENN.

[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

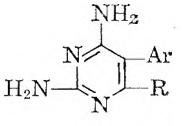
2,4-Diamino-5-[4′-fluoro-3′-halogenophenyl]pyrimidines

RICHARD BALTZLY, LINDA WRIGHT SHEEHAN, AND ALAN STONE

Received December 7, 1960

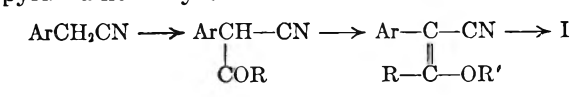
The preparation of 2,4-diamino-6-alkyl-5-[3′,4′-difluorophenyl- and 3′-chloro-4′-fluorophenyl]pyrimidines is described. The route followed involved the chloromethylation of *o*-difluorobenzene and *o*-chlorofluorobenzene and orientation of the product in the latter case.

The 2,4-diamino-6-alkyl-5-[3′,4′-dichlorophenyl] pyrimidines[1] (I. Ar = 3,4-dichlorophenyl; R = alkyl) have appreciable though not spectacular activity against Adenocarcinoma 755 in mice. The corresponding 3′,4′-dibromophenyl derivatives were found to be less active. Hence the synthesis of 3′,4′-difluorophenyl and of chlorofluorophenyl analogs was indicated.



I

The general line of synthesis of this type of pyrimidine is by the route:

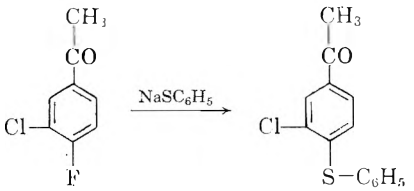


No difficulty was anticipated in following this route except for possible lability of fluorine on aryl during the first and last steps which require strongly alkaline conditions. The necessary starting materials, however, were not readily accessible and it was necessary to prepare them from available compounds. Since *o*-chlorofluorobenzene could be purchased, the preparation was worked out starting with it rather than with the still more expensive *o*-difluorobenzene. Substitution into *o*-chlorofluorobenzene could give rise to isomers.[2] Ingold and Vass reported that nitration took place predominantly *para* to the fluorine (ratio *ca.* 4:1). Since it was desired to avoid a mixture of isomers we first attempted a route through a Friedel-Crafts reaction (which is known to be highly selective). It was hoped to convert the expected 3-chloro-4-fluoroacetophenone to 3-chloro-4-fluorophenylacetic acid by the Willgerodt reaction and thence obtain the desired nitrile.

(1) P. B. Russell and G. H. Hitchings, *J. Am. Chem. Soc.*, **73**, 3763 (1951).

(2) C. K. Ingold and C. C. N. Vass, *J. Chem. Soc.*, 417 (1928).

The Friedel-Crafts reaction on *o*-chlorofluorobenzene gave an acceptable yield of a solid ketone and careful examination of mother-liquors (through formation of the semicarbazone) afforded no evidence of the presence of isomers. A portion of this ketone reacted with sodium thiophenolate to give the diphenyl sulfide II the analyses of whose phenylhydrazone and semicarbazone demonstrate that fluorine rather than chlorine had been displaced. Since halogen *para* to the carbonyl ought to be somewhat activated, we consider this transformation to be evidence that acetylation had taken place *para* to the fluorine.



II

The Willgerodt reaction of 3-chloro-4-fluoroacetophenone (with morpholine and sulfur) gave a most intractable mixture from which (after hydrolysis) only a very small quantity (around 2%) of an acid melting at 53° could be isolated.

The originally preferred approach having failed, recourse was had to the chloromethylation reaction. Since the acid melting at 53° must be the 3-chloro-4-fluorophenyl acetic acid a means of identifying isomers would be available if necessary. While no example of the use of this reaction on *ortho*-dihalogenobenzenes was found, the original paper of Stephen, Short, and Gladding,[3] which describes the chloromethylation of *o*- and *p*-nitrotoluenes under rather drastic conditions, suggested that suitable conditions could be found in this case also. Such indeed proved to be the case. When dissolved in equal parts of sulfuric and acetic acids in the presence of chloromethyl ether and heated on the steam-bath chlorofluorobenzyl chloride was obtained in 12–33% yield depending on the time of heating. When a portion of the acetic acid was replaced by acetic anhydride the yield was raised to about 50%.

This chloromethyl derivative was smoothly converted to a liquid nitrile and a portion of this was hydrolyzed (under acid conditions) to a single chlorofluorophenyl acetic acid, identical with that obtained previously from 3-chloro-4-fluoroacetophenone.

This method of chloromethylation gave similar yields from *o*-difluorobenzene from which only one isomer would be expected. Further operations by the projected route led smoothly to 2,4-diamino-5-[3′-chloro-4′-fluorophenyl]-6-methylpyrimidine, 2,4-diamino-5-[3′,4′-difluorophenyl]-6-methyl and 6-ethylpyrimidines. In tests against transplantable tumors in mice, all three compounds showed no more than trace activity at best.

(3) H. Stephen, W. F. Short, and G. Gladding, *J. Chem. Soc.*, **117**, 510 (1920); *cf.* S. Nishida, *Repts. Sci. Research Inst. (Japan)*, **25**, 399 (1949).

EXPERIMENTAL

3-Chloro-4-fluoroacetophenone. In 100 cc. of carbon bisulfide was dissolved 40 g. (0.3 mole) of *o*-chlorofluorobenzene. To this was added 45 g. of aluminum chloride and gradual addition of acetyl chloride (30 g. = 0.32 mole) was begun, with stirring. When about half of the acetyl chloride had been added there were definite signs of reaction (warming and evolution of hydrogen chloride). The solution was warmed to gentle reflux and the rest of the acetyl chloride was added gradually. After refluxing for 2 hr. the reaction mixture (now in two layers) was allowed to stand overnight. It was then refluxed 2 hr. longer. The upper layer was decanted and the two layers were hydrolyzed separately with ice and hydrochloric acid. The lower layer, taken into ether, dried over calcium chloride, and evaporated contained 30 g. of oil (A). The upper layer, after similar treatment, was found to contain 13 g. of oil (B).

Fraction A was distilled at 7 mm. pressure. After a fore-run (3 g.) boiling around 50° there was obtained a main fraction (19 g.) boiling at 100°. This material solidified and melted about 30°. After two crystallizations from pentane there was obtained 10.5 g. of flat prisms melting at 41–42°.

Anal. Calcd. for C_8H_6ClFO: C, 55.7; H, 3.5. Found: C, 55.9; H, 3.9. This ketone forms a phenylhydrazone, m.p., 116–119°.

Anal. Calcd. for $C_{14}H_{12}ClFN_2$: C, 64.0; H, 4.6. Found: C, 63.9; H, 4.2. The semicarbazone melts at 212–213.5°.

Anal. Calcd. for $C_9H_9ClFN_3O$: C, 47.1; H, 4.0. Found: C, 47.2; H, 3.7. Both the phenylhydrazone and semicarbazone melted somewhat irregularly, apparently with decomposition.

Fraction B together with the fore-run of A was distilled at atmospheric pressure, 10 g. of *o*-chlorofluorobenzene being recovered. From the residue of this distillation and from the mother liquors from crystallization of the crystalline ketone, phenylhydrazones and semicarbazones were prepared. The melting points of these indicated presence of not more than traces of isomeric ketone.

3-Chloro-4-phenylmercaptoacetophenone. To 10 cc. of absolute ethanol was added 2.2 g. (0.02 mole) of thiophenol and 1 g. of the crystalline 3-chloro-4-fluoroacetophenone. The solution was heated to gentle reflux and 0.6 g. (0.11 mole) of solid sodium methoxide was added. The solution was refluxed 4.5 hr., cooled, diluted with water, and partitioned between ether and dilute sodium hydroxide solution. The ethereal layer was washed again with alkali, then with water, and dried over calcium chloride. Evaporation of solvent left a pale-colored oil that did not crystallize. It was distilled at 20–30 μ pressure. The highest-boiling fraction (furnace temperature, 100–117°) was dissolved in ether and shaken with sodium sulfide solution and alkali (to remove traces of diphenyl disulfide). On evaporation of the ether, 1 g. of oil remained. This could not be crystallized; it was dissolved in alcohol and 1 g. of phenylhydrazine and 1 cc. of acetic acid were added. After warming for an hour, cooling and diluting with water a yellow oil separated and subsequently solidified. It was recrystallized from aqueous alcohol forming pale yellow diamond-shaped plates. Since these appeared to be solvated they were recrystallized again from ether-hexane mixture, m.p., 112°.

Anal. Calcd. for $C_{20}H_{17}ClN_2S$: C, 68.1; H, 4.9. Calcd. for $C_{20}H_{17}FN_2S$: C, 71.4; H, 5.1. Found: C, 67.9; H, 4.9.

Another portion of this ketone was converted to the semicarbazone (0.6 g. from 0.5 g. of oily ketone). Colorless crystals from alcohol, m.p., 203°.

Anal. Calcd. for $C_{15}H_{14}ClN_3OS$: C, 56.3; H, 4.4. Calcd. for $C_{15}H_{14}FN_3OS$: C, 59.4; H, 4.7. Found: C, 56.5; H, 4.9.

Willgerodt reaction with 3-chloro-4-fluoroacetophenone. The ketone (8.5 g. 0.05 mole), 2.5 g. of sulfur and 7 g. of morpholine were heated to reflux for 9.5 hr.; 20 cc. of alcohol was added and the mixture was allowed to stand overnight. Attempts to obtain a crystalline thioamide being unsuccessful, the entire material was subjected to hydrolysis with 1:1:2 sulfuric acid–water–acetic acid. The hydrolysate contained much tarry material insoluble in benzene, ether, acid, and alkali. By extraction of the ether-benzene layers with sodium carbonate solution and acidification there was obtained a small amount of organic acid. This was distilled at 20–40 μ pressure and the distillate was crystallized twice from ether-hexane mixture, m.p., 51–53°.

3-Chloro-4-fluorobenzyl chloride. In 70 cc. of glacial acetic acid was dissolved 26 g. (0.2 mole) of *o*-chlorofluorobenzene. To this was added 70 cc. of concd. sulfuric acid, 35 cc. of chloromethyl ether, and 30 cc. of acetic anhydride. The reaction mixture was heated under a reflux condenser for 18 hr. on the steam bath. At the start there was some evolution of gas but at no time was there condensation in the condenser. The reaction mixture was poured onto ice and partitioned between ether and water. The ethereal layer was washed three times with water, once with sodium carbonate solution, and once again with water. After drying over calcium chloride and evaporation of the ether the residue was distilled *in vacuo*. There was a small fore-run followed by a main fraction of 18 g. boiling at 86–93° at 7 mm. This corresponds to a 50% yield. When the acetic anhydride was omitted the conversion was 33% after 18 hr. heating and 12–15% after 3.5 hr.

From the distillation residues was obtained a solid that melted at 85–87° after crystallization from pentane.

Anal. Calcd. for $C_{13}H_8Cl_2F_2$: C, 57.2; H, 3.0. Found: C, 56.9; H, 2.8. This is presumably 3,3′-dichloro-4,4′-difluorodiphenylmethane. It was obviously not the only higher-boiling component of the distillation residues.

3-Chloro-4-fluorophenylacetonitrile. Thirty-four grams of crude chlorofluorobenzylchloride was refluxed 5 hr. with 20 g. of potassium cyanide in 120 cc. of methanol. The solvent was boiled off and the product was taken into ether, washed until neutral, dried over calcium chloride, and distilled at 7 mm. pressure. There was obtained 17 g. of oil boiling from 130–134°.

A 1-g. portion of this nitrile was hydrolyzed in a mixture of 5 cc. each of sulfuric acid, water and acetic acid (22 hr. on the steam-bath). The hydrolysis mixture was cooled, diluted, and partitioned between ether and water. Extraction of the ethereal layer with sodium carbonate solution followed by acidification gave a low-melting organic acid. This was recrystallized from hexane, needles, m.p., 55–56°. There was no depression of melting point when mixed with the 53° melting acid obtained from the Willgerodt procedure.

Anal. Calcd. for $C_8H_6ClFO_2$: C, 50.9; H, 3.2. Found: C, 51.1; H, 2.9.

3,4-Difluorophenylacetonitrile. The chloromethylation of *o*-difluorobenzene was conducted essentially as described for *o*-chlorofluorobenzene and with yields of 42–45%. Omission of the acetic anhydride resulted in 25–30% yields. The 3,4-difluorobenzyl chloride boiled at 76–80° at 15 mm. pressure. It was not possible to isolate a crystalline tetrafluorodiphenylmethane from the distillation residues.

The difluorobenzyl chloride was converted to the nitrile which boils at 110–120° at 13 mm. A 1-g. portion was hydrolyzed to the acid (3,4-difluorophenylacetic acid) which melted at 40–42° after crystallization from hexane.

Anal. Calcd. for $C_8H_6F_2O_2$: C, 55.8; H, 3.5. Found: C, 55.7; H, 3.4.

α-Aryl-β-hydroxycrotononitriles[4] (*α-aryl-α-acyl-acetonitriles*). The dihalogenophenylacetonitriles were condensed with ethyl acetate or ethyl propionate (*ca.* 3 eq.) and sodium ethoxide (1.5 eq.) in absolute alcohol at reflux for 6 hr. essentially as described by Russell and Hitchings.[1] The ketonitriles were obtained fairly pure through solution in alkali followed by acidification and were crystallized from ether-hexane mixture and from methanol for analysis.

α-[3-Chloro-4-fluorophenyl]-β-hydroxycrotononitrile was obtained in 72% yield, as colorless needles, m.p., 136°, from methanol.

Anal. Calcd. for $C_{10}H_7ClFNO$: C, 56.8; H, 3.4 Found: C, 56.8; H, 3.4.

α-[3,4-Difluorophenyl]-β-hydroxycrotononitrile was obtained as colorless prisms from methanol, m.p., 137–138°, yield, 80%.

Anal. Calcd. for $C_{10}H_7F_2NO$: C, 61.6; H, 3.6. Found: C, 61.4; H, 3.4. The ultraviolet absorption spectrum in 95% ethanol showed: λmax., 265 mμ (ε max., 13,500); λ min., 235 mμ (ε min., 4,400).[4]

α-[3,4-Difluorophenyl]-β-hydroxy-Δ-α-pentenonitrile formed colorless prisms from aqueous methanol, m.p. 67–69°; yield, 71%.

Anal. Calcd. for $C_{11}H_9F_2NO$: C, 63.2; H, 4.3. Found: C, 63.3; H, 4.6.

2,4-Diamino-6-alkyl-5-[dihalogenophenyl]pyrimidines. The hydroxycrotononitriles were methylated (to the enol ethers) with excess diazomethane in ether and the enol ethers, without isolation, were condensed with guanidine in absolute ethanol at reflux for 2–3 hr. The pyrimidines were purified by recrystallization from alcohol.

2,4-Diamino-5-[3′-chloro-4′-fluorophenyl]-6-methylpyrimidine formed colorless needles, m.p., 290–291°.

Anal. Calcd. for $C_{11}H_{10}ClFN_4$: C, 52.4; H, 4.0. Found: C, 52.1; H, 4.3.

2,4-Diamino-5-[3′,4′-difluorophenyl]-6-methylpyrimidine formed colorless platelets, m.p., 280–281°.

Anal. Calcd. for $C_{11}H_{10}F_2N_4$: C, 56.0; H, 4.3; N, 23.8. Found: C, 56.2; H, 4.2; N (Kjeldahl), 23.8.

2,4-Diamino-5-[3′,4′-difluorophenyl]-6-ethylpyrimidine formed colorless plates, m.p., 245–247°.

Anal. Calcd. for $C_{12}H_{12}F_2N_4$: C, 57.6; H, 4.8. Found: C, 57.4; H, 4.7.

Acknowledgment. The authors wish to express their gratitude to Dr. S. W. Blackman and Mr. Charles Marr for the micro-analyses here recorded.

TUCKAHOE, N. Y.

(4) For evidence that these compounds are predominantly enolic, *cf.* P. B. Russell and J. Mentha, *J. Am. Chem. Soc.*, **77**, 4245 (1955).

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE POLYTECHNIC INSTITUTE OF BROOKLYN]

Chlorination of Some Alkylpyrazines[1]

ALBERT HIRSCHBERG[2a,b] AND PAUL E. SPOERRI[3]

Received September 9, 1960

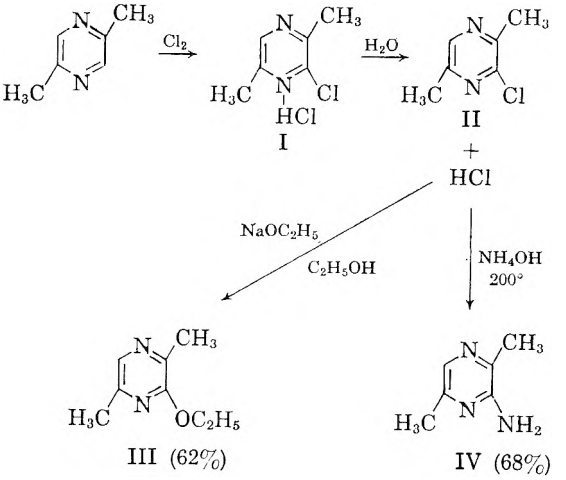
A reinvestigation of the reaction of 2,5-dimethylpyrazine in carbon tetrachloride solution with chlorine under ultraviolet light revealed that the product was 2-chloro-3,6-dimethylpyrazine (II) and that recourse to ultraviolet treatment was unnecessary. Treatment of 2-methylpyrazine with chlorine afforded a mixture of 2-chloro-3-methyl- (VII) and 2-chloro-5-methylpyrazine (VIII). In allowing 2,6-dimethylpyrazine to react with chlorine, it was found that ultraviolet radiation was essential and that the product was an unstable side chain halogenated compound, 2,6-bis(α-chloromethyl)pyrazine (XV). Alcoholysis converted XV to the bis ether XVI. Treating 2-methyl- and 2,5-dimethylpyrazine with one equivalent of *N*-chlorosuccinimide and a small quantity of benzoyl peroxide afforded unstable α-chloromethyl derivatives V and XI which were converted to the corresponding side chain ethers VI and XII.

While a general procedure for preparing 2-chloropyrazines from the corresponding hydroxypyrazines has been described in the literature,[4] it however seemed of interest to study the direct chlorination of various alkylpyrazines. This synthetic approach had been examined previously by C. Larson[5] who reported the preparation of a halogenated compound believed to be 2-(α-chloromethyl)-5-methylpyrazine (V), by treatment of 2,5-dimethylpyrazine with chlorine gas under the influence of ultraviolet radiation. Unexpectedly, however, the attempted ammonolysis and hydrolysis of this alleged α-chloromethylpyrazine were unsuccessful. It was found, however, that the chlorinated compound did react quite readily with sodium ethoxide in absolute ethanol to form the corresponding ether.

In analogy with α-chloromethyl- and α-bromomethylpyridine[6,7,8] which are strong lachrymators and skin irritants and also slowly polymerize on standing, similar properties could be expected from chloromethylpyrazines. However, the compound reported by Larson[5] was found to be quite stable and without offensive properties. These facts prompted a reinvestigation of the photo chlorination of 2,5-dimethylpyrazine.

Duplication of Larson's procedure[5] was accomplished by passing chlorine gas through a carbon tetrachloride solution of 2,5-dimethylpyrazine under the influence of ultraviolet radiation. As expected, an almost immediate reaction occurred with the formation of heavy white precipitate, the strongly exothermic reaction causing the solvent to boil. The precipitated material, with a neutralization equivalent of 169–171 was the hydrochloride salt I, indicating the addition of chlorine to the original molecule. Hydrolysis of I occurred readily in water, affording the free halogenated base as an insoluble oil, the aqueous solution becoming quite acidic.

The physical properties and stability of this oil indicated that nuclear rather than side chain chlorination had occurred and that the product was 2-chloro-3,6-dimethylpyrazine (II). The infrared absorption curves of both II and an authentic sample[4] were identical. Further verification was obtained by preparation of the identical amines as well as comparison of the hydrochloride salts of II. Finally, the oil by ethanolysis afforded a 62% yield of 2-ethoxy-3,6-dimethylpyrazine, whose infrared spectrum was identical with the ethoxy derivative prepared from authentic II. Both curves exhibited strong peaks at 1037 and 1172 cm.$^{-1}$ which are consistent for a nuclear ether.[9,10]



(1) Presented before the eleventh Meeting in Miniature of the Metropolitan Long Island Subsection of the New York Section, American Chemical Society, March 11, 1960.

(2) (a) The work here reported is based on a dissertation by Albert Hirschberg in partial fulfillment of the requirements for the degree of Doctor of Philosophy at the Polytechnic Institute of Brooklyn, June 1960; (b) Du Pont Teaching Fellow, 1958–59; Texaco Research Fellow, 1959–60.

(3) To whom all inquiries should be addressed.

(4) G. Karmas and P. E. Spoerri, *J. Am. Chem. Soc.*, **74**, 1580 (1952).

(5) C. Larson, Doctoral Dissertation, Polytechnic Institute of Brooklyn, June 1949.

(6) J. Overhoff, J. Boeke, and A. Gorter, *Rec. trav. chim.*, **55**, 293 (1936).

(7) F. Sorm and L. Sedevy, *Collection Czechoslov. Communs.*, **13**, 288 (1948).

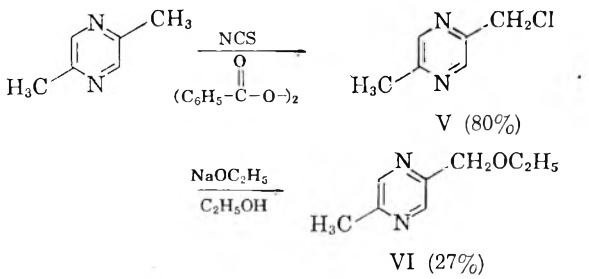
(8) M. Hasagawa, *Pharm. Bull. (Japan)*, **1**, 293 (1953); *Chem. Abstr.*, **49**, 8275 (1954).

(9) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley & Sons, Inc., New York, 1958, p. 115.

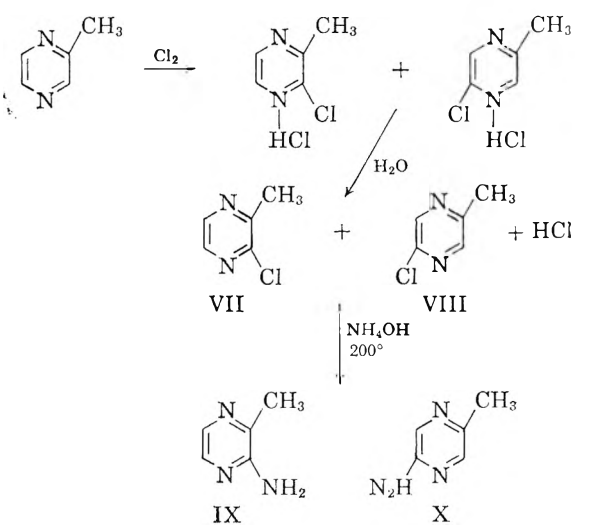
It was now apparent that the photochlorination of 2,5-dimethylpyrazine was not a free radical process since such a reaction course in analogy with the photochlorination of alkylbenzenes should have led to chlorination on the alkyl side chains.[11] Additional experiments, wherein the chlorination readily took place in the dark with comparable yields, further demonstrated the nonradical mechanism of this reaction.

The chlorination of 2,5-dimethylpyrazine was now studied under conditions favoring a free radical process.[12] Accordingly, 2,5-dimethylpyrazine was treated with an equivalent of *N*-chlorosuccinimide (NCS) and a catalytic amount of benzoyl peroxide and the resulting mixture was refluxed. This procedure afforded, upon work-up, 70–80% of a crude brownish oil, which could not be distilled, and which was highly lachrymatory and extremely irritating to the skin. Upon standing, the oil slowly polymerized to a dark brown tacky solid, which still retained the unpleasant properties of the original oil. It was therefore necessary when working with this material to use it immediately after the solvent had been removed.

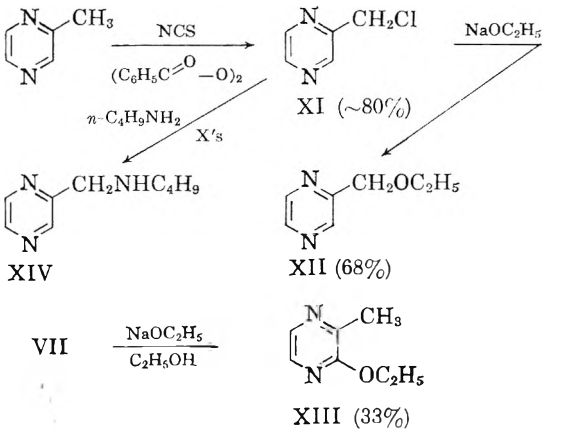
The general physical properties of the product led us to assume that 2-(α-chloromethyl)-5-methylpyrazine (V) had been formed. Attempts at preparing a picrate as well as a stable hydrochloride were unsuccessful. Ethanolysis, however, afforded a 27% yield of a stable, pungent oil presumably 2-methyl-5-pyrazinylmethyl ethyl ether (VI). This was confirmed by examination of the compound's infrared spectrum which indicated the presence of an aliphatic ether grouping due to a strong peak at 1122 cm.$^{-1}$ [9] The elemental analysis indicated that this compound was isomeric with the nuclear ether III previously prepared. These facts indicated that as expected, side chain halogenation had occurred and the following reaction scheme could be formulated



A parallel series of chlorinations were carred out using 2-methylpyrazine. Passage of chlorine through a carbon tetrachloride solution of 2-methylpyrazine, even in the dark, afforded a heavy white hydrochloride having a neutralization equivalent of 158–160. Hydrolysis of this hydrochloride in water afforded a heavy stable chlorinated oil, insoluble in the resulting aqueous acidic solution. Distillation of the oil afforded a 65% yield of stable compounds assumed to be a mixture of ring chlorinated methylpyrazines (VII and VIII). Repeated distillation having failed to bring about a good separation the oil was subjected to ammonolysis at 200° which yielded a solid mixture of amines which on fractional crystallization afforded 60% of 2-amino-3-methylpyrazine (IX) and 5% of 2-amino-5-methylpyrazine (X). The identity of both amines was demonstrated by comparison with authentic amines prepared independently.[4]



The treatment of 2-methylpyrazine with one equivalent of *N*-chlorosuccinimide using benzoyl peroxide as a catalyst afforded a highly unstable lachrymatory oil, presumably α-chloromethylpyrazine (XI). Ethanolysis of this oil using sodium ethoxide afforded a stable compound exhibiting a strong aliphatic ether peak at 1121 cm.$^{-1}$ in the infrared.[9] In addition, elemental analysis indicated the product to be pyrazinylmethyl ethyl ether (XII). For comparison purposes, the isomeric nuclear ether, 2-ethoxy-3-methylpyrazine (XIII), was prepared by ethanolysis of VII. The infrared



(10) N. B. Colthup, *J. Opt. Sci. Amer.*, 40, 397 (1950).
(11) J. Hine, *Physical Organic Chemistry*, McGraw-Hill, 1956, p. 433.
(12) J. Hine, *Physical Organic Chemistry*, McGraw-Hill, 1956, p. 429.

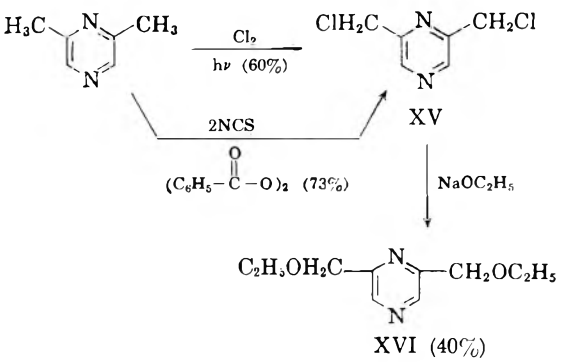
curve of this material exhibited two strong peaks at 1038 cm.$^{-1}$ and 1192 cm.$^{-1}$, indicative of an aromatic ether.[9,10]

While attempts to convert XI into the corresponding hydroxymethyl or aminomethyl derivative were unsuccessful, a higher amine derivative was obtained, however, by allowing the chloromethyl compound to react with excess *n*-butylamine. By this procedure, an oil was isolated whose infrared spectrum exhibited a medium peak at 3200 cm.$^{-1}$ indicative of a secondary amine.[9] Elemental analysis of both the oil and its phenyl isothiocyanate derivative indicated the secondary amine was pyrazinylmethyl-*n*-butylamine (XIV).

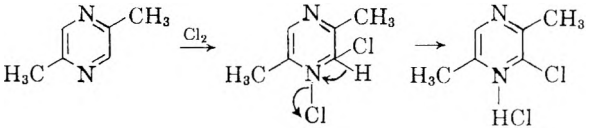
Chlorination of 2,6-dimethylpyrazine in carbon tetrachloride, in strong contrast to the 2- or 2,5 isomer, proceeded extremely slowly, as evidenced by the small amount of precipitate formed even after several hours. Strong illumination with ultraviolet light, on the other hand, apparently accelerated the reaction for within twenty minutes a heavy white precipitate appeared which surprisingly was found to be 2,6-dimethylpyrazine hydrochloride.

Evaporation of the carbon tetrachloride filtrate left a residual, lachrymatory oil, which polymerized on standing, and which could not be distilled. Ethanolysis of this product afforded a stable material exhibiting strong aliphatic ether peaks at 1104 cm.$^{-1}$ and 1122 cm.$^{-1}$ Elemental analysis showed the product to be the bis ether XVI, and hence that the oil obtained originally was 2,6-bis-α-chloromethylpyrazine (XV).

An independent synthesis of XV was accomplished by treating 2,6-dimethylpyrazine with two equivalents of *N*-chlorosuccinimide and a catalyst quantity of benzoyl peroxide in carbon tetrachloride solution. The unstable, lachrymatory oil obtained from this procedure was subjected to ethanolysis, affording the bis ether XVI.



In the absence of detailed mechanistic studies, the mechanism of the reaction between chlorine and 2-methyl- and 2,5-dimethylpyrazine must remain a matter of conjecture. While a free radical reaction seems to be ruled out, it seems on the other hand unlikely that the reaction proceeds *via* electrophilic substitution on the pyrazine nucleus because of the known resistance of pyrazine and its alkyl and aryl derivatives to this type of attack.[13] A possible reaction course might involve an addition of chlorine across the azomethine linkage of the pyrazine ring followed by a rearrangement forming the hydrochloride salt.



The mechanism of the reaction of 2,6-dimethylpyrazine with chlorine appears to be a free radical process due to its dependence on ultraviolet radiation and the formation of a side chain halogenated product. This marked contrast to the cases of 2-methyl- and 2,5-dimethylpyrazine is rather curious, however, since it is not clear why this particular isomer should show such a difference in reaction behavior.

Further work on this problem as well as chlorination reactions of other alkyl and arylpyrazines is being carried out and will be reported on in due course.

EXPERIMENTAL[14]

A. *2 Chloro-3,6-dimethylpyrazine* II. In 500 ml. of carbon tetrachloride 20.0 g. (0.185 mole) of 2,5-dimethylpyrazine was dissolved. Chlorine gas was bubbled in and within a few minutes the solution started to boil and a voluminous white precipitate formed. The passage of chlorine was continued for another 0.5 hr. and the precipitate was then collected, washed with two fresh 100-ml. portions of carbon tetrachloride, and dried in a vacuum desiccator. The dry powdery solid was added to 300 ml. of water whereupon a heavy oil separated at once, and collected at the bottom of the flask. This oily material was extracted completely from the aqueous solution with ether. The ether extracts were dried over magnesium sulfate and then concentrated on a steam bath. The oily residue was distilled through a 6-inch Vigreux column to yield 16.0 g. (61%) of 2-chloro-3,6-dimethylpyrazine (II), boiling at 112–114° (70 mm.), n_D^{25} 1.5247.

B. *Chlorination of methylpyrazine.* The procedure as outlined in A was applied to 2-methylpyrazine affording a 65% yield of an oily mixture of 2-chloro-3-methylpyrazine (VII) and 2-chloro-5-methylpyrazine (VIII).

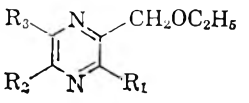
C. *Ammonolysis of the 2-chloro-3-methylpyrazine* (VII) *and 2-chloro-5-methylpyrazine* (VIII) *mixture.* A mixture of 2.56 g. (0.02 mole) of the mixture of the chlorinated isomers obtained from B and 80 ml. of 28% aqueous ammonia was heated in a stainless steel autoclave at 200° for 36 hr. The resulting solution was made strongly basic with sodium hydroxide at 0°, and then thoroughly extracted with ether. The ether extract was dried over sodium sulfate and then evaporated, yielding a solid residue which was recrystallized

(13) I. J. Krems and P. E. Spoerri, *Chem. Revs.*, 40, 328 (1947).

(14) All melting points are corrected. Infrared curves were taken using potassium bromide disks on a Perkin-Elmer Model 21 recording infrared spectrophotometer. Microanalyses were performed by Schwarzkopf Laboratories in New York or M. Manser, Basel, Switzerland. The syntheses of all chloropyrazines referred to in this section have been described in a previous publication or are given below.

TABLE I

PYRAZINYLMETHYL ETHYL ETHERS



	R_1	R_2	R_3	B.P./Mm.	n_D^t	t°	Yield,[a] %	N% Calcd.	N% Found
VI	H	H	H	110–112/53	1.4909	22	68	20.58	20.58
XII	H	CH_3	H	98–104/20	1.4869	28	27	18.41	18.59

[a] Yields based on assuming 100% purity of starting chloromethylpyrazines.

from ethanol to yield 1.30 g. (60%) of 2-amino-3-methylpyrazine melting at 166–167°.

Anal. Calcd. for $C_5H_7N_3$: N, 38.51. Found: N, 38.44.

The ethanol mother liquor was evaporated to dryness and the residue recrystallized from benzene affording 0.11 g. (5%) of 2-amino-5-methylpyrazine melting at 111–112° (lit.,[15] m.p. 116–118°).

Anal. Calcd. for $C_5H_7N_3$: N, 38.51. Found: N, 38.19.

D. *2-Amino-3,6-dimethylpyrazine* (IV). The ammonolysis procedure described in C was applied to 2.84 g. (0.02 mole) of 2-chloro-3,6-dimethylpyrazine (II). The residue was recrystallized from benzene affording 1.77 g. (68%) of IV as white prisms melting at 111–113° (lit.,[16] m.p. 112–113°).

E. *2-Ethoxy-3,6-dimethylpyrazine* (III). To 150 ml. of absolute ethanol was added 0.69 g. (0.03 mole) of sodium and 1.42 g. (0.01 mole) of 2-chloro-3,6-dimethylpyrazine (II) dissolved in 50 ml. of absolute ethanol. The resulting mixture was allowed to reflux for 10 hr. during which time a precipitate of sodium chloride formed. The mixture was cooled, filtered, and the residue of sodium chloride washed with several portions of absolute ethanol. The filtrate and washings were combined and 25 ml. of water added. The resulting solution was concentrated on a water bath and the residual oil was then extracted completely from the alkaline aqueous liquor with ether. The ether extracts were dried over magnesium sulfate and concentrated on a water bath. The residual oil was carefully distilled at 86–88°/20 mm. yielding 2.8 g. (62%) of the ethoxy compound III, n_D^{26} 1.4934.

Anal. Calcd. for $C_8H_{12}N_2O$: C, 63.16; H, 7.95; N, 18.41. Found: C, 63.38; H, 81.22 N, 18.16.

F. *2-Ethoxy-3-methylpyrazine* (XIII). The procedure as described in E was applied to 1.28 g. (0.01 mole) of 2-chloro-3-methylpyrazine (VII) affording 0.45 g. (33%) of the ethoxy compound XIII boiling at 88–90°/48 mm., n_D^{26} 1.4938.

Anal. Calcd. for $C_7H_{10}N_2O$: C, 60.86; H, 7.30; N, 20.28. Found: C, 60.57; H, 7.47; N, 20.24.

G. *2-(α-Chloromethylpyrazines* (*Compounds* V *and* XI).

Two 2-(α-chloromethyl)pyrazines were prepared by the reaction of *N*-chlorosuccinimide with an equimolar quantity of the corresponding alkyl pyrazine, using a catalytic amount of benzoyl peroxide. These α-chloromethyl derivatives could not be distilled and are unstable. They were therefore used immediately after isolation and converted to the corresponding pyrazinylmethyl ethyl ethers (procedures J and K). The obnoxious and toxic properties of these compounds makes it imperative that they be handled with extreme caution.

In 250 ml. of carbon tetrachloride was dissolved 0.10 mole of 2-methyl- or 2,5-dimethylpyrazine. To the solution was added 13.0 g. (0.10 mole) of *N*-chlorosuccinimide and 0.1 g. of benzoyl peroxide and the resulting mixture refluxed for 12 hr., cooled to 0°, and carefully filtered. The residue (mostly succinimide) was washed with two 50-ml. portions of carbon tetrachloride. The washings and filtrate were combined and evaporated under vacuum at room temperature. The residual oils were then used immediately for the preparation of the corresponding ethers. The yields of these crude oils ranged from 70 to 80% (assuming the oils to be pure).

H. *2,6-Bis(α-chloromethyl)pyrazine* (XV). 1. To 500 ml. of carbon tetrachloride was added 20 g. (0.185 mole) of 2,6-dimethylpyrazine. Chlorine gas was bubbled in while the flask was irradiated with ultraviolet radiation (Burdick—Type QA-250N). A heavy white precipitate formed almost immediately. The chlorination and irradiation continued for 2 hr., after which time the contents of the flask were carefully filtered and the residue of 2,6-dimethylpyrazine hydrochloride was washed with 100 ml. of fresh carbon tetrachloride. The filtrate and washings were combined and allowed to stand for 2 days in a hood to allow the excess chlorine to evaporate. The remaining carbon tetrachloride solution was then evaporated under reduced pressure leaving 10.82. g. of XV as a residual lachrymatory oil, which was used directly for the preparation of the corresponding ether XVI. A 31% conversion to the bischloromethyl derivative XV was obtained, based on 10.3 g. of free 2,6-dimethylpyrazine recovered from its hydrochloride. The yield was 60%, assuming the oil to be pure.

2. To 250 ml. of carbon tetrachloride was added 10 g. of (0.10 mole) of 2,6-dimethylpyrazine. To this solution was added 26 g. (0.20 mole) of *N*-chlorosuccinimide and 0.1 g. of benzoyl peroxide. The mixture was refluxed for 24 hr. and then worked up as described in G. The yield was 70 to 80%.

I. *Pyrazinylmethyl-n-butylamine* (XIV). To 120 ml. of freshly distilled *n*-butylamine was added 5.0 g. (0.039 mole) of α-chloromethylpyrazine (XI). The resulting mixture was allowed to reflux for 5 hr. and then evaporated under reduced pressure, at room temperature, leaving an oily residue behind. The residue was taken up in ether yielding a precipitate (butylamine hydrochloride) which was filtered off and washed with fresh ether. The ether washings and filtrate were combined, dried over sodium sulfate, and evaporated on a water bath. The residual oil was distilled through a 6-inch Vigreux column affording 4.89 g. (68%) of the secondary amine XIV boiling at 76–78°/0.5 mm., n_D^{22} 1.5089.

Anal. Calcd. for $C_9H_{15}N_3$: C, 65.42; H, 9.15; N, 25.06. Found: C, 65.16; H, 9.61; N, 25.43.

A phenyl isothiocyanate derivative was prepared according to the procedure of Shriner, Fuson, and Curtin,[17] m.p. 97.5–98.5°.

Anal. Calcd. for $C_{16}H_{20}N_4S$: C, 63.96; H, 6.71; N, 18.65; S, 10.67. Found: C, 64.11; H, 6.92; N, 18.40; S, 10.75.

J. *2-Pyrazinylmethyl ethyl ethers* (*Compounds* VI *and* XII). Two 2-pyrazinylmethyl ethyl ethers (VI and XII) were prepared from the corresponding 2-(α-chloromethyl)pyrazines (Compounds V and XI) by the Williamson synthesis

(15) J. Weilgard, M. Tishler, and A. E. Erickson, *J. Am. Chem. Soc.*, **67**, 802 (1945).

(16) R. R. Joiner and P. E. Spoerri, *J. Am. Chem. Soc.*, **63**, 1929 (1941).

(17) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *The Systematic Identification of Organic Compounds*, John Wiley & Sons, Inc., New York, 1956, p. 227.

using a 3*M* excess of sodium ethoxide in absolute ethanol as described in E. These two ethers are listed in Table I, together with the pertinent analytical and physical data.

K. *2,6-Bispyrazinylmethyl diethyl ether* (XVI). The procedure was the same as in E, in which 7.0 g. (0.036 mole) of 2,6-bis(α-chloromethyl)pyrazine (XV) was allowed to react with a 3*M* excess of sodium ethoxide in absolute ethanol. Work-up afforded 2.86 g. (37%) of the bis ether XVI which boiled at 130–133°/20 mm., n_D^{25} 1.4892.

Anal. Calcd. for $C_{10}H_{16}N_2O_2$: C, 61.20; H, 8.22; N, 14.28. Found: C, 61.24; H, 8.25; N, 14.00.

Acknowledgment. The authors wish to express sincere thanks to Prof. F. M. Beringer and Dr. J. G. Lombardino for helpful discussions. The technical assistance of Mr. H. Talts and Mr. R. Parla is also gratefully acknowledged. We also wish to acknowledge the generous samples of alkylpyrazines used for this work supplied by the Wyandotte Chemicals Corp.

BROOKLYN 1, N. Y.

[CONTRIBUTION FROM THE RESEARCH DIVISION, WYANDOTTE CHEMICALS CORP.]

Chlorination of Alkylpyrazines[1]

HAROLD GAINER, MICHAEL KOKORUDZ, AND W. KEITH LANGDON

Received October 26, 1960

Methyl-, 2,5-dimethyl-, or 2,5-diethylpyrazine, when treated in carbon tetrachloride at 40° with excess chlorine, gave 2-chloro-3-methyl-, 3-chloro-2,5-dimethyl-, and 3-chloro-2,5-diethylpyrazine, respectively, in good yields. A nuclear chlorinated product under these mild conditions was unexpected. The chlorine atom of the alkylchloropyrazines was very reactive towards nucleophilic reagents. Replacement of the halogen was readily effected by reaction of the chloro compounds with alcohols, ammonia, aliphatic amines, and aqueous alkali to give ethers, amines, and hydroxy derivatives.

A chlorination study of alkylpyrazines was begun initially with the objective of preparing α-chloromethylpyrazine. When methylpyrazine in carbon tetrachloride was treated with an excess of elemental chlorine at room temperature and with irradiation from an incandescent lamp a monochloro product was obtained. One might expect a methyl substituted chloro derivative to form under these conditions but the chemical and physical properties of the product indicated that 2-chloro-3-methylpyrazine, a ring substituted compound, had formed instead. Light was later found to have no effect on the reaction. The reaction was applied to the chlorination of 2,5-dimethyl- and 2,5-diethylpyrazine and the products were also ring substituted alkylchloropyrazines.

In addition to the derivatives of the chloro compounds prepared in the course of their identification, several other amino and alkoxy compounds were prepared. When 2-chloro-3-methyl- or 3-chloro-2,5-dimethylpyrazine was heated in an autoclave at about 200° with aqueous ammonia, methylamine, dimethylamine, or ethanolamine the corresponding substituted amines were obtained. To prepare the pyrazyl ethers from 2-chloro-3-methylpyrazine the sodium alkoxides were usually employed. Later we found that simply refluxing a mixture of the chloropyrazine in alcohol with potassium hydroxide was sufficient to afford the corresponding ethers in good yield. By these methods ethers were made from allyl, *n*-butyl and myristyl alcohols and from ethylene glycol. Since ethylene glycol is bifunctional both possible ethers were obtained: the hydroxyethyl ether and the ethylene bispyrazyl ether. 3-Chloro-2,5-dimethylpyrazine presumably reacts in a similar fashion since the corresponding ethyl ether was made in good yield from the chloropyrazine, ethanol and potassium hydroxide.[2]

(1) Presented before the Division of Organic Chemistry at the 138th Meeting of the American Chemical Society, New York, N. Y., September, 1960.

EXPERIMENTAL[3]

2-Chloro-3-methylpyrazine. To 5.4 l. of carbon tetrachloride heated to 40° in a 12 l. flask equipped with stirrer, Dry Ice-acetone condenser and dropping funnel was added 142 g. (2 moles) of chlorine through a tube ending above the surface of the carbon tetrachloride. This was followed by 94 g. (1 mole) of methylpyrazine added within 5 min. Warming was necessary to maintain the temperature at 40° until an exothermic reaction took place and precipitation of 2-chloro-3-methylpyrazine hydrochloride occurred. Addition of reactants was repeated in this manner (with cooling when necessary) except that the ratio of chlorine to methylpyrazine was adjusted so that final total amounts, 937 g. (13.2 moles) of chlorine and 1128 g. (12 moles) of methylpyrazine, had been added in 6 hr.

After standing overnight the hydrochloride was removed by filtration and washed with carbon tetrachloride. The filter cake was slurried with 500 ml. of water and the mixture was neutralized with 1.2 l. of 35% aqueous sodium hydroxide while the temperature was kept below 40° by cooling. The 2-chloro-3-methylpyrazine precipitated as an oil. It was separated and distilled. Yield: 1029 g. (67%), b.p. 55–65°/15 mm., n_D^{25} 1.5262 (reported[4] b.p. 94–96°/65 mm. and n_D^{25} 1.5302). The compound was unreactive towards hot alcoholic silver nitrate.

3-Chloro-2,5-dimethylpyrazine. This chloro compound was prepared from 2,5-dimethylpyrazine as above. Yield: 87%, b.p. 64°/10 mm.–65°/12 mm., n_D^{25} 1.5237 (reported[4]

(2) H. Gainer, M.S. thesis, Polytechnic Institute of Brooklyn, 1951.

(3) All melting points are uncorrected.

(4) G. Karmas and P. E. Spoerri, *J. Am. Chem. Soc.*, 74, 1580 (1952).

b.p. 112–113°/70 mm., n_D^{26} 1.5243). The compound was unreactive towards hot alcoholic silver nitrate.

2,5-Diethylpyrazine. This dialkylpyrazine was obtained[5] *via* reaction of 1,2-epoxybutane and ammonia to give 2-hydroxybutylamine which was then simultaneously condensed and dehydrogenated[6] to yield finally 2,5-diethylpyrazine, b.p. 188–189°/760 mm., n_D^{26} 1.4908 (b.p. 185–186°/767 mm.) was reported[7] for 2,5-diethylpyrazine prepared by oxidation of the condensation product of 1-amino-2-butanone with mercuric chloride. This synthesis is similar to the series of reactions recently reported[8] for the preparation of ethylpyrazine.

3-Chloro-2,5-diethylpyrazine. A stream of chlorine was passed over the surface of 500 ml. of stirred carbon tetrachloride heated to 40°. When the solvent was saturated 30 ml. of 2,5-diethylpyrazine was added with stirring and the temperature was maintained at 40°. After about 30 min. the addition of reagents was repeated except that the quantity of 2,5-diethylpyrazine added depended upon the amount of chlorine retained by the reaction mixture. The mole ratio of chlorine to 2,5-diethylpyrazine was 2:1. After 15 min. enough 2,5-diethylpyrazine was added to make the mole ratio of chlorine to 2,5-diethylpyrazine present in the reaction mixture 1.27:1. In this manner was added a total of 205.5 g. (1.5 moles) of 2,5-diethylpyrazine and 140 g. (1.9 moles) of chlorine. Though the temperature was carefully maintained at 40° throughout most of the run by heating or cooling, at one point the temperature rose spontaneously to 60° despite efforts to prevent the rise. The hydrochloride of 3-chloro-2,5-diethylpyrazine did not precipitate.

A mixture of 176 g. of sodium bicarbonate and 250 ml. of water was added with stirring and the mixture was filtered. The organic layer was separated, dried over anhydrous magnesium sulfate and fractionally distilled. Yield: 194 g. (76%) b.p. 81°/5 mm. – 91°/6 mm., n_D^{25} 1.5148.

Anal. Calcd. for $C_8H_{11}ClN_2$: C, 56.31; H, 6.50; N, 16.42. Found: C, 56.61; H, 6.42; N, 16.56.

2-Hydroxy-3-methylpyrazine, Method A. For comparison with the product of Method B this compound was prepared from alanineamide and glyoxal.[4] The melting point of the material prepared according to this method was 149.5–150.5° in agreement with the m.p. 151–152° reported by Karmas and Spoerri (reported[9] m.p. 140–142° by the same method).

Method B. A heterogeneous mixture of 360 g. (2.8 moles) of 2-chloro-3-methylpyrazine, 600 g. of potassium hydroxide, and 2.4 l. of water was refluxed for 9 hr. The resultant homogeneous solution was carefully neutralized with concentrated hydrochloric acid and the water was removed by warming *in vacuo*. The dry residue was extracted with hot absolute alcohol. After evaporating the solution to dryness *in vacuo* the residue was recrystallized several times from isopropyl alcohol and finally from absolute alcohol. Yield: 170.5 g. (55%), m.p. 138–145°.

Anal. Calcd. for $C_5H_6N_2O$: C, 54.54; H, 5.49; N, 25.44. Found: C, 54.60; H, 5.53; N, 25.38.

A mixed melting point from samples obtained from both Method A and B was 139.5–149°. The comparative infrared spectra for both compounds were essentially identical. A strong absorption band at 6 μ and a medium band at 6.4 μ indicated the presence of an amide group so that the compound probably exists in the keto tautomeric form.[10] The hydroxyl absorption band is absent.

2,5-Dimethyl-3-hydroxypyrazine. This derivative of 3-chloro-2,5-dimethylpyrazine was made in 29% yield by refluxing the chloro compound with 20% aqueous potassium hydroxide according to Baxter and Spring,[11] m.p. 206–207°; (reported[11] m.p. 208–210°).

2-Amino-3-methylpyrazine. A mixture of 240 g. (1.87 moles) of 2-chloro-3-methylpyrazine and 1 l. of 30% aqueous ammonia (16 moles) was heated in an autoclave at 180° for 8 hr. A pressure of 390 p.s.i. developed. The reaction mixture was filtered to obtain the product which was washed with a little alcohol and recrystallized from 600 ml. of absolute alcohol. Yield: 93 g. (46%), m.p. 165–167°.

Anal. Calcd. for $C_5H_7N_3$: C, 55.03; H, 6.47; N, 38.51. Found: C, 55.19; H, 6.42; N, 38.78.

3-Amino-2,5-dimethylpyrazine. A mixture of 107 g. (0.75 mole) of 3-chloro-2,5-dimethylpyrazine with 300 ml. of 30% aqueous ammonia and 66 g. of anhydrous ammonia (total of 9.3 moles) was heated at 180° in an autoclave for 10 hr. A pressure of 525 p.s.i. developed. The solvents were then removed by evaporation *in vacuo* with heating and the solid residue was extracted with hot benzene. Cooling the benzene precipitated the product which after filtration gave 66 g. of 3-amino-2,5-dimethylpyrazine. Recrystallization of the crude product from 350 ml. of benzene gave finally 57 g. (62%), m.p. 111–112° (reported[12] 112°, prepared from 3 - phenylacetamido - 2,5 - dimethylpyrazine). Karmas and Spoerri[4] have reported the method of preparing amino derivatives of the chloro compounds from the corresponding aqueous amines.

The correspondence of the melting points of the hydroxy and amino compounds with the melting points of the corresponding compounds reported in the literature serves as a proof of structure of the 3-chloro-2,5-dimethylpyrazine.

2-Methyl-3-methylaminopyrazine hydrochloride. A mixture of 64 g. (0.5 mole) of 2-chloro-3-methylpyrazine and 160 ml. (2 moles) of 40% aqueous methylamine was heated in an autoclave at 200° for 6.5 hr. The autoclave was charged with 200 p.s.i. of hydrogen and 600 p.s.i. developed with heating. The homogeneous reaction mixture was evaporated *in vacuo* on the steam bath and the syrupy residue was continuously extracted with ether. After removal of the solvent by warming *in vacuo* the residue was dissolved in 50 ml. of absolute alcohol and acidified with 60 ml. of 8*N* alcoholic hydrogen chloride. A little ether was added to complete the precipitation and the product was filtered. Several recrystallizations from methanol-ether mixture gave 25 g. (31%), m.p. 236–240°. A sample was sublimed at *ca.* 175°/760 mm. for the analysis.

Anal. Calcd. for $C_6H_{10}ClN_3$: C, 45.14; H, 6.31; N, 26.32. Found: C, 44.89; H, 6.05; N, 25.94.

2,5-Dimethyl-3-methylaminopyrazine hydrochloride. A mixture of 49.5 g. (0.35 mole) of 3-chloro-2,5-dimethylpyrazine and 150 ml. of 40% aqueous methylamine (2 moles) was heated in an autoclave at 195–210° for 12 hr. The autoclave was charged with 200 p.s.i. of hydrogen and 700 p.s.i. developed with heating. After removal of most of the solvent by heating *in vacuo* the residue was continuously extracted with ether. The ethereal extract was dried over anhydrous magnesium sulfate and the solvent was removed by warming *in vacuo* and gave a non-crystallizing oil. This residue was dissolved in absolute alcohol and acidified with 8*N* alcoholic hydrogen chloride. The hydrochloride precipitated; the mixture was cooled, treated with ether, filtered and the precipitate was washed with a 1:1 alcohol and ether mixture, then ether alone. Yield, 18.9 g. (29%), m.p. 225–226.5°. Several recrystallizations from absolute alcohol raised the melting point to 228.5–229°.

(5) These preparations were made by Walter F. Schulz, Wyandotte Chemicals Corp., and Ernest Jaul, General Tire and Rubber Co.

(6) W. K. Langdon, U. S. Patent 2,813,869, Nov. 19, 1957.

(7) E. Kolshorn, *Ber.*, **37**, 2474 (1904).

(8) H. Gainer, *J. Org. Chem.*, **24**, 691 (1959).

(9) R. G. Jones, *J. Am. Chem. Soc.*, **71**, 78 (1949).

(10) A. Albert and J. N. Phillips, *J. Chem. Soc.*, 1294 (1956).

(11) R. A. Baxter and F. S. Spring, *J. Chem. Soc.*, 1179 (1947).

(12) G. T. Newbold, F. S. Spring, and W. Sweeney, *J. Chem. Soc.*, 300 (1949).

Anal. Calcd. for $C_7H_{12}ClN_3$: C, 48.42; H, 6.97; N, 24.20. Found: C, 48.51; H, 6.93; N, 24.36.

2-Dimethylamino-3-methylpyrazine hydrochloride. A mixture of 12.8 g. (0.1 mole) of 2-chloro-3-methylpyrazine and 100 ml. (0.55 mole) of 25% aqueous dimethylamine was heated in an autoclave at 200° for 13 hr. The autoclave was charged with 200 p.s.i. of nitrogen and 550 p.s.i. developed with heating. Most of the solvent was removed by heating *in vacuo* and the residue was continuously extracted with ether. After removal of the ether by warming *in vacuo* the residue was dissolved in a little absolute alcohol and the solution was acidified with alcoholic hydrogen chloride. Some ether was added to complete the precipitation. The product was removed by filtration, washed with an alcohol-ether mixture and recrystallized from an alcohol-ether mixture. Yield: 1.2 g. (7%), m.p. 228–230° dec. For the analysis a small sample was sublimed at *ca.* 70°/3 mm., m.p. 224–230° dec.

Anal. Calcd. for $C_7H_{12}ClN_3$: C, 48.42; H, 6.97; N, 24.20; Cl, 20.42. Found: C, 48.09; H, 6.77; N, 24.26; Cl, 20.53.

2,5-Dimethyl-3-dimethylaminopyrazine. A mixture of 106.9 g. (0.75 mole) of 3-chloro-2,5-dimethylpyrazine and 475 ml. (4.2 moles) of 40% aqueous dimethylamine was heated in an autoclave at 200° for 8 hr. A pressure of 400 p.s.i. developed. The reaction mixture was distilled and the fraction collected, b.p. 100–103°/20 mm., was redistilled to yield the product; 42 g. (37%), b.p. 100°/20 mm., and n_D^{25} 1.5338.

Anal. Calcd. for $C_8H_{13}N_3$: C, 63.54; H, 8.67; N, 27.79. Found: C, 63.89; H, 8.74; N, 27.52.

2,5-Dimethyl-3-(2-hydroxyethylamino)pyrazine. A mixture of 0.4 ml. (0.003 mole) of 3-chloro-2,5-dimethylpyrazine, 3 ml. (0.05 mole) of ethanolamine and 5 ml. of water was heated in a sealed tube at 180–200° for 24 hr. The homogeneous mixture was extracted continuously with ether and the solvent and excess reagent were removed by heating *in vacuo* on the steam bath. The crystalline residue was recrystallized several times from benzene. Yield: 140 mg., (28%), m.p. 119.5–120.5°.

An infrared spectrum showed bands at 2.95 and 9.45 μ which is indicative of a primary hydroxyl group and the absence of an ether band at 8.9 μ indicates that the possibility of a 3-(2-aminoethoxy) substituent can be eliminated.

Anal. Calcd. for $C_8H_{13}N_3O$: C, 57.46; H, 7.84; N, 25.13. Found: C, 57.67; H, 7.46; N, 26.33.

Allyl 2-(3-methylpyrazyl) ether. A mixture of 30 g. (0.23 mole) of 2-chloro-3-methylpyrazine, 60 ml. (0.9 mole) of allyl alcohol, and 15 g. (0.23 mole) of potassium hydroxide was refluxed for 15.5 hr. To the reaction mixture was added 100 ml. of petroleum ether. The precipitated salt was removed by filtration and the filtrate was fractionally distilled to yield finally the ether; 22 g. (64%), b.p. 61–62°, n_D^{25} 1.5091.

Anal. Calcd. for $C_8H_{10}N_2O$: C, 63.98; H, 6.71; N, 18.65. Found: C, 63.90; H, 6.71; N, 18.72.

Butyl 2-(3-methylpyrazyl) ether. A solution from 4.6 g. (0.2 g.-atom) of sodium and 175 ml. of 1-butanol prepared by heating the solvent and sodium together was refluxed with 28 g. (0.2 mole) of 2-chloro-3-methylpyrazine for 45 min. The precipitated salt was removed by filtration and the filtrate was fractionally distilled to yield the product, 29 g. (87%), b.p. 98°/14 mm., n_D^{25} 1.4841.

Anal. Calcd. for $C_9H_{14}N_2O$: N, 16.85 Found: N, 17.02.

Ethylene glycol bis-2-(3-methylpyrazyl) ether and 2-hydroxyethyl 2-(3-methylpyrazyl) ether. To a solution prepared from 13.3 g. (0.33 mole) of powdered sodium hydroxide and 62 g. (1.0 mole) of hot ethylene glycol was added 125 ml. of toluene. This mixture was refluxed 1.5 hr. while water was removed as an azeotrope with toluene. In this manner, 6.5 ml. of water was collected. The mixture was cooled and treated dropwise at 85° with a solution of 43 g. (0.33 mole) of 2-chloro-3-methylpyrazine in 50 ml. of toluene. After heating an additional 45 min. at 100° the mixture was cooled and filtered. The filtrate was fractionally distilled giving two fractions. One fraction was a liquid and corresponded to 2-hydroxyethyl 2-(3-methylpyrazyl) ether; 16 g., b.p. 100–106°/2 mm., n_D^{25} 1.5297.

Anal. Calcd. for $C_7H_{10}N_2O_2$: N, 18.17. Found: N, 18.31.

The second fraction, b.p. 150°/3 mm., crystallized in the condenser during its distillation and after recrystallization from 25% aqueous methyl alcohol had m.p. 84–85°. This fraction was considered to be the disubstituted ether, ethylene glycol bis-2-(3-methylpyrazyl) ether.

Anal. Calcd. for $C_{12}H_{14}N_4O_2$: N, 22.75 Found: N, 22.63.

Myristyl 2-(3-methylpyrazyl) ether. A mixture of 45 g. (0.2 mole) of myristyl, alcohol, 8 g. (0.2 mole) of powdered sodium hydroxide, and 100 ml. of xylene was refluxed while removing some of the water formed. To this mixture was added 26 g. (0.2 mole) of 2-chloro-3-methylpyrazine and the mixture was refluxed again for 2.5 hr. Most of the xylene was then distilled, the precipitated salt removed by filtration and the filtrate was fractionally distilled. Yield: 41 g. (70%), b.p. 175–179°/2 mm., n_D^{25} 1.4775.

Anal. Calcd. for $C_{19}H_{34}N_2O$: N, 9.14. Found: N, 9.21.

DISCUSSION

The method of preparation of alkylmonochloropyrazines in our laboratories makes readily available these chloropyrazines and many interesting pyrazine compounds derived from them.

2-Chloro-3-methyl- and 3-chloro-2,5-dimethylpyrazine are known compounds. 3-Chloro-2,5-diethylpyrazine was not previously reported. 2-Chloro-3-methylpyrazine was first described by Karmas and Spoerri[4] who prepared it from the reaction between 2-hydroxy-3-methylpyrazine and phosphorus oxychloride. There are several syntheses of 3-chloro-2,5-dimethylpyrazine previously described; they are the reactions of phosphorus oxychloride with either diketodimethylpiperazine,[11] the mono-*N*-oxide of 2,5-dimethylpyrazine[13,14] or with 2,5-dimethyl-3-hydroxypyrazine.[4] Larson and Spoerri more recently described a synthesis of 2-chloromethyl-5-methylpyrazine by the reaction of 2,5-dimethylpyrazine with chlorine in carbon tetrachloride.[15]

Since these are the conditions in which we obtain 3-chloro-2,5-dimethylpyrazine, Larson and Spoerri probably obtained the ring substituted chloro compound instead of the formulated chloromethyl derivative. Hirschberg and Spoerri[16] have since prepared authentic α-chloromethylpyrazine and 2-chloromethyl-5-methylpyrazine as unstable undistillable oils.

Our assignments of structures were based on comparisons of derivatives of the chloropyrazines with compounds of unequivocal structure as well as on physical data. 2-Chloro-3-methylpyrazine was

(13) G. T. Newbold and F. S. Spring, *J. Chem. Soc.*, 1183 (1947).

(14) B. Klein and P. E. Spoerri, *J. Am. Chem. Soc.*, **73**, 2949 (1951).

(15) C. W. Larson, Ph.D. Dissertation, Polytechnic Inst. of Brooklyn, 1949.

(16) A. Hirschberg, Ph.D. Dissertation, Polytechnic Inst. of Brooklyn, 1960.

hydrolyzed with aqueous alkali to 2-hydroxy-3-methylpyrazine.

2-Hydroxy-3-methylpyrazine was also prepared from alanineamide and glyoxal[4] and was shown to be identical with the compound prepared by alkaline hydrolysis of 2-chloro-3-methylpyrazine. 2-Hydroxy-3-methylpyrazine probably exists in the tautomeric keto form as shown by infrared spectra. If the chloro derivative had given hydroxymethylpyrazine upon hydrolysis then a tautomeric keto form would not be possible. These reactions verified that the chlorine atom of the chlorinated pyrazine was therefore a ring substituent and was not on the alkyl group.

Both NMR spectroscopy and the dipole moment of 2-chloro-3-methylpyrazine furnished additional confirmation of structure.[17] The NMR spectrum showed peaks with chemical shifts (relative to benzene) of $\delta = +4.9$ and $\delta = 1.25$ (parts per million) and intensity ratio 3:2 in agreement with the values expected for ring substitution. The low dipole moment of the compound (1.33 D in benzene at 25°) is nearly the same as that (1.35 D) calculated for 2-chloro-3-methylpyrazine from bond moments. The calculated moments of 2-chloro-5-methyl-, 2-chloro-6-methyl-, and α-chloromethylpyrazine, which are all the other possibilities, are 1.90, 1.73, and 1.85, respectively.

To prove the structure of 3-chloro-2,5-dimethylpyrazine it was treated with aqueous alkali and aqueous ammonia to obtain 2,5-dimethyl-3-hydroxy- and 3-amino-2,5-dimethylpyrazine, respectively. The melting points of these derivatives compared favorably with those reported in the literature for the same compounds made by unequivocal methods.[11,12]

The pyrazines were previously not known to react readily with electrophilic reagents. To prepare monochloropyrazine from pyrazine and chlorine a vapor phase reaction at 365° and the presence of sulfur dioxide was necessary. These conditions are more conducive to free radical attack of chlorine rather than polar reaction. A plausible explanation of this lack of reactivity towards electrophilic reaction hinged on the influence of the hetero atoms on the aromatic ring. Because of the inductive effect of the two nitrogen atoms in addition to a resonance effect, the carbon atoms of pyrazine should be relatively positive.[18] The experimental conditions involved in electrophilic substitutions causes the pyrazine ring to be converted into the pyrazinium ion. The inductive effect is then enhanced by the resultant positive ionic charge. The positively charged nitrogen atom is ordinarily meta directing and should deactivate the ring.

A reaction of an alkylpyrazine with excess chlorine in carbon tetrachloride at 40° to yield the monoalkylchloropyrazine is one which is occurring under very mild conditions and this was quite unexpected. If the reagents, alkylpyrazine and excess chlorine, were mixed in carbon tetrachloride directly the reaction was marked by an induction period followed by an exothermic reaction difficult to control. Irradiation from an incandescent or an ultraviolet lamp had no effect upon the induction period or the yield of product when 2-chloro-3-methylpyrazine was prepared in this manner. The difficulty of an uncontrollable exothermic reaction was mitigated by addition of the alkylpyrazine and chlorine initially in the molar ratio of two to one portionwise to preheated carbon tetrachloride.

The first step in the chlorination of methylpyrazine is probably the formation of a methylpyrazine perchloride. An excess of chlorine is essential to the reaction. If one mole or less of chlorine was used the reaction invariably failed. Examples of addition compounds of the alkylpyrazines or other six-membered nitrogen heterocyclics with halogens are well known.[19]

Of the two nitrogen atoms of methylpyrazine the one closest to the methyl group most likely forms salts and influences orientation during electrophilic substitution. The base strength of the nitrogen atom closest to the methyl group probably is greater than that of the more remote nitrogen atom. The ionization constant of 2-methylpyridine is 5.4×10^{-8} and that of pyridine at the same temperature is 1.3×10^{-9}.[20] Methylpyrazine (pK, 12.5) is likewise a stronger base than pyrazine (pK, 12.9).[21] Carbon atoms three and five are relatively electronegative because of the inductive effect of the positively charged nitrogen atom in the perchloride of methylpyrazine. An additional increase in electronegativity of carbon atom three may be due to the presence of the adjacent methyl group. The second step in the chlorination then involves the three position.

It should be emphasized that these considerations apply only to the orientation of the substituting chlorine atom. They do not explain the ease of ring chlorination of a heterocyclic compound under such mild conditions.

Acknowledgment. We acknowledge the assistance given by Mr. R. Polakowski and Mr. Gene Rak.

WYANDOTTE, MICH.

(17) These physical measurements were done by Dr. Max T. Rogers, Michigan State University, East Lansing, who kindly supplied us with these results.

(18) R. C. Elderfield, *Heterocyclic Compounds*, Wiley, New York, 1957, Vol. 6, p. 399

(19) J. Eisch, *Chem. & Ind.*, 1449 (1959).

(20) V. H. Veley, *J. Chem. Soc.*, **93**, 2122 (1908).

(21) D. A. Keyworth, *J. Org. Chem.*, **24**, 1355 (1959).

[CONTRIBUTION FROM THE ORGANIC CHEMICAL RESEARCH SECTION, LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID CO.]

Pteridine Chemistry. VI. The Synthesis and Alkaline Degradation of 3-(2-Cyanoethyl)-7-methyl-4(3H)-pteridinone and Some Related Reactions

WILLIAM V. CURRAN AND ROBERT B. ANGIER

Received November 9, 1960

The reaction of acrylonitrile with 4-hydroxy-7-methylpteridine (I) in pyridine-water (5-1) has been shown to proceed to 3-(2-cyanoethyl)-7-methyl-4(3H)-pteridinone (II) and 3-formamido-5-methylpyrazine-2-[*N*-(2-cyanoethyl)]carboxamide (III). Both II and III gave rise to the same products when treated with hot 1*N* sodium hydroxide. 3,7-Dimethyl-4(3H)-pteridinone (VII) and 3-formamido-5-methylpyrazine-2-(*N*-methyl)carboxamide (VIII) also have been synthesized and have been shown to exist in equilibrium in a hot pyridine-water (5-1) solution. A possible mechanism for this ring opening is discussed.

In continuing our study of the reaction of acrylonitrile with hydroxypteridines[1,2] we decided to investigate a simple 4-hydroxypteridine. Therefore 4-hydroxy-7-methylpteridine (I) was synthesized from 3-amino-5-methyl-2-pyrazinamide *via* the ethyl orthoformate-acetic anhydride method.[3,4]

When this pteridine (I) was treated with acrylonitrile by refluxing for four hours in a 50% aqueous-pyridine solution, 3-amino-5-methylpyrazine-2-[*N*-(2-cyanoethyl)]carboxamide (IV) was isolated in approximately 50% yield. The structure of this product was established by comparison with an authentic specimen which was synthesized by treating methyl 3-amino-5-methyl-2-pyrazinoate with 3-aminopropionitrile. It was therefore evident that the conditions under which the reaction was carried out resulted in cleavage of the cyanoethylated pteridine and, furthermore, this must have been the 3-cyanoethyl derivative (II). In an attempt to preserve the intact pteridine ring, many other variations in reaction conditions and solvents were tried, the most satisfactory of which was refluxing in pyridine-water (5:1) for three hours. This gave a crude product which consisted of two compounds as shown by paper chromatography in 3% ammonium chloride. These were conveniently separated by extracting with cold water. The water soluble compound, after purification, gave elemental analyses and spectral characteristics indicative of 3-(2-cyanoethyl)-7-methyl-4-(3H)-pteridinone (II). This structure was confirmed when it was found that boiling for thirty seconds in 1*N* sodium hydroxide resulted in the formation of the cyanoethyl amide (IV) along with a small amount of 3-amino-5-methyl-2-pyrazinoic acid (V). Compound V was not formed by hydrolysis of the cyanoethylamide (IV), as heating the latter compound in 1*N* sodium hydroxide for one minute gave no reaction. However, longer heating (one hour on the steam bath) resulted in hydrolysis of the nitrile function to give 3-amino-5-methylpyrazine-2-[*N*-(2-carboxyethyl)] carboxamide (VI). Albert *et al.*[5a] and Wood[5b] have described a similar series of reactions during the alkaline degradation of 3-methyl-4-pteridinone. These authors found that 3-aminopyrazine-2(*N*-methyl)carboxamide and 3-amino-2-pyrazinoic acid were obtained by treating the above-mentioned pteridinone with refluxing 1*N* sodium hydroxide for thirty seconds. As the methylamide was unaffected by the same reagent under more vigorous conditions, it was concluded by Wood[5b] that ring fission of the 3-methyl-4-pteridinone took place in two ways, namely, cleavage of the N_1—C_2 bond or the C_2—N_3 bond resulting finally in the formation of the pyrazinemethylamide and cleavage of the N_3—C_4 bond which would lead to 3 amino-2-pyrazinoic acid.

The water-insoluble product from the cyanoethylation reaction gave elemental analyses consonant with a formyl derivative of compound IV. When this compound was refluxed in 1*N* sodium hydroxide for thirty seconds the same two compounds, IV and V, were obtained as were found after similar treatment of the pteridinone II. Furthermore, in 0.1*N* sodium hydroxide a third compound was present as shown by paper chromatography. At this point we felt that the the nitrile function might be responsible for some of the seemingly anomalous behavior and therefore we decided to investigate a simple 3-alkyl-4-pteridinone. As a result of the latter study the water-insoluble compound was subsequently shown to be 3-formamido-

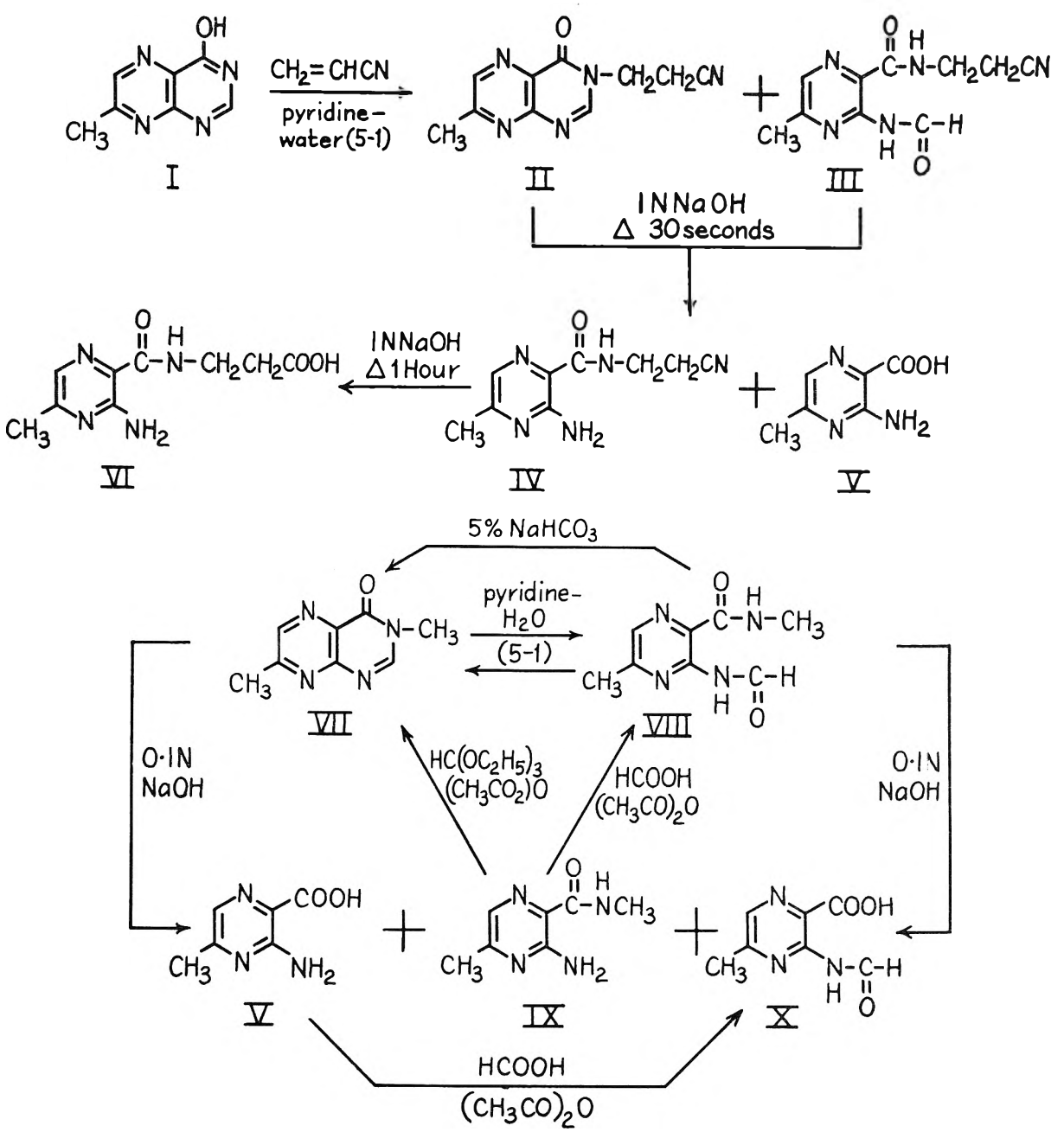
(1) R. B. Angier and W. V. Curran, *J. Am. Chem. Soc.*, 81, 5650 (1959).

(2) R. B. Angier and W. V. Curran, *J. Org. Chem.*, in press.

(3) A. Albert, D. J. Brown, and G. Cheeseman, *J. Chem. Soc.*, 474 (1951).

(4) This compound has previously been synthesized by A. Albert, D. J. Brown, and G. Cheeseman, *J. Chem. Soc.*, 4219 (1952), *via* the condensation of 4,5-diamino-6-hydroxypyrimidine with methylglyoxal in the presence of sodium sulfite.

(5) (a) A. Albert, D. J. Brown, and H. C. S. Wood, *J. Chem. Soc.*, 2066 (1956). (b) H. C. S. Wood, *The Chemistry and Biology of Pteridines*, a Ciba Foundation Symposium, J. and A. Churchill, Ltd., England, 1954, p. 35.



5 - methylpyrazine - 2 - [*N* - (2 - cyanoethyl)]-carboxamide (III).[6]

3,7-Dimethyl-4-(3H)-pteridinone (VII) was synthesized by ring closure of 3-amino-5-methylpyrazine-2-(*N*-methyl)carboxamide (IX) using ethyl orthoformate-acetic anhydride. When this pteridinone (VII) was refluxed for twelve hours in pyridine-water (5:1), a small amount of a new compound was isolated which was identical to the product obtained by treating the pyrazineamide (IX) with formic acid–acetic anhydride. This demonstrated that the compound was 3-formamido-5 - methylpyrazine - 2 - (*N* - methyl)carboxamide (VIII).[7] Furthermore, by treating compound VIII with hot pyridine-water (5:1) for eight hours a 40% yield of 3,7-dimethyl-4(3H)-pteridinone (VII) was

(6) Albert *et al.*[5a] have shown that the methylation of 4-hydroxypteridine at *p*H 8 with dimethyl sulfate and dilute sodium hydroxide gave both the 1- and 3-methyl isomers. No 1-cyanoethyl isomer has been isolated from any of the reactions carried out on I. However, it is not possible to conclude that it was not formed. In many attempts, such a variety of products were formed, as shown by paper chromatography, that one may well have been the 1-substituted isomer. The isolation of the 3-cyanoethyl product (II) and the formyl compound (III), which is a degradation product of II, in recrystallized yields of 36% and 10.5%, respectively, indicates that, at least in the pyridine-water (5:1) reaction, the acrylonitrile adds predominantly to the 3-nitrogen of the pteridine ring system.

(7) The ultraviolet absorption spectrum in methanol of this product was almost identical to that given by the water-insoluble product obtained in the cyanoethylation reaction allowing the assignment of structure III to this compound.

obtained, showing that, under these conditions, an equilibrium exists between the pteridinone VII and the formylpyrazine VIII. A more convenient method of cyclizing compound VIII involved warming for four to five minutes on a steam bath in a 5% sodium bicarbonate solution, in which case a slightly higher yield of the pteridinone was obtained. However, when either the formyl derivative (VIII) or the pteridinone (VII) was subjected to more rigorous alkaline treatment (hot 1*N* sodium hydroxide), it was shown by paper chromatography that they were both converted to the same products, namely 3-amino-5-methylpyrazine-2-carboxylic acid (V) and 3-amino-5-methylpyrazine-2-(*N*-methyl)-carboxamide (IX). This indicates that the mechanism for the alkaline degradation of 3-alkyl-4-pteridinones may be a nucleophilic attack of hydroxide ion at C_2 followed by rupture of the C_2—N_3 bond with the formation of the 3-formyl derivative (VIII). The fact that compound VIII is capable of hydrolyzing to give both the acid (V) and the amide (IX) obviates the necessity for two different methods of ring cleavage as previously proposed.[8]

When the formamidoamide (VIII) or the pteridinone (VII) was heated in 0.1*N* sodium hydroxide on a steam bath for one minute a third compound appeared. This was the same "third compound" noted in the similar treatment of the 3-cyanoethylpteridinone (II) and was shown to be 3-formamido-5-methylpyrazine-2-carboxylic acid (X) by comparison of the R_f values in several different solvent systems with an authentic specimen synthesized by formylation of compound V with formic acid-acetic anhydride. The lability of the formyl group accounts for the absence of X when hot 1*N* sodium hydroxide was employed.

It is interesting to note the striking contrast in the stability of the secondary amide linkages of compounds VIII and IX. The amide (IX) is unaffected by boiling for one minute in 1*N* sodium hydroxide while the 3-formyl derivative (VIII), by heating for one minute on a steam bath on 0.1*N* sodium hydroxide gives, in addition to IX, two products (V and X) in which the *N*-methylamide portion of the molecule has been hydrolyzed.

Several mechanisms involving intramolecular hydrogen bonding or neighboring group participation have been considered to explain this ready hydrolysis of VIII. However, the simplest explanation is that in compound IX the amide linkage is resonance stabilized by the electron donating amino group while in VIII the electron withdrawing carbonyl of the formyl group partially counteracts this stabilization to permit ready hydrolysis of VIII to X. Partial confirmation of this explanation was obtained when it was found that pyrazinecarboxamide was quickly hydrolyzed to pyazinoic acid by a 1.0*N* sodium hydroxide solution under conditions where IX was completely stable.

Both formyl compounds behave normally in dilute aqueous acid. Compound VIII, after two hours in 0.1*N* hydrochloric acid at room temperature, suffered loss of the formyl group as shown by the change in the ultraviolet absorption spectra. Similarly the formyl acid (X) was converted to 3-amino-5-methylpyrazine-2-carboxylic acid (V). In fact, the formyl group of X was hydrolyzed even in boiling water. Apparently this was caused by acid catalysis from the ionization of the carboxyl group since no hydrolysis occurred in hot dilute sodium acetate solution. The pteridinone (VII) was unaffected by 0.1*N* hydrochloric acid at room temperature.

EXPERIMENTAL

Paper chromatographic experiments were carried out using the descending technique. The spots were detected with an ultraviolet lamp provided with a filter to give mainly light of 254 mμ. A zinc silicate plate coated with DuPont phosphor No. 609235[9] was used to facilitate the detection of absorbing spots. Considerable variation in R_f values was noticed using acetone-water (4:1) depending on the size of the chromatographic jar. The best results were obtained using a jar 15 cm. in diameter and 45 cm. in length. A beaker of the solvent was placed in the bottom of the jar while the paper strips were being run.

Methyl 3-amino-5-methyl-2-pyrazinoate. 3-Amino-5-methyl-2-pyrazinoic acid[10] (12.2 g., 0.078 mole) was suspended in 600 ml. of absolute methanol, cooled in an ice bath, and saturated with anhydrous hydrogen chloride. After the solution had been refluxed for 1 hr. it was stored in the cold for 48 hr., then retreated with hydrogen chloride and refluxed again for 1.5 hr. The solution was then evaporated to half volume, treated with Norit and filtered. The filtrate was taken down to an oil *in vacuo*, dissolved in 75 ml. of absolute methanol, and again evaporated *in vacuo*. The residue was dissolved in 200 ml. of water and the free ester obtained by adding sodium acetate to *p*H 4; yield 9.8 g. (78%),[11] m.p. 161–165°. Recrystallization of a portion of this product from water for analytical purposes raised the melting point to 167–169°. R_f 0.68 in 0.5% sodium carbonate 0.66 in 3% ammonium chloride, 0.75 in ethanol–water–concentrated ammonium hydroxide (80:16:4) (purple fluorescence in all cases). Ultraviolet absorption spectra in 0.1*N* sodium

(8) As it has been proved that an equilibrium exists between 3,7-dimethyl-4(3H)-pteridinone (VII) and 3-formamido-5-methylpyrazine-2-(*N*-methyl)carboxamide (VIII) in hot aqueous-pyridine and also as compound VIII is not stable in hot 1*N* sodium hydroxide, it is not possible to rule out two modes of cleavage of VII.[5b] However, we feel that the isolation and degradation of the formyl derivative (VIII) described herein lends greater support for only one method of ring rupture.

(9) Commercially available from E. I. du Pont de Nemours, Inc., Polychemicals Dept., 350 5th Ave., New York 1, N. Y.

(10) This pyrazine derivative has been synthesized by C. K. Cain, M. F. Mallette, and E. C. Taylor, *J. Am. Chem. Soc.*, **70**, 3026 (1948) from 2,4-diamino-7-methylpteridine and also by J. Weijlard, M. Tishler, and A. Erickson, *J. Am. Chem. Soc.*, **67**, 802 (1945) using 7-methyllumazine. We have obtained this compound from 2-amino-4-hydroxy-7-methylpteridine employing conditions similar to the above-mentioned references.

(11) The yields of ester obtained in this manner were much superior to those employing sulfuric acid as a catalyst.

hydroxide λ_{max} 244 mμ (ε 9,030), 340 mμ (ε 7,240); 0.1*N* hydrochloric acid, λ_{max} 247 mμ (ε 9,830), 357 mμ (ε 8,870).

Anal. Calcd. for $C_7H_9N_3O_2$ (161.2): C, 50.3; H, 5.4; N, 25.2. Found: C, 50.4; H, 5.7; N, 24.9.

3-Amino-5-methyl-2-pyrazinecarboxamide. Methyl 3-amino-5-methyl-2-pyrazinoate (9.8 g., 0.061 mole) was stirred for 4 hr. in 250 ml. of concd. ammonium hydroxide. After chilling, the product was collected and dried; yield 7.1 g. (85%), m.p. 239–242° with some previous softening.[12] R_f 0.57 and 0.61 (purple fluorescence) in 0.5% sodium carbonate and 3% ammonium chloride. Ultraviolet absorption spectra in 0.1*N* sodium hydroxide, λ_{max} 249 mμ (ε 11,000), 349 mμ (ε 7,950); 0.1*N* hydrochloric acid λ_{max} 244 mμ (ε 11,800), 356 mμ (ε 9,340).

4-Hydroxy-7-methylpteridine (I). 3-Amino-5-methyl-2-pyrazine-carboxamide (7.1 g., 0.052 mole) was refluxed for 2 hr. 15 min. in a solution of 200 ml. of acetic anhydride and and 200 ml. of ethyl orthoformate. After chilling the mixture overnight the product was collected and dried; yield 4.5 g. The addition of 300 ml. of ether to the mother liquor gave another crop of 1.4 g. (70.5%) total). Both of these products gave the same paper chromatographic pattern in several solvent systems (see below). A small portion of the first crop was recrystallized from water for analysis. R_f 0.72 (dull blue fluorescence) in 0.5% sodium carbonate, 0.71 (absorption) in 3% ammonium, chloride 0.51 (absorption) in butanol-5*N* acetic acid (7:3). Ultraviolet absorption spectra in 0.1*N* sodium hydroxide λ_{max} 244 mμ (ε 17,800), 330mμ (ε 7,140); 0.1*N* hydrochloric acid, λ_{max} 207 mμ (ε 16,200), 232 mμ (ε 10,150), 310 mμ (ε 8,350).

Anal. Calcd. for $C_7H_6N_4O$ (161.15): C, 51.9; H, 3.7; N, 34.6. Found: C, 51.6; H, 3.7; N, 34.5.

3-Amino-5-methylpyrazine-2-[N-(2-cyanoethyl)]carboxamide (IV). Methyl 3-amino-5-methyl-2-pyrazinoate (1.0 g., 6.2 mmoles) and 5 ml. of 3-aminopropionitrile were added to 20 ml. of 95% ethanol and refluxed for 12 hr. Paper chromatography in methyl ethyl ketone–water (9:1) revealed that a substantial amount of starting ester was still present. The solution was concentrated to 10 ml. and 10 ml. of 1-propanol added. After the solution had been refluxed for an additional 8 hr., paper chromatography indicated that the reaction was practically complete. The solvents were removed *in vacuo* to give an oil. This oil was taken up in absolute alcohol and again evaporated *in vacuo* to an oil which was crystallized from 20 ml. of 50% ethanol; yield 0.37 g., m.p. 123–130°. Recrystallization from water gave 0.23 g. (18%), m.p. 135–137°. R_f 0.67 in 3% ammonium chloride, and 0.67 in 0.5% sodium carbonate (bright purple fluorescence in all cases). Ultraviolet absorption spectra in 0.1*N* sodium hydroxide, λ_{max} 251 mμ (ε 12,500), 350 mμ (ε 8,900); in 0.1*N* hydrochloric acid λ_{max} 246 mμ (ε 12,500), 358 mμ (ε10,000).

Anal. Calcd. for $C_9H_{11}N_5O$ (205.2): C, 52.7; H, 5.4; N, 34.1. Found: C, 52.2; H, 5.5; N, 33.8.

3-Amino-5-methylpyrazine-2-[N-(2-carboxyethyl)]carboxamide (VI). 3-Amino-5-methylpyrazine-2[*N*-2-cyanoethyl)] carboxamide (IV) (250 mg., 1.2 mmoles) was heated in 10 ml. of 1*N* sodium hydroxide for 1 hr. on a steam bath. Acidification of the hot solution to *p*H 3 with concentrated hydrochloric acid gave crystals which were collected after cooling; yield 170 mg. This product was recrystallized from about 15 ml. of water; yield 120 mg. (44%), m.p. 207–209.°. R_f 0.80 (purple fluorescence) in 0.5% sodium carbonate and 0.87 (purple fluorescence) in butanol-5*N* acetic acid (7:3). Ultraviolet absorption spectra in 0.1*N* sodium hydroxide, λ_{max} 250 mμ (ε 12,770), 349 mμ (ε 8,970); 0.1*N* hydrochloric acid, λ_{max} 244 mμ (ε 12,770), 357 mμ (ε 10,300).

Anal. Calcd. for $C_9H_{12}N_4O_3$ (224.3): C, 48.2; H, 5.4; N, 25.0. Found: C, 48.3; H, 5.6; N, 25.1.

Cyanoethylation of 4-hydroxy-7-methylpteridine. 4-Hydroxy-7-methylpteridine (1.0 g., 6.2 mmoles) was added to a solution of 50 ml. of pyridine and 10 ml. of water containing 2 ml. of acrylonitrile and refluxed for 3 hr. The solvents were removed *in vacuo* and the resulting oil was taken up in 12 ml. of absolute alcohol, treated with Norit and filtered. The solution was cooled and the crystals were collected and dried; yield 0.85 g. This crude product was extracted with 20 ml. of water and filtered, leaving an insoluble residue (0.236 g.). The filtrate was evaporated to dryness *in vacuo* and taken up in about 10 ml. of absolute alcohol, treated with Norit, and filtered to remove a small amount of amorphous solid. The filtrate deposited crystals of 3-(2-cyanoethyl)-7-methyl-4 (3H)-pteridinone (II) on standing; yield 0.42 g. (31.6%), m.p. 172–173.5°. R_f 0.86 (absorption) in 3% ammonium chloride. Ultraviolet absorption spectra in 0.1*N* hydrochloric acid λ_{max} 236 mμ (ε 11,900), 308 mμ (ε 7,750), in methanol the spectra is essentially the same as in 0.1*N* hydrochloric acid.

Anal. Calcd. for $C_{10}H_9N_5O$ (215.2): C, 55.8; H, 4.2; N, 32.5. Found: C, 55.7; H, 4.5; N, 32.2.

The water-insoluble portion (0.236 g.) was recrystallized from aqueous-ethanol to give 0.152 g. of III (10.5%), m.p. 186.5–189°. R_f 0.90 (dull purple fluorescence) in butanol-5*N* acetic acid (7:3). This compound gave a dull purple, tailed spot which traveled directly behind II in 3% ammonium chloride. Ultraviolet absorption spectra in methanol, λ_{max} 265 mμ (ε 22,000), 315 mμ (ε 8,600).

Anal. Calcd. for $C_{10}H_{11}N_6O_2$ (233.2): C, 51.5; H, 4.8; N, 30.0. Found: C, 51.3; H, 30.2.

Alkaline degradation of 3-(2-cyanoethyl)-7-methyl-4(3H)-pteridinone (II). Two hundred and fifty milligrams (1.16 mmoles) of II was boiled for 30 seconds in 2.5 ml. of 1*N* sodium hydroxide, then cooled in an ice bath immediately. After standing several hours in the cold, the crystals were collected and dried; yield 141 mg. (59.3%), of 3-amino-5-methylpyrazine-2-[*N*-(2-cyanoethyl)]carboxamide (IV), m.p. 134.5–137.5°. The filtrate, after acidification to *p*H 3 with concentrated hydrochloric acid, deposited 23 mg. (13%) of 3-amino-5-methyl-2-pyrazinoic acid (V), m.p. 210–212° dec.[13] Both of these products traveled side by side with authentic specimens when chromatographed in several different solvent systems.

Alkaline degradation of 3-formamido-5-methypyrazine-2-[N-(2-cyanoethyl)]carboxamide (III). The formyl compound (100 mg., 0.43 mmole) was treated in the same manner as described above for I to give 56 mg. (63.5%) of the cyanoethylamide (IV), m.p. 136–139° and 7 mg. (10.6%) of the pyrazinoic acid (V), m.p. 206–210° dec.[13] Confirmation of the structures was again provided through paper chromatography.

3-Amino-5-methylpyrazine-2-(N-methyl)-carboxamide (IX). 3-Amino-5-methyl-2-pyrazinoic acid (15.0 g., 0.098 mole) was converted to the methyl ester as described above. The crude ester was added to 250 ml. of 25% aqueous methylamine solution and stirred for 20 min. at room temperature, then chilled for several days; yield 6.9 g. (42%), m.p. 126–128°. R_f 0.85 in butanol-5*N* acetic acid (7:3), 0.64 in 3% ammonium chloride, 0.88 in acetone-water (4:1), 0.63 in 0.5% sodium carbonate (purple fluorescence in all cases). Ultraviolet absorption spectra in 0.1*N* sodium hydroxide, λ_{max} 250 mμ (ε 11,500), 348 mμ (ε 8,080); in 0.1*N* hydrochloric acid, λ_{max} 244 mμ (ε 11,900), 358 mμ (ε 9,550); in methanol, λ_{max} 250 mμ (ε 12,400), 351 mμ (ε 8,700).

Anal. Calcd. for $C_7H_{10}N_4O$ (166.2): C, 50.6; H, 6.1; N, 33.7. Found: C, 50.6; H, 6.2; N, 33.7.

3,7-Dimethyl-4(3H)-pteridinone (VII). Two grams (12 mmoles) of 3-amino-5-methylpyrazine-2-(*N*-methyl)carboxamide (IX) was added to a solution of 20 ml. of ethyl orthoformate and 20 ml. of acetic anhydride and refluxed for 2 hr. The reaction mixture was cooled and the product collected; yield 1.9 g. (90%). The crude product was recrystallized from 80 ml. of hot water using Norit to give 1.3 g. (62%), dec. slowly above 300°. R_f 0.83 in 3%, ammonium

(12) E. C. Taylor, J. W. Barton, and T. S. Osdene, *J. Am. Chem. Soc.*, **80**, 421 (1958), give m.p. 235–236°.

(13) M.p. 211–212° dec. reported in ref. 12.

chloride 0.80 in acetone-water (4:1), 0.58 in butanol-5*N* acetic acid (7:3) (absorption in all cases). Ultraviolet absorption spectra in methanol, λ_{max} 238 mμ (ε 12,100), 312 (ε 7,200); in 0.1*N* hydrochloric acid the spectra is essentially the same as methanol.

Anal. Calcd. for $C_8H_8N_4O$ (176.2): C, 54.5; H, 4.6; N, 31.8. Found: C, 54.5; H, 4.8; N, 31.6.

Method 2. 3-Formamido-5-methylpyrazine-2-(*N*-methyl)-carboxamide (VIII) (100 mg., 0.52 mmole) was heated on a steam bath for 8 hr. in a solution of 5 ml. of pyridine and 1 ml. of water. After the solution stood at room temperature overnight the crystals were collected; yield 40 mg. (44%). The infrared spectra of this product and that obtained by method 1 were identical.

Method 3. Compound VIII (100 mg., 0.52 mmole) was warmed on a steam bath in 10 ml. of 5% sodium bicarbonate solution until solution was complete (4–5 min). The crystals were filtered off after standing 2 days at room temperature, yield 54 mg. (59%). The infrared spectrum of this material was identical to spectra of the products obtained by methods 1 and 2.

3-Formamido-5-methylpyrazine-2-(N-methyl)carboxamide (VIII). *Method 1.* 3-Amino-5-methylpyrazine-2-(*N*-methyl)-carboxamide (1.0 g., 6.0 mmoles) was dissolved in a solution containing 5 ml. of formic acid and 10 ml. of acetic anhydride and warmed on a steam bath for several minutes to initiate the reaction. After standing at room temperature for a few minutes, crystals separated; yield 0.75 g. (71%), m.p. 225–231° (resolidifies to give crystals which do not melt below 300° indicating ring closure to VII). R_f 0.84 in butanol-5*N* acetic acid (7:3), 0.87 in acetone-water (4:1) (dull purple fluorescence), tailed spot between VII and IX in 3% ammonium chloride. Ultraviolet absorption spectra in methanol, λ_{max} 256 mμ (ε 19,000), 316 mμ (ε 7,480).

Anal. Calcd. for $C_8H_{10}N_4O_2$ (194.2): C, 49.5; H, 5.2; N, 28.9. Found: C, 49.2; H, 5.4; N, 29.2.

Method 2. 3,7-Dimethyl-4(3H)-pteridinone (0.50 g., 2.8 mmoles) was refluxed for 12 hr. in 30 ml. of a pyridine-water (5 : 1) solution. On cooling 0.33 g. of starting material was filtered off and the filtrate was taken to dryness *in vacuo*. This was extracted with 30 ml. of water and filtered from the insoluble residue; yield 106 mg., m.p. 226.5–230°. Recrystallization from 10 ml. of 50% ethanol yielded 50 mg., m.p. 232–235°. This material was identical to that prepared by Method 1 as shown by infrared spectra, mixed melting point, and paper chromatography.

When this formyl compound (VIII) or 3,7-dimethyl-4-(3H)-pteridinone (VII) was refluxed for 1 min. in 1*N* sodium hydroxide, they were converted to 3-amino-5-methyl-2-pyrazinoic acid (V) and 3-amino-5-methylpyrazine-2-(*N*-methyl)carboxamide (IX) as shown by chromatography in 3% ammonium chloride 0.5% sodium carbonate and acetone-water (4:1). By heating for 1 min. on a steam bath in 0.1*N* sodium hydroxide a third yellow-green fluorescent product was formed which traveled side-by-side with compound X in the three above-mentioned solvent systems. This compound (X) was slowly hydrolyzed to the acid (V) on standing in 0.1*N* sodium hydroxide at room temperature.

3-Formamido-5-methylpyrazine-2-carboxylic acid (X). One gram of 3-amino-5-methylpyrazine-2-carboxylic acid was added to a solution of 5 ml. of formic acid in 10 ml. of acetic anhydride and warmed on the steam bath for a few minutes to initiate the reaction. After standing at room temperature for 5 min. the solution was refluxed for 30 min., then treated with Norit and filtered. Twenty milliliters of anhydrous ether was added to the filtrate. This solution was protected with a tube of Drierite and allowed to stand for several hours at room temperature, then chilled overnight. The product was collected and dried; yield 0.45 g. (38%), m.p. 184–185° dec. R_f 0.82 in 3% ammonium chloride 0.84 in 0.5% sodium carbonate, 0.64 in acetone-water (4:1) (yellow-green fluorescence). Ultraviolet absorption spectra in methanol, λ_{max} 252 mμ (ε 15,500), 311 mμ (ε 6,920).

Anal. Calcd. for $C_7H_7N_3O_3$ (181.2): C, 46.4; H, 3.9; N, 23.2. Found: C, 46.6; H, 4.2; N, 23.4.

Acknowledgment. We are indebted to Mr. L. Brancone and staff for the microanalyses and to Mr. W. Fulmor and Mr. G. Morton for spectral data.

PEARL RIVER, N. Y.

[CONTRIBUTION FROM AVERY LABORATORY, UNIVERSITY OF NEBRASKA]

Benzacridines. V.[1] Dibenz[a,c]acridine and 1,4-Dimethylbenz[c]acridine

JULES L. ADELFANG AND NORMAN H. CROMWELL

Received November 28, 1960

Application of the α-dehydrobromination-rearrangement reaction previously reported for 6-bromo-5,5-dimethyl-5,6-dihydrobenz[c]acridine has led to a new synthesis of dibenz[a,c]acridine. Several other possible conditions for carrying out this transformation have been investigated. A new benz[c]acridine, namely, 1,4-dimethylbenz[c]acridine, is reported.

The initial paper in this series[2] reported a new pathway to benz[c]acridine derivatives substituted in the five and six positions. These positions, which involve the carbon atoms of the "K-region" for this ring system, provide interesting derivatives for further studies of chemical carcinogenesis.[3] It was also of importance to find further examples of the "α-dehydrobromination-rearrangement" of 6-bromo-5,5-dimethyl-5,6-dihydrobenz[c]acridine (VIII) that led to the isolation of 5,6-dimethylbenz[c]acridine (XI) in high yield.

Condensation of 4,4-tetramethylene-1-tetralone (I) with *o*-nitrobenzaldehyde was carried out in the presence of acetic acid and sulfuric acid providing 2-(*o*-nitrobenzal)-4,4-tetramethylene-1-tetralone (II) in 84% yield. Reduction of the ketone II with iron and acetic acid followed by direct cycliza-

(1) For paper IV, see N. H. Cromwell and J. C. David, *J. Am. Chem. Soc.*, **82**, 2046 (1960).

(2) V. L. Bell and N. H. Cromwell, *J. Org. Chem.*, **23**, 789 (1958).

(3) See (a) C. A. Coulson, *Advances in Cancer Research*, Academic Press, Inc., New York, N. Y., 1953, Vol. I, pp. 1–56 and (b) A. Lacassagne, N. P. Buu-Hoi, R. Daudel, and F. Zajdela, *Advances in Cancer Research*, Academic Press, Inc., New York, N. Y., 1956, Vol. IV, pp. 316–369.

tion of the intermediate aminoketone with hydrochloric acid produced 5,5-tetramethylene-5,6-dihydrobenz[c]acridine (IV) in 83% over-all yield. Reaction of the tetralone I with isatin under basic conditions afforded a 75% yield of 7-carboxy-5,5-tetramethylene-5,6-dihydrobenz[c]acridine (III). Thermal decarboxylation of the acid III also gave the dihydrobenz[c]acridine IV. The unstable bromide V, obtained by treatment of IV with *N*-bromosuccinimide in carbon tetrachloride, was directly heated at 170° affording the hydrobromide of 5,6,7,8-tetrahydrodibenz[a,c]acridine (VI). The over-all yield of VI from the dihydrobenz[c]-acridine IV was 76%. As expected, the ultraviolet absorption spectra of III and IV closely resemble those obtained for 5,6-dihydrobenz[c]acridines while VI provided a spectrum very similar to that observed for 5,6-dimethylbenz[c]acridine.[2] Dehydrogenation of the tetrahydro compound VI produced dibenz[a,c]acridine (VII) that was shown to be identical with an authentic sample prepared from phenanthraquinone and *o*-nitrobenzyl chloride. This conversion provides additional evidence for the structure of the products obtained from thermal dehydrobromination-rearrangement of the bromides V and VIII.

Various other conditions for carrying out the conversion of the bromide VIII to 5,6-dimethylbenz[c]acridine have been attempted affording lower yields of the desired product compared to those obtained by direct thermal decomposition. Heating of the bromide VIII with pyridine provided only a 20% yield of 5,6-dimethylbenz[c]acridine (XI). Treatment of the bromide VIII with γ-picoline at room temperature for an extended period gave the stable γ-picolinium bromide IX in 89% yield. At approximately the same temperature observed for the decomposition of the bromide VIII the salt IX evolves γ-picoline and the neutralized residue afforded a 58% yield of 5,6-dimethylbenz[c]acridine. A quantitative yield of silver bromide was isolated from the reaction of VIII with silver nitrate in dry acetonitrile. After hydrolysis and neutralization of the reaction mixture the major product (49%), probably obtained by hydrolysis of the nitrate, was 6-hydroxy-5,5-dimethyl-5,6-dihydro-benz[c]acridine (X) while only a 20% yield of 5,6-dimethylbenz[c]acridine was isolated.

Previously reported carcinogenic testing of the mono- and dimethylbenz[c]acridines indicated that activity was largely dependent on the presence of a substituent at the seven position.[3b] Since the known methylbenz[c]acridines did not include methyl substitutions at the one and four positions, 1,4-dimethylbenz[*c*]acridine (XV) was synthesized from the readily available 5,8-dimethyl-1-tetralone (XII). Condensation of the tetralone XII with *o*-nitrobenzaldehyde produced 2-(*o*-nitrobenzal)-5,8-dimethyl-1-tetralone (XIII) which upon reduction with iron and acetic acid and cyclization in the presence of hydrochloric acid yielded 1,4-dimethyl-5,6-dihydrobenz[c]acridine (XIV). Dehydrogenation of XIV with palladium-charcoal provided 1,4-dimethylbenz[c]acridine (XV).

EXPERIMENTAL[4]

4,4-Tetramethylene-1-tetralone (I). Cyclization of 2.80 g. of 4-phenyl-4,4-tetramethylenebutyric acid,[5] prepared by the method of Arnold, was accomplished by heating on a steam bath for 25 min. with 10 ml. of polyphosphoric acid. The cooled reaction mixture was poured on ice and, after the addition of ether and benzene, the organic layer was washed with water and sodium carbonate solution and dried over anhydrous sodium sulfate. After concentration the solution was passed through an alumina column and the benzene eluates were concentrated under reduced pressure to constant weight providing 2.30 g. (90%) of 4,4-tetramethylene-1-tetralone (I), $n_D^{27°}$ 1.5720, reported[5] $n_D^{24°}$ 1.5732.

2-(o-Nitrobenzal)-4,4-tetramethylene-1-tetralone (II). A solution of 1.80 g. (0.0090 mole) of 4,4-tetramethylene-1-tetralone (I) and 1.36 g. (0.0090 mole) of *o*-nitrobenzaldehyde in 2.3 ml. of sulfuric acid and 14 ml. of acetic acid was allowed to stand at room temperature for 5 days. The crystals that had formed were collected by filtration and washed with methanol providing 2.25 g. of 2-(*o*-nitrobenzal)-4,4-tetramethylene-1-tetralone (II), m.p. 121–123°. The solid obtained by addition of water to the filtrate was dissolved in ethyl acetate, treated with Norite, and allowed to crystallize affording an additional 0.27 g. of II, m.p. 123–124°, making the total yield 2.52 g. (84%). An analytical sample, m.p. 125–125.5°, λ_{max} 276 mμ (ε 19,200), was prepared by crystallization from ethyl acetate.

Anal. Calcd. for $C_{21}H_{19}NO_3$: C, 75.65; H, 5.74; N, 4.20. Found: C, 75.84; H, 5.63; N, 4.02.

7-Carboxy-5,5-tetramethylene-5,6-dihydrobenz[c]acridine (III). A mixture of 0.50 g. (0.0025 mole) of 4,4-tetramethylene-1-tetralone, 0.40 g. (0.0025 mole) of isatin, 0.52 g. of potassium hydroxide, 0.8 ml. of methanol, and 0.5 ml. of water was refluxed for 11 hr. The reaction mixture was diluted with water and acidified to bromophenol blue with hydrochloric acid. The resulting solid was collected, washed with water, and crystallized from ethyl acetate providing 0.62 g. (75%) of 7-carboxy-5,5-tetramethylene-5,6-dihydrobenz[c]acridine (III), m.p. 210.5–213°. Recrystallization from ethyl acetate yielded an analytical sample, m.p. 211.5–213°, λ_{max} 209, 214, 226, 260 sh, 267, 300, 316, 331,346 mμ (ε × 10^{-4}, 4.05, 3.89, 2.48, 2.94, 3.65, 0.82, 0.87, 1.13, 1.29).

Anal. Calcd. for $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81; N, 4.25. Found: C, 79.70; H, 5.88; N, 4.02.

5,5-Tetramethylene-5,6-dihydrobenz[c]acridine (IV). Powdered electrolytic iron, 1.3 g., was added in small portions to a solution of 2.80 g. (0.0084 mole) of 2-(*o*-nitrobenzal)-4,4-tetramethylene-1-tetralone (II) dissolved in 35 ml. of acetic acid and 4 ml. of water and heated on a steam bath. The reaction mixture was heated for an additional 15 min., cooled, and treated with a solution of 35 g. of potassium hydroxide in 200 ml. of water. The resulting suspension was extracted with four 150-ml. portions of ether. The ether extracts were washed with water and after concentration the residue was heated on a steam bath for 0.5 hr. with 5 ml. of concd. hydrochloric acid and 30 ml. of ethanol. After dilution with water the reaction mixture was neutralized with sodium carbonate solution and the solid that formed was collected and washed with water. A benzene solution of this

(4) Ultraviolet spectral determinations were made at about 25° with a Cary recording spectrophotometer, model 11 MS, using 95% ethanol unless otherwise specified.

(5) R. T. Arnold, J. S. Buckley, and R. M. Dodson, *J. Am. Chem. Soc.*, 72, 3153 (1950).

material was passed through a column of basic alumina and crystallization of the concentrated benzene eluates from methanol afforded 2.00 g. (83%) or 5,5-tetramethylene-5,6-dihydrobenz[c]acridine (IV), m.p. 162–165°. Preparation of an analytical sample was accomplished by crystallization from methanol and ethyl acetate giving colorless needles, m.p. 165–166°, λ_{max} 211, 215, 226 sh, 259 sh, 267, 299, 317, 332, 346 mμ ($\epsilon \times 10^{-4}$, 4.22, 4.13, 3.00, 2.96, 3.63, 0.85, 0.87, 1.26, 1.47).

Anal. Calcd. for $C_{21}H_{17}N$: C, 88.38; H, 6.71; N, 4.91. Found: C, 88.23; H, 6.59; N, 5.00.

Thermal decarboxylation of 7-carboxy-5,5-tetramethylene-5,6-dihydrobenz[c]acridine (III). Decarboxylation of 0.95 g. of the acid III was accomplished by heating for 1.5 hr. at 240°. The crude product was dissolved in benzene and extraction with sodium hydroxide solution led to the recovery of 0.15 g. of starting material. The dried benzene solution was passed through an alumina column and the concentrated benzene eluates were crystallized from methanol providing 0.35 g. (50%) of 5,5-tetramethylene-5,6-dihydrobenz(c)acridine (IV), m.p. 162–164°. This compound was shown to be identical with the preparation obtained *via* 2-(*o*-nitrobenzal)-4,4-tetramethylene-1-tetralone (II) by a mixture melting point determination.

5,6,7,8-Tetrahydrodibenz[a,c]acridine (VI). A solution of 1.42 g. (0.0045 mole) of 5,5-tetramethylene-5,6-dihydrobenz-[c]acridine (IV) in 25 ml. of carbon tetrachloride was refluxed 45 min. with 0.98 g. (0.0056 mole) of*N*-bro mosuccinimide and a trace of benzoyl peroxide. The reaction mixture was cooled, diluted with ether, and washed with sodium carbonate solution. The organic layer was washed with water, dried over anhydrous sodium sulfate, and concentrated at room temperature under reduced pressure. The resulting unstable yellow solid was heated for 10 min. at 170° under a nitrogen atmosphere. The red colored solid produced was heated with sodium hydroxide solution and benzene. The benzene solution was washed with water, dried by azeotropic distillation, and passed through a column of basic alumina. Concentration of the benzene eluates and crystallization of the residue from ethyl acetate produced 1.07 g. (76%) of 5,6,7,8-tetrahydrodibenz[a,c]acridine (VI), m.p. 193–196°. Recrystallization from ethyl acetate yielded an analytical sample as yellow needles, m.p. 196–197°, λ_{max} 223, 235 sh, 270 sh, 277, 292, 321, 337, 352, 369, 387 mμ ($\epsilon \times 10^{-4}$, 3.62, 2.72, 4.61, 5.39, 5.14, 0.57, 0.62, 0.65, 0.70, 0.58).

Anal. Calcd. for $C_{21}H_{17}N$: C, 89.01; H, 6.05. Found: C, 88.87; H, 6.20.

Dibenz[a,c]acridine (VII). Following the procedure of Austin[6] phenanthraquinone was allowed to react with *o*-nitrobenzyl chloride in the presence of stannous chloride, concentrated hydrochloric acid, and methanol. Purification of the crude product was accomplished by chromatography in benzene on basic alumina followed by concentration of the benzene eluates providing dibenz[a,c]acridine in 50% yield as pale yellow needles, m.p. 204–205°, reported m.p. 205°, λ_{max} 257, 272, 282, 304, 338, 354, 372 mμ ($\epsilon \times 10^{-4}$, 6.08, 6.49, 8.14, 1.04, 0.70, 1.16, 1.35).

Dehydrogenation of 5,6,7,8-tetrahydrodibenz[a,c]acridine (VI). Dehydrogenation of 0.08 g. of 5,6,7,8-tetrahydrodibenz[a,c]acridine (VI) was carried out in the presence of 10% palladium-charcoal under a nitrogen atmosphere for 10 min. at 300°. The crude product was dissolved in benzene, treated with Norite, and allowed to crystallize yielding 0.02 g. (25%) of dibenz[a,c]acridine (VII), m.p. 199–202°, mixture melting point determination with the dibenz[a,c]-acridine prepared above and comparison of ultraviolet spectra showed the two compounds to be identical.

Reactions of 6-bromo-5,5-dimethyl-5,6-dihydrobenz[c]acridine (VIII). A. *5,5-Dimethyl-5,6-dihydrobenz[c]acridine 6-(γ-Picolinium bromide)* (IX). A solution of 1.95 g. (0.0058 mole) of 6-bromo-5,5-dimethyl-5,6-dihydrobenz[c]acridine (VIII)[2] in 10 ml. of γ-picoline was allowed to stand at room temperature for 9 days. The crystals that had formed were collected and washed with acetone affording 2.20 g. (89%) of 5,5-dimethyl-5,6-dihydrobenz[c]acridine 6-(γ-picolinium bromide) (IX). Recrystallization from isopropyl alcohol-ether yielded an analytical sample, m.p. 165–185° dec., λ_{max} in methanol 213, 223 sh, 266, 302, 316, 330, 345 mμ ($\epsilon \times 10^{-4}$, 4.18, 3.21, 4.16, 0.85, 0.85, 0.94, 0.87).

Anal. Calcd. for $C_{25}H_{22}N_2Br$: C, 69.60; H, 5.37; N, 6.50; Br, 18.53. Found: C, 68.96; H, 5.27 N, 6.50; Br, 18.56.

B. *Reaction with pyridine.* A solution of 2.0 g. of the bromo compound VIII in 20 ml. of dry pyridine was heated on a steam bath for 4 hr. Water was added and the precipitated solid was collected, dissolved in acetone, and treated with Norite. Addition of water gave 0.3 g. (20%) of yellow crystals shown by a mixture melting point determination to be 5,6-dimethylbenz[c]acridine (XI).[2]

C. *Reaction with silver nitrate in acetonitrile.* To a solution of 2.0 g. (0.0059 mole) of the bromo compound VIII in 40 ml. of warm, dry acetonitrile 1.02 g. (0.0059 mole) of silver nitrate dissolved in 10 ml. of acetonitrile was added dropwise. The reaction mixture was filtered hot, removing the theoretical amount of silver bromide. The filtrate was neutralized with sodium carbonate solution and the precipitated crystals were filtered from the warm mixture yielding 0.30 g. (20%) of 5,6-dimethylbenz[c]acridine. Upon addition of water and cooling, the mother liquor gave 0.80 g. (49%) of 5,5-dimethyl-6-hydroxy-5,6-dihydrobenz[c]acridine (X).[2] The products were identified by mixture melting point determinations with authentic samples.

Thermal decomposition of 5,5-dimethyl-5,6-dihydrobenz[c]acridine 6-(γ-Picolinium bromide) (IX). A 1.00-g. sample of the salt IX was heated for 15 min. at 165–185°. As the decomposition proceeded, the solid became red in color and the evolution of γ-picoline was observed. After cooling, the residue was dissolved in hot dioxane and neutralized with sodium carbonate solution. A dry benzene solution of the solid obtained was passed through an alumina column and the concentrated eluates yielded, after crystallization from benzene-methanol, 0.35 g. (58%) of 5,6-dimethylbenz-[c]acridine, m.p. 161–163°. A mixture melting point determination with a sample obtained by heating 6-bromo-5,5-dimethyl-5,6-dihydrobenz(c)acridine[2] demonstrated the compounds to be identical.

5,8-Dimethyl-1-tetralone (XII). Preparation of this tetralone was accomplished by modification of the procedure used by Barnett.[7] During a period of 1 hr. 300 g. of aluminum chloride was added to a mixture of 106 g. (1.0 mole) of *p*-xylene, 98 g. (0.98 mole) of succinic anhydride and 375 ml. of methylene chloride. Hydrolysis and extraction of the reaction mixture in the usual manner provided a quantitative yield of crude acidic material. Direct reduction of 100 g. of keto acid using the Wolff-Kishner method was carried out with 65 g. of potassium hydroxide, 54 ml. of 95% hydrazine, and 525 ml. of diethylene glycol. The crude γ-(*p*-xylyl)-butyric acid, obtained in quantitative yield, was cyclized with polyphosphoric acid in the usual manner and chromatography on alumina in benzene followed by crystallization of the eluates from petroleum ether at about −30° gave a 60% yield of 5,8-dimethyl-1-tetralone (XII), m.p. 32–33.5°, reported m.p. 33°.

2-(o-Nitrobenzal)-5,8-dimethyl-1-tetralone (XIII). After a mixture of 8.70 g. (0.05 mole) of 5,8-dimethyl-1-tetralone, 7.50 g. (0.05 mole) of *o*-nitrobenzaldehyde, 10 ml. of sulfuric acid, and 60 ml. of acetic acid was allowed to stand for 40 hr., the crystals that had formed were collected and washed with a small amount of acetic acid and methanol. Recrystallization from benzene–petroleum ether (b.p. 30–60°) afforded 7.35 g. (48%) of 2-(*o*-nitrobenzal)-5,8-dimethyl-1-tetralone (XIII), m.p. 133–134.5°. An analytical sample,

(6) P. C. Austin, *J. Chem. Soc.*, 1765 (1908).

(7) E. de Barry Barnett and F. G. Sanders, *J. Chem. Soc.*, 434 (1933).

m.p. 133.5–134.5°, λ_{max} 273 mμ (ε, 24,400), was prepared by crystallization from methanol and benzene.

Anal. Calcd. for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.54; H, 5.72; N, 4.39.

1,4-Dimethyl-5,6-dihydrobenz[c]acridine (XIV). As described for the ketone II, 4.64 g. (0.015 mole) of 2-(*o*-nitrobenzal)-5,8-dimethyl-1-tetralone (XIII) was reduced with iron powder and cyclized in the presence of hydrochloric acid producing, after chromatography and crystallization from methanol, 3.05 g. (78%) of 1,4-dimethyl-5,6-dihydrobenz[c]acridine (XIV), m.p. 96.5–98°. Recrystallization from methanol provided an analytical sample, m.p. 102–102.5°, λ_{max} 220, 258 sh, 266, 312, 327, 342 mμ (ε × 10^{-4}, 4.50, 2.64, 3.36, 0.88, 1.17, 1.38).

Anal. Calcd. for $C_{19}H_{17}N$: C, 88.00; H, 6.60; N, 5.40. Found: C, 88.16; H, 6.61; N, 5.13.

1,4-Dimethylbenz[c]acridine (XV). Dehydrogenation of 2.0 g. of 1,4-dimethyl-5,6-dihydrobenz[c]acridine (XIV) was carried out at 210–220° in the presence of 10% palladium-charcoal. This provided, after dissolving in benzene and passage through an alumina column followed by crystallization from ethyl acetate, 0.50 g. (25%) of 1,4-dimethylbenz[c]acridine (XV), m.p. 108–110°. Recrystallization from ethyl acetate yielded an analytical sample, m.p. 110–111°, λ_{max} 229, 244, 272 sh, 277 sh, 280, 338, 356, 373, 391 mμ (ε × 10^{-4}, 4.95, 4.51, 8.70, 9.20, 9.50, 0.68, 0.62, 0.96, 1.33).

Anal. Calcd. for $C_{19}H_{15}N$: C, 88.68; H, 5.88; N, 5.44. Found: C, 88.85; H, 5.82; N, 5.32.

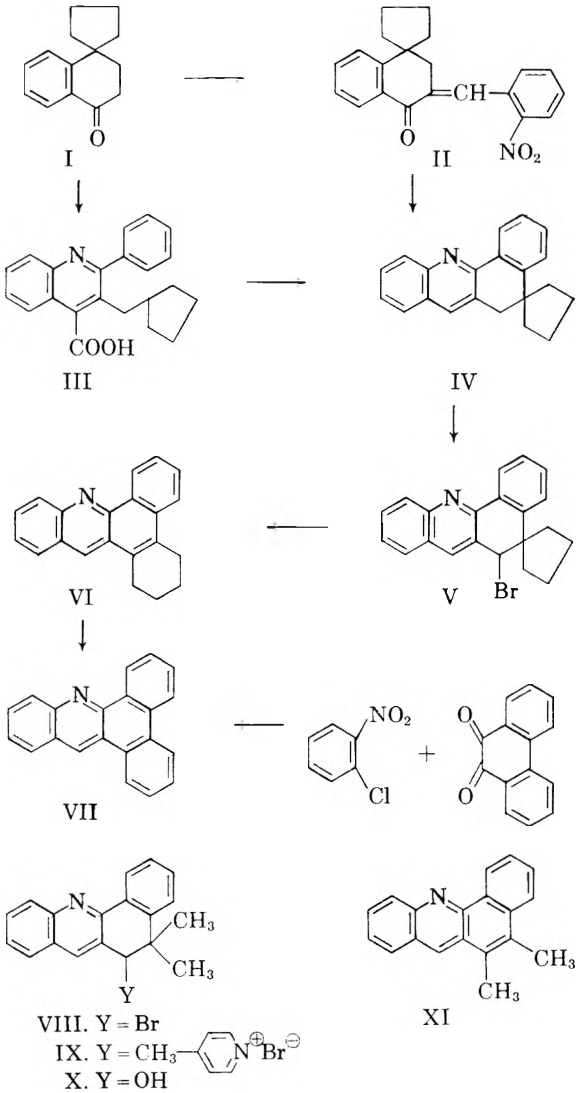
A picrate was prepared in the usual manner and after crystallization from acetone melted with decomposition at 181–183°, λ_{max} 226, 242, 280, 342, 356, 372, 392 mμ (ε × 10^{-4}, 3.19, 2.86, 4.52, 0.80, 1.02, 1.07, 0.78).

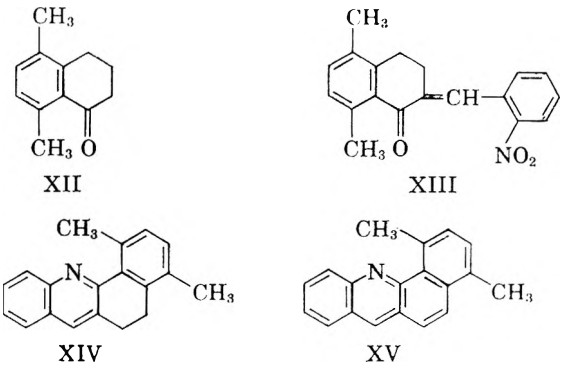
Anal. Calcd. for $C_{25}H_{18}N_4O_7$: C, 61.73; H, 3.73; N, 11.52. Found: C, 61.90; H, 3.91; N, 11.24.

For the purpose of comparison the ultraviolet spectrum of 5,6-dimethylbenz[c]acridine picrate[2] was determined, λ_{max} 223, 236 sh, 271 sh, 278, 293, 340 sh, 356, 370, 388 sh, mμ (ε × 10^{-4}, 4.14, 3.22, 3.58, 4.22, 4.04, 0.74, 1.08, 1.00, 0.60).

Acknowledgment. This investigation was supported in part by a grant from the National Cancer Institute, U. S. Public Health Service, CY-2931.

LINCOLN, NEB.





[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MICHIGAN STATE UNIVERSITY]

The Degradative Benzoylation of 5-Phenyltetrazole

ROBERT M. HERBST

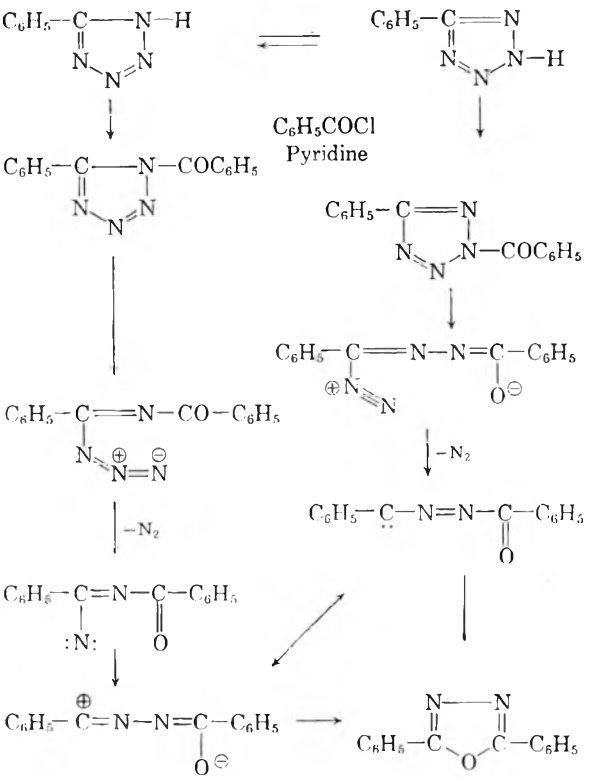
Received November 21, 1960

The degradative benzoylation of 5-phenyltetrazole labeled with N^{15} in the 1- (or 4)position has been investigated. Half of the isotope is recovered in the 2,5-diphenyl-1,3,4-oxidazole formed in the reaction, indicating that nitrogen in the 3,4- (or 1,2) positions of the tetrazole ring is eliminated. These results support the mechanism proposed by Huisgen for the reaction.

Recently Huisgen, Sauer and Sturm[1,2] described a degradative acylation of 5-substituted tetrazoles during which nitrogen is eliminated from the tetrazole ring and a 2,5-disubstituted 1,3,4-oxadiazole is formed. The reaction provides an elegant, controlled degradation of the tetrazole ring. These authors suggested a mechanism that involves attack by the acylating agent at position 2 (or 3) of the tetrazole ring, breaking of the ring at the 2,3-position, elimination of nitrogen, and recyclization through the acyl oxygen to form the oxadiazole (Scheme B).

A similar degradation of 1-*p*-nitrophenyl-5-aminotetrazole during acylation with acetic anhydride was observed in this laboratory.[3] The formation of 2-methyl-5-*p*-nitrophenylamino-1,3,4-oxadiazole under these conditions could be explained most easily by a pathway suggested by Stollé[4] for the degradation of 5-aminotetrazole on prolonged heating with acetic anhydride to 2-acetamido-5-methyl-1,3,4-oxadiazole. It was also suggested[3] that the degradative acylation of 5-substituted tetrazoles could be explained by assumption of attack by the acyl group at the 1- (or 4)position of the tetrazole ring followed by ring opening at the 1,2- (or 3,4)position, elimination of nitrogen from the resulting azido group, migration of the acylimido group from carbon to nitrogen, and recyclization to the oxadiazole (Scheme A).

Scheme B involves elimination of the nitrogen at the 3,4-(or 1,2)positions of the tetrazole ring, while Scheme A requires elimination of nitrogen at the 2,3-positions. A choice between the two courses should be possible by use of suitably labeled tetrazole derivatives. Because of tautomerism inherent in the 5-substituted tetrazole structure, or resonance phenomena of the tetrazolyl anion, it is not possible to distinguish between the 1- and 4-positions on the one hand or the 2- and 3-positions on the other. However, inability to distinguish between the 1- and 4-positions is not critical. Labeling of the tetrazole ring in the 1- (or 4-) position with N^{15} could be accomplished by unequivocal reactions. If the acylation reaction with the 5-substituted tetrazole followed Scheme A, the labeled position would be unaffected and all of the isotope would appear in the oxadiazole. As half of the tetrazole nitrogen is eliminated during the degradation, the isotope content of the oxadiazole should be double that of the starting tetrazole. On the other hand, if Scheme B is involved, the 3,4- (or 1,2)nitrogens would be eliminated. Half of the isotope and half of the tetrazole nitrogen would be lost; the oxadiazole and the original tetrazole should have the same isotope content.



Scheme A Scheme B

Nitrogen labeled benzamide (16.8 at. per cent N^{15}) was prepared by interaction of N^{15} enriched ammonium salts with benzoyl chloride in presence of aqueous sodium hydroxide. The benzamide was dehydrated with thionyl chloride and the labeled benzonitrile was allowed to react without purification with sodium azide and acetic acid in *n*-butyl

(1) R. Huisgen, J. Sauer, and H. J. Sturm, *Angew. Chem.*, 70, 272 (1958).

(2) R. Huisgen, J. Sauer, H. J. Sturm, and J. H. Markgraf, *Chem. Ber.*, 93, 2106 (1960).

(3) R. M. Herbst and J. K. Klingbeil, *J. Org. Chem.* 23, 1912 (1958).

(4) R. Stollé, *Ber.*, 62, 1118 (1929).

alcohol[5] to form 5-phenyltetrazole labeled in the 1-(or 4)-position. The isotope content of 5-phenyltetrazole could not be determined directly. No mass was observed below 240°; at this temperature complete decomposition occurred. Although no peak corresponding to mass 146 was apparent peaks at masses comparable to nitrogen and benzonitrile could be identified along with peaks associated with unidentified decomposition products. The isotope content of the identifiable fragments was not consistent in different runs. Methylation of 5-phenyltetrazole gave a mixture of 1-methyl- and 2-methyl-5-phenyltetrazole[6] both of which gave mass spectra indicating isotope contents of 4.4 and 4.5 at. percent N^{15}, respectively. Treatment of the 5-phenyltetrazole with benzoyl chloride in pyridine[2] gave 2,5-diphenyl-1,3,4-oxidiazole containing 4.4 at. percent N^{15}.

Since half of the isotope was lost during acylation of the tetrazole, it must be concluded that nitrogen was eliminated from the 3,4- (or 1,2)positions and that Scheme B represents the course of the reaction correctly. The *N*-acyl 5-substituted tetrazoles described by Huisgen and co-workers[2] must be the 2-acyl derivatives as suggested by these authors.

EXPERIMENTAL[7]

Benzamide (N^{15}). The interaction of 1.66 g. (0.02 mole) of ammonium nitrate (NH_4^+, 34.7 at. % N^{15}), 1.32 g. (0.01 mole) of ammonium sulfate (normal N distribution), 8.43 g. (0.06 mole) of benzoyl chloride, and 5.6 g. (0.14 mole) of sodium hydroxide in 28 ml. of cold water gave 4.19 g. (86.4%) of benzamide. Recrystallization of 350 mg. of this material from water gave pure benzamide, m.p. and mixture m.p. 128–129°. Found: N^{15}, 16.8 at. %.

5-Phenyltetrazole [1 (or 4) N^{15}]. Dehydration of 3.84 g. (0.032 mole) of benzamide (N^{15}, 16.8 at. %) was accomplished by heating on a steam bath with 7.62 g. (0.064 mole) of thionyl chloride for 1 hr. Excess thionyl chloride was decomposed by addition of 0.6 ml. of water to the cold reaction mixture. Hydrogen chloride and sulfur dioxide were removed as completely as possible at room temperature and atmospheric pressure. The crude benzonitrile was dissolved in 40 ml. of *n*-butyl alcohol. Sodium azide (8.3 g., 0.13 mole) and 11.5 g. (0.19 mole) of glacial acetic acid were added and the mixture boiled under reflux for 4 days. After dilution of the reaction mixture with 80 ml. of water, butyl alcohol and butyl acetate were removed by distillation until 80 ml. of distillate had collected. The residual aqueous solution was made distinctly alkaline to litmus with sodium hydroxide, warmed with charcoal, and the hot, colorless filtrate acidified to Congo Red with concentrated hydrochloric acid. (Care: hydrazoic acid!) 5-Phenyltetrazole crystallized from the hot solution during acidification, yield 3.85 g. (83%). Recrystallization of 2.85 g. of this material from 20% ethanol gave pure 5-phenyltetrazole, m.p. and mixture m.p. 215° with decomposition.[5]

1-Methyl-5-phenyltetrazole and 2-methyl-5-phenyltetrazole [1 (or 4) N^{15}] Methylation of 1 g. of 5-phenyltetrazole [1 (or 4) N^{15}] following the procedure of Henry[6] gave 0.14 g. (13%) of pure 1-methyl-5-phenyltetrazole, m.p. 103–104°, recrystallized from water. Found: 4.4 at. % N^{15}; 0.58 g. (53%) of pure 2-methyl-5-phenyltetrazole, recrystallized from cyclohexane, m.p. 49–50°. Found: 4.5 at. % N^{15}.

2,5-Diphenyl-1,3,4-oxadiazole [3 (or 4) N^{15}]. A solution of 1 g. (0.0068 mole) of 5-phenyltetrazole [1 (or 4) N^{15}] and 0.98 g. (0.007 mole) of benzoyl chloride in 10 ml. of pyridine was heated under reflux on a steam bath for 1 hr. The solution was poured into 75 ml. of ice and water to precipitate the product, yield 1.25 g. (83%). Recrystallization of the crude material from 70% ethanol gave 1.12 g. of pure product, m.p. and mixture m.p. 139–140°, (found: 4.4 at. % N^{15}). Stollé[8] reported m.p. 138°.

Mass spectra of all the labeled compounds were obtained with a magnetic scanning, 90° sector type mass spectrometer at 200°. Temperature of the ion source was 260°, of the leak line 230°, and energy of the ionizing beam was 75 ev. Isotope concentrations were determined by comparison of spectra of similar compounds with normal and enriched N^{15} distribution. 5-Phenyltetrazole alone failed to give a mass spectrum at 200–235°. When the temperature was raised to 240°, a complex spectrum was obtained with no peak at mass 146, but peaks corresponding to the mass of numerous decomposition products including nitrogen (4.1 and 4.3 at. % N^{15}) and benzonitrile (4.7 and 7.4 at. % N^{15}).

Acknowledgment. Our sincere thanks are due Mr. Roland S. Gohlke of the Chemical Physics Research Laboratories of the Dow Chemical Company, Midland, Mich., for determination and interpretation of mass spectra for all compounds.

EAST LANSING, MICH.

(5) R. M. Herbst and K. R. Wilson, *J. Org. Chem.*, **22**, 1142 (1957).

(6) R. A. Henry, *J. Am. Chem. Soc.*, **73**, 4470 (1951).

(7) Melting points were done in open capillaries and are not corrected.

(8) R. Stollé, *J. prakt. Chem.*, (2) **69**, 145 (1904).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NEW MEXICO]

Cinnoline Chemistry. VI. Basic Esters, Ethers, and Amides[1,2]

RAYMOND N. CASTLE AND MASAYUKI ONDA[3]

Received May 19, 1960

Seven new basic esters and five new basic amides have been prepared from cinnoline-4-carboxoyl chloride and the corresponding tertiary amino alcohols or the corresponding primary-tertiary diamines. Eleven new tertiary aminoalkyl 4-cinnolyl ethers have been prepared from 4-chlorocinnoline and the sodium derivative of the corresponding amino alcohols. The esters, ethers, and amides are all water soluble. Salts of each of the esters, ethers, and amides have been prepared.

In other ring systems, basic esters, ethers, and amides have displayed a variety of pharmacological activities. It appeared of interest to prepare a series of basically substituted esters, ethers, and amides for pharmacological screening.

Cinnoline-4-carboxylic acid prepared by the method of Jacobs *et al.*[4] was converted into the potassium salt. Treatment of the salt with oxalyl chloride by the method of Wingfield *et al.*[5] produced cinnoline-4-carboxyoyl chloride as the free base. This was not isolated due to instability,[4] but was treated directly with the amino alcohol to produce the series of esters whose properties are listed in Table I. The esters as free bases were all soluble in water and were very hygroscopic. Upon distillation in vacuum they were decomposed; thus they were purified as salts of organic acids.

The amides were prepared by allowing the cinnoline-4-carboxoyl chloride to react with the appropriate primary-tertiary diamine. The amide free bases were all hygroscopic and water soluble. These were identified and analyzed as the picrates. The properties of the cinnoline-4-carboxamides and their salts are shown in Table II.

The ethers reported were prepared by allowing 4-chlorocinnoline to react with the sodio derivative of an amino alcohol in anhydrous benzene solution. The ether linkage in this series is sensitive to mineral acid. In fact, attempts to recrystallize the hydrochloride salts from 95% ethanol resulted in cleavage of the ether. From these crystallizations 4-hydroxycinnoline was isolated. It was for this reason that the acidic *d*-tartrates were prepared in several instances. These salts were used for screening as well as for a solid derivative for identification of the free base. The ethers and their salts which were prepared are listed in Table III.

The infrared spectra of the cinnolines all possess the cinnoline ring absorption band at 6.3–6.4 μ. The infrared spectra of the amides also have an intense absorption band in the 6μ region indicative of the amide linkage. The infrared spectrum of β-dimethylaminoethyl cinnoline-4-carboxylate shows a strong ester band at 5.8 μ.

β-Dimethylaminoethyl cinnoline-4-carboxylate was inactive as an antifungal agent, in the inhibition of cholesterol biosynthesis and in tryptamine potentiation in rats. 4-Dimethylaminoethoxycinnoline had slight CNS stimulatory activity in rats but was inactive in the inhibition of cholesterol biosynthesis. 4-β-Morpholinoethoxycinnoline was inactive in both the inhibition of cholesterol biosynthesis and in the plasma cholesterol lowering test. 4-[γ-(*N*-Methylpiperazino)propoxy]cinnoline had slight CNS depressant activity in rats. γ-Dimethylaminopropyl cinnoline-4-carboxamide was inactive in the tryptamine potentiation in rats. γ-Piperidinopropyl cinnoline-4-carboxamide was inactive as a CNS depressant and γ-diethylaminopropyl cinnoline-4-carboxamide was inactive as an antifungal agent. Screening data on the other compounds are not available.

EXPERIMENTAL[6]

Cinnoline-4-carboxylic acid. This compound was prepared by the method of Jacobs *et al.*[4]

Potassium cinnoline-4-carboxylate. To a solution of 4.0 g. of potassium carbonate in 50 ml. of water was added 10.0 g. of cinnoline-4-carboxylic acid. The clear orange solution was treated with charcoal, filtered, and evaporated to dryness on the steam bath. The resultant yellow solid was ground to pass a 100 mesh sieve and dried overnight at 110°.

Preparation of the tertiary aminoalkyl cinnoline-4-carboxylates. The procedure is illustrated with the synthesis of β-dimethylaminopropyl cinnoline-4-carboxylate. These esters were isolated and analyzed as their salts because of the instability of the basic esters during vacuum distillation.

To a stirred and ice-cooled suspension of 3.0 g. of potassium cinnoline-4-carboxylate in 20 ml. of dry benzene was added a solution containing 1.9 g. of oxalyl chloride in 10 ml. of dry benzene over a period of 5 min. The reaction mixture was stirred for an additional 20 min. in an ice bath and then for 30 min. at room temperature. The mixture was then refluxed on a steam bath for 1 hr. After the mixture had cooled, 3.1 g. of dimethylaminopropanol in 10 ml. of

(1) For paper V in this series see R. N. Castle, H. Ward, N. White, and K. Adachi, *J. Org. Chem.*, **25**, 570 (1960).

(2) The authors are grateful to Dr. S. Yamada and Dr. K. Abe of the Tanabe Seiyaku Co., Ltd., Tokyo, Japan, for the carbon, hydrogen, and nitrogen analyses.

(3) Smith, Kline and French Laboratories Post-doctoral Research Fellow, 1958–1960. Present address: Tokyo Research Laboratory, Tanabe Seiyaku Co., Ltd., Toda-Cho, Saitama-Ken, Japan.

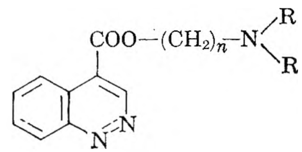
(4) T. L. Jacobs, S. Winstein, R. B. Henderson, and E. C. Spaeth, *J. Am. Chem. Soc.*, **68**, 1310 (1946.)

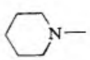
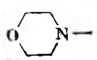
(5) H. N. Wingfield, Jr., W. R. Harlan, and H. R. Hanmer, *J. Am. Chem. Soc.*, **75**, 4364 (1953).

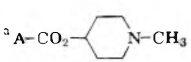
(6) All melting points are uncorrected. The infrared spectra of all the free bases were determined on a Perkin-Elmer Infracord.

TABLE I

BASIC ESTERS



n	R_2N—	Salt	M.P.	Yield, %	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Description of Salt and Solvent Used for Crystallization
2	$(CH_3)_2N$—	Monopicrate	194–196	70	$C_{19}H_{19}N_6O_9$	48.10	3.82	17.72	48.35	3.92	17.89	Yellow needles, methanol
2	$(C_2H_5)_2N$—	Acidic *d*-tartrate	110–112	82	$C_{19}H_{25}O_8N_3 \cdot {}^3/_4H_2O$	52.22	6.11		52.19	6.15		Yellow rosettes, acetone
2		Acidic *d*-tartrate	119–121	68	$C_{20}H_{25}O_8N_3 \cdot 4H_2O$	47.33	6.55		47.45	6.56		Yellow prisms, acetone
2		Acidic *d*-tartrate	126–128	83	$C_{19}H_{23}O_9N_3 \cdot 1{}^1/_2H_2O$	49.13	5.64		48.73	5.90		Orange granules, ethanol
3	$(CH_3)_2N$—	Acidic *d*-tartrate	142–144	60	$C_{18}H_{23}N_3O_8 \cdot 3H_2O$	46.63	6.31		46.38	6.48		Yellow granules, ethanol
3	$(C_2H_5)_2N$—	Acidic *d*-tartrate	114–116	78	$C_{20}H_{27}N_3O_8$	54.91	6.22		55.24	6.19		Yellow rosettes, ethanol
	[a]	Acidic *d*-tartrate	193–195 dec.	67	$C_{19}H_{23}N_3O_8 \cdot {}^1/_4H_2O$	53.57	5.56		53.45	5.70		Yellowish green granules, ethanol

[a] 

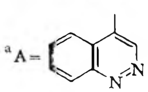
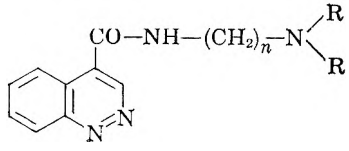
[a] A = 

TABLE II

CINNOLINE-4-CARBOXAMIDES



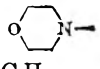
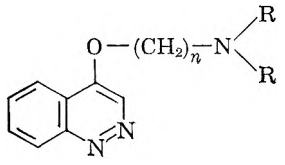
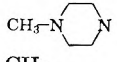
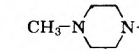
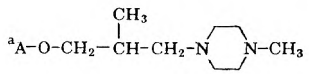
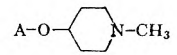
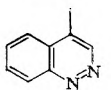
n	R, R N—	B.P.	Mm.	Description	Yield, %	Salt	M.P.	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Description of Salt and Solvent Used for Crystallization
3	CH_3, CH_3 N—	202–205	0.07	Solid, hygroscopic	72	Monopicrate	174–176	$C_{20}H_{21}N_7O_8$	49.28	4.34	20.12	49.12	4.45	20.44	Yellow needles, acetone
3	C_2H_5, C_2H_5 N—	210–212	0.07	Red sirup, hygroscopic	79	Monopicrate	140–142	$C_{22}H_{25}N_7O_8$	51.26	4.89	19.02	51.00	5.28	18.46	Pale yellow needles, acetone
3		224–227	0.02	Red sirup	56	Monopicrate	196–198	$C_{23}H_{25}N_7O_8$	52.37	4.73	18.58	52.27	4.27	18.30	Yellow needles, acetone
3		245–248	0.025	Red sirup	60	Monopicrate	181–184	$C_{22}H_{23}N_7O_9$	49.90	4.38	18.51	49.48	4.63	18.14	Yellow needles, acetone
2	C_2H_5, C_2H_5 N—	210–214	0.02	Red sirup	64	Monopicrate	148–150	$C_{21}H_{23}N_7O_7$	50.29	4.62		49.95	4.72		Yellowish green needles, acetone and ethanol

TABLE III. ETHERS AND SALTS



n	R, R =	B.P.	Mm.	Description	Yield, %	Salt	M.P.	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Description of Salt and Solvent Used for Crystallization
2	$(CH_3)_2N-$	162–167	0.05	Solid, m.p. 76–77°	83	Acidic *d*-tartrate	129–131	$C_{16}H_{21}N_3O_7 \cdot 1\frac{1}{2}H_2O$	48.72	6.14	10.67	48.48	6.40	10.67	Colorless needles, methanol
2	$(C_2H_5)_2N-$	154–160	0.08	Red sirup	88	Acidic *d*-tartrate	131–133	$C_{18}H_{25}N_3O_7 \cdot \frac{1}{2}H_2O$	53.45	6.48	10.39	53.06	6.38	10.53	Cream granules, ethanol
2		170–178	0.065	Red sirup	77	Acidic *d*-tartrate	128–131	$C_{19}H_{25}N_3O_7 \cdot H_2O$	53.64	6.40	9.87	53.41	6.87	10.11	Cream rosettes, ethanol
2		205–210	0.02	Red sirup	75	Acidic *d*-tartrate	170–171	$C_{18}H_{23}N_3O_8$	52.80	5.66	10.26	53.07	5.94	10.41	Cream rosettes, ethanol
2		205–208	0.04	Red sirup	68	Dipicrate	230–232	$C_{27}H_{26}N_{10}O_{15}$	44.38	3.58	19.17	44.52	3.43	18.64	Yellow leaves, acetone
3	$(CH_3)_2N-$	151–153	0.01	Red sirup	90	Dipicrate	160–162	$C_{25}H_{23}N_9O_{15}$	43.54	3.36	18.28	43.97	3.52	18.13	Yellow needles, acetone
3	$(C_2H_5)_2N-$	164–169	0.05	Red sirup	78	Acidic *d*-tartrate	190–193 dec.	$C_{19}H_{27}N_3O_7$	55.74	6.64		55.65	6.48		Cream needles, ethanol
3		177–181	0.02	Semisolid	56	Acidic *d*-tartrate	166–168	$C_{20}H_{27}N_3O_7$	56.99	6.45		57.14	6.27		Cream needles, ethanol
3		195–198	0.01	Red sirup	80	Tripicrate	243–245 dec.	$C_{34}H_{31}N_{13}O_{22}$	41.93	3.21	18.70	41.64	3.36	18.86	Yellow needles, acetone
		193–196	0.02	Red sirup	87	Dipicrate	213–215	$C_{29}H_{30}N_{10}O_{15} \cdot 2H_2O$	43.83	4.06	17.62	44.14	3.85	17.19	Yellow needles, acetone
		178–181	0.02	Solid, m.p. 88–90°	88	Dipicrate	192–194	$C_{25}H_{23}N_9O_{15}$	44.56	3.30		44.75	3.27		Yellowish green needles, acetone

[a] A = 

dry benzene was added and the mixture refluxed for 3 hr. on the steam bath. The cooled mixture was diluted with benzene, filtered with charcoal, and evaporated under reduced pressure. The residue (*ca.* 2.8 g.) was dissolved in 8 ml. of commercial absolute ethanol and to this solution was added 1.6 g. of *d*-tartaric acid. This was dissolved by heating until the solution was clear. After standing in the refrigerator, there was obtained 3.9 g. (60%) of a yellow crystalline solid, m.p. 140–142°. Upon recrystallization from commercial absolute ethanol, fine yellow granules separated, m.p. 142–144°.

β-Dimethylaminoethyl cinnoline-4-carboxylate. After cooling the acid chloride mixture as prepared above, a solution of 5.5 g. of dimethylaminoethanol in 10 ml. of dry benzene was added and the mixture heated and stirred on the steam bath for 2 hr. The cooled mixture was diluted with ether, treated with charcoal, and filtered. After evaporation of the solvents, there was obtained 4.86 g. (70%) of a red sirup, boiling at 165–173° at 0.073 mm.

Monopicrate, m.p. 194–196°, yellow needles from methanol.

Anal. Calcd. for $C_{19}H_{18}N_6O_9$: C, 48.10; H, 3.82; N, 17.72. Found: C, 48.35; H, 3.92; N, 17.89.

Preparation of the tertiary aminoalkyl cinnoline-4-carboxamides. The procedure is illustrated with the synthesis of *N*-γ-dimethylaminopropyl cinnoline-4-carboxamide. After cooling the acid chloride mixture as prepared above, 4.2 g. of γ-dimethylaminopropylamine in 10 ml. of dry benzene was added over a period of 10 min. with stirring while the reaction mixture was kept in an ice bath. The mixture was stirred for 1 hr. at room temperature. The mixture was diluted, treated with charcoal, and filtered. After evaporation of the solvents there was obtained 3.5 g. (72%) of a red sirup, boiling at 202–205° at 0.07 mm.

4-Chlorocinnoline. This compound was prepared by the method of Leonard and Boyd.[7] Since this compound is unstable,[8] it was prepared in small quantities and used immediately. It was not necessary to purify the 4-chlorocinnoline by recrystallization but it was used directly upon recovery from the dried ether solution, m.p. 74–76°.

Preparation of aminoalkoxy ethers. The procedure is illustrated with the synthesis of 4-β-dimethylaminoethoxycinnoline.

To a solution of 4.3 g. of β-dimethylaminoethanol in 34 ml. of anhydrous benzene was added 0.57 g. of metallic sodium. The reaction mixture was refluxed on a steam bath until all the sodium had dissolved. In this instance 1 hr. heating was required. After cooling the reaction mixture in an ice bath, 3.4 g. of 4-chlorocinnoline was added and the mixture refluxed for 4 hr. on a steam bath, whereupon the solution became dark red. After allowing the reaction mixture to cool, it was diluted with dry ether, filtered with charcoal, and the solution evaporated.[9] The ether residue was distilled under reduced pressure. There was obtained 3.7 g. (83%) of a red sirup, bp. 162–167° at 0.05 mm. which after standing solidified to a pale yellow solid, m.p. 70–73°C., which after recrystallization from petroleum ether (b.p. 60–90°) gave pale yellow plates, m.p. 74–76°.

Acknowledgment. The authors are grateful to Smith, Kline and French Laboratories for a research grant which made this work possible and to Dr. James W. Wilson for his interest in this work.

ALBUQUERQUE, N. M.

(7) N. J. Leonard and S. N. Boyd, Jr., *J. Org. Chem.*, 11, 423 (1946).

(8) M. Busch and K. Klett, *Ber.*, 25, 2849 (1892).

(9) The ethers were very water soluble and, thus, it was necessary to avoid the use of water in the isolation procedure in order to obtain satisfactory yields.

[CONTRIBUTION FROM WYETH LABORATORIES, INC., RESEARCH AND DEVELOPMENT DIVISION]

A New Class of Local Anesthetics: Hydroxyalkyliminobisacetamides[1]

MEIER E. FREED, WILLIAM F. BRUCE, ROY S. HANSLICK, AND ALBERT MASCITTI

Received June 30, 1960

A series of hydroxyalkyliminobisacetamides and their esters was prepared and examined for local anesthetic action. The compounds derived from *N*-α,α-trimethylphenethylamine showed a high degree of activity, some examples being 4000 times as active as procaine. Structure-activity relationships were studied in the course of this investigation.

During an investigation of the synthesis and pharmacology of basically substituted derivatives of acetamide several hydroxyalkylaminoacetamides[2] possessed appreciable local anesthetic activity. A more critical study of one of these, *N*-methyl-*N*-α,α-dimethylphenethyl-2-hydroxyethylaminoacetamide (I), revealed that this action was not due to the acetamide, but to a trace of commingled 2-hydroxyethyliminobis[*N*-methyl-*N*-(α,α-dimethylphenethyl)acetamide] (II).

$$HOCH_2CH_2NHCH_2CON(CH_3)C(CH_3)_2CH_2C_6H_5$$

I

The preparation of the latter compound and its subsequent testing showed it to be an extremely potent local anesthetic, at least 4000 times as active as procaine.[3]

To establish the structural requirements for activity in this series a study was made of the effect of variation in sections of the molecule on activity. The compounds prepared had the general formula III, wherein X is alkyl, cycloalkyl, or

$$HO.X.N\begin{cases} CH_2{-}CONRR^1 \\ CH_2CONR^2R^3 \end{cases}$$

III

II. X = CH_2CH_2—
R = R_2 = CH_3
R_1 = R_3 = $C(CH_3)_2CH_2C_6H_5$

(1) Presented in part before the Medicinal Chemistry Section, Delaware Valley Regional Meeting, Philadelphia, Feb. 25, 1960, abstracts p. 21.

(2) W. F. Bruce and J. Seifter, U. S. Patents: (a) 2,778,834 (1957); (b) 2,856,427 (1958).

(3) J. M. Glassman, G. H. Hudyma, and J. Seifter, *J. Pharm. Exptl. Therap.*, 119, 150 (1957).

TABLE I

HYDROXYALKYLAMINOACETAMIDES

R—NHCH$_2$CON(R′)(CH$_3$)

No.	R	R′	HCl Salt M.P.	Formula	Nitrogen Calcd.	Nitrogen Found	Chlorine Calcd.	Chlorine Found
1	$HOCH_2CH_2$	$C_6H_5CH_2C(CH_3)_2$	[a]	$C_{15}H_{24}N_2O_2$	10.60	10.90		
2	$C_6H_5CHOHCH_2$	$C_6H_5CH_2C(CH_3)_2$	201–202	$C_{21}H_{28}ClN_2O_2$	7.43	7.34	9.42	9.50
3	$C_6H_5CHOHC(CH_3)_2$	$C_6H_5CH_2C(CH_3)_2$	189–190	$C_{21}H_{29}ClN_2O_2$	6.92	6.75	8.77	8.55
4	$HOCH_2C(CH_3)_2$	$C_6H_5CH_2C(CH_3)_2$	169–170	$C_{17}H_{29}ClN_2O$	8.00	8.26	10.82	11.01
5	$(HOCH_2)_3C$	$C_6H_5CH_2C(CH_3)_2$	175–176	$C_{17}H_{29}ClN_2O_4$	7.80	7.77	9.88	9.58
6	$HOCH(CH_3)CH_2$	$C_6H_5CH_2$	134–135	$C_{13}H_{21}ClN_2O_2$	10.25	10.20	13.12	13.47

[a] Free base (from petroleum ether): m.p. 76–77°.

aralkyl, R, R^1, R^2, R^3 represent lower alkyl or aralkyl, and where RR^1 may or may not equal R^{2}R^3.

The symmetrically substituted compounds (RR^1 = R^{2}R^3) were prepared by treatment of an amino alcohol with two equivalents of a chloroacetamide. The asymmetrically substituted compounds were obtained in two steps by treatment of an amino alcohol with one equivalent of chloroacetamide to yield the hydroxyalkylaminoacetamide which was then converted to the iminoacetamide by further treatment with one equivalent of a second chloroacetamide.

These alkylations were generally carried out in refluxing butanol in the presence of excess potassium carbonate. In the case of several sterically hindered amino alcohols, *e.g.*, 2-amino-2-methylpropanol, it was necessary to use a higher boiling solvent such as anisole to obtain the bis compounds. The required chloroacetamides were prepared by literature methods.

As a result of these studies a number of structure-activity relationships became apparent. Of the iminoacetamides which we examined, those in which the amido nitrogen was derived from aliphatic amines had relatively little local anesthetic action and were more toxic than those derived from aralkylamines. The use of a sterically hindered amine, *N* - α,α - trimethyl - β - phenethylamine (mephentermine), produced the highest degree of local anesthetic activity found in these bisacetamides; substitution of *N*-α-dimethylphenethylamine for mephentermine in one amide group halved the activity. In the alkanolamine portion, use of a sterically hindered base such as 2-amino-2-methylpropanol produced the opposite effect, markedly reducing activity. A more critical factor, however, was the number of methylene groups separating the hydroxyl from the tertiary amino group. Activity dropped sharply with the addition of even one methylene. Thus the 3-hydroxypropyl derivative (Table III, No. 4) shows only 1/500 the effectiveness of the homologous 2-hydroxyethyl compound (Table III, No. 1).

The effect of altering the chemical type was also examined. Replacement of hydroxyl by amino or chloro, quaternarization of the tertiary amine, reduction of the amide groups to tertiary amines, all resulted in nearly complete loss of activity (Table VI). Ester formation with either aliphatic or aromatic acids yielded active compounds (Table V), but in no instance was the activity increased by this change.

A portion of the results of pharmacologic studies of the hydroxyalkyliminobisacetamides has been presented elsewhere.[4,5] The more detailed pharmacology of these materials will appear in a forthcoming publication from these laboratories.

EXPERIMENTAL

Since the preparation of all chloroacetamides, hydroxyalkylaminoacetamides, hydroxyalkyliminoacetamides, and their esters was carried out in essentially the same manner, one example of each is given.

N-Methyl-N-α,α-dimethylphenethylchloroacetamide. To a solution of 140 g. (0.86 mole) of *N*-methyl-*N*-α,α-dimethylphenethylamine in 500 ml. of toluene was added, with stirring, and at −20°, 45 g. (0.40 mole) of chloroacetyl chloride. The rate of addition was such that the temperature remained below −15°. The reaction was stirred 1 hr. in the cold and allowed to come to room temperature. The solid amine hydrochloride was removed by filtration and washed with a little toluene. The filtrate was dried, concentrated under reduced pressure, and the residue distilled to give 67.5 g. (70.5%) of product, b.p. 140–141° (0.5 mm.).

Anal. Calcd. for $C_{13}H_{18}ClNO$: Cl, 14.83; N, 5.85. Found: Cl, 14.51; N, 5.62.

N-Methyl-N-α,α-dimethylphenethyl-2-hydroxyethylaminoacetamide.[6] To a well stirred mixture of 6.1 g. (0.1 mole) of ethanolamine and 30 g. of anhydrous powdered sodium carbonate in 300 ml. of boiling 1-butanol, was added slowly 23.9 g. (0.1 mole) of *N*-methyl-*N*-α,α-dimethylphenethylchloroacetamide in 50 ml. 1-butanol. The reaction mixture was refluxed for 12 hr., cooled, and filtered. The solution was concentrated and the residue crystallized from hexane. There was obtained 16.6 g. (63%), m.p. 74.5–76.5°.

Anal. Calcd. for $C_{15}H_{24}N_2O_2$: C, 68.30; H, 9.16; N, 10.58. Found: C, 67.94; H, 8.90; N, 10.90.

The hydrochloride had a m.p. of 163–164°.

Anal. Calcd. for $C_{15}H_{25}ClN_2O_2$: N, 9.32; Cl, 11.78. Found: N, 9.15; Cl, 11.59.

2-Hydroxyethyliminobis[N-methyl-N(α,α-dimethylphen-

(4) D. H. Baeder, J. M. Glassman, G. M. Hudyma, and J. Seifter, *Proc. Soc. Exptl. Biol. Med.*, 89, 645 (1955).

(5) J. M. Glassman, G. M. Hudyma, and J. Seifter, *J. Pharm. Exptl. Therap.*, 119, 150 (1957).

(6) J. Seifter, R. S. Hanslick, and M. E. Freed, U. S. Patent 2,780,646 (1957).

TABLE II

HYDROXYALKYLIMINOBISACETAMIDES

R—N($CH_2CONR^1R^2$)$_2$

No.	R	R^1	R^2	B.P.	Formula	Carbon		Hydrogen		Nitrogen		Duration of Activity[a]	(% Soln.)
						Calcd.	Found	Calcd.	Found	Calcd.	Found		
1	$HOCH_2CH_2$	CH_3CH_2	CH_3CH_2	203–205/1 mm.	$C_{14}H_{29}N_3O_3$	58.20	57.90	10.17	9.83	14.61	14.35	Neg.	0.1
2	$HOCH_2CH_2$	$CH_3(CH_2)_2CH_2$	$CH_3(CH_2)_2CH_2$	208–210/0.5 mm.	$C_{22}H_{45}N_3O_3$	66.21	65.89	11.30	11.08	10.50	10.24	25 min.	0.01
3	$CH_3CHOHCH_2$	$CH_3(CH_2)_2CH_2$	$CH_3(CH_2)_2CH_2$	200–205/0.1 mm.	$C_{23}H_{47}N_3O_4$	66.75	66.40	11.40	11.62	10.13	10.26	Neg.	0.1
4	$HOCH_2CH_2$	$(CH_3)_2CHCH_2$	$(CH_3)_2CHCH_2$	170–171/0.5 mm.	$C_{22}H_{45}N_3O_3$	66.21	66.58	11.30	11.18	10.50	10.26	Neg.	0.1
5	$HOCH_2CH_2CH_2$	$(CH_3)_2CHCH_2$	$(CH_3)_2CHCH_2$	190–192/0.5 mm.	$C_{23}H_{47}N_3O_3$	66.75	67.1	11.40	11.25	9.33	9.63	Neg.	0.1
6	$HOCH_2C(CH_3)_2$	$CH_3(CH_2)_2CH_2$	$CH_3(CH_2)_2CH_2$	155–160/0.5 mm.	$C_{24}H_{49}N_3O_3$	67.3	67.7	11.5	11.3	9.35	9.52	Neg.	0.1
7	$HOCH_2C(CH_3)_2$	CH_3CH_2	$CH_3(CH_2)_2CH_2$	170–175/0.5 mm.	$C_{20}H_{41}N_3O_3$	64.80	64.42	11.12	10.87	11.30	11.20	Neg.	0.1
8	$HOCH_2CH_2$	$CH_3(CH_2)_3CH_2$	$CH_3(CH_2)_3CH_2$	230–235/1 mm.	$C_{26}H_{53}N_3O_3$	68.10	68.1	11.98	11.75	9.22	8.91	25 min.	0.01
9	$HOCH_2CH_2$	C_6H_{11}	C_6H_{11}	[b]	$C_{30}H_{54}ClN_3O_3$	[c]				7.82	7.50	Neg.	0.1
10	$HOCH_2CH_2$	$CH_3(CH_2)_4CH_2$	$CH_3(CH_2)_4CH_2$	194–196/0.5 mm.	$C_{30}H_{61}N_3O_3$	70.5	70.18	12.00	11.85	8.25	8.15	48 min.	0.1

[a] Compounds were not tested at concentrations greater than 0.1%. Compounds were tested by application to the corneas of rabbits. [b] Hydrochloride, m.p. 215–216°. [c] Cl, Calcd. 6.62; found, 6.41.

ethyl)acetamide].[6] To a stirred mixture of 23.9 g. (0.1 mole) of *N*-methyl-*N*-α,α-dimethylphenethylchloroacetamide and 20 g. of potassium carbonate in 250 ml. of boiling butanol was added a solution of 3.1 g. (0.05 mole) of freshly distilled ethanolamine. After 20 hr. under reflux the reaction mixture was cooled and filtered. The filtrate was washed with aqueous 5% sodium carbonate, then with water, and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residue recrystallized from benzene-hexane, yielding 33.2 g. (71%) of product, m.p. 104–105°.

Anal. Calcd. for $C_{28}H_{41}N_3O_3$: C, 71.90; H, 8.84; N, 8.98. Found: C, 71.93; H, 8.80; N, 9.0.

The hydrochloride twice crystallized from methanol-acetone melted at 146–147°.

Anal. Calcd. for $C_{28}H_{42}ClN_3O_3$: N, 8.35; Cl, 7.04. Found: N, 8.20; Cl, 6.87.

2-Hydroxyethyliminobis[*N-methyl-N*(α,α-*dimethylphenethyl*)*acetamide*], *nicotinic acid ester*.[6] A solution of 2 g. (0.004 mole) of product and 0.1 g. (0.004 mole) of nicotinic anhydride in 50 ml. of dry benzene was heated under reflux for 16 hr. Nicotinic acid was removed from the cooled mixture by filtration and the filtrate concentrated under vacuum. The residue was dissolved in acetone and filtered. The acetone solution was treated with dry hydrogen chloride and the precipitate collected on a filter, washed with acetone, and dried: 2.15 g. (83%), m.p. 158–159°.

Anal. Calcd. for $C_{34}H_{46}Cl_2N_4O_4$: N, 8.68; Cl, 11.05. Found: N, 8.74; Cl, 11.33.

2-Chloroethyliminobis[*N-methyl-N*(α,α-*dimethylphenethyl*)-*acetamide*]. A solution of 20 g. (0.042 mole) of product in 100 ml. of dry chloroform was treated with a solution of 5 g. (0.04 mole) of thionyl chloride in 25 ml. of chloroform. The reaction mixture was stirred for 3 hr. The solvent was removed and the residue crystallized from ethanol-ether, weighed 16.5 g. (79%), m.p. 155–156°.

Anal. Calcd. for $C_{28}H_{41}Cl_2N_3O_2$: N, 8.04; Cl, 13.58. Found: N, 7.80; Cl, 13.35.

2-Aminoethyliminobis[*N-methyl-N*(α,α-*dimethylphenethyl*)-*acetamide*]. 2-Chloroethyliminobis[*N*,-methyl-*N*-(α,α-dimethylphenethylacetamide] hydrochloride, 3 g. (0.006 mole), in 20 ml. of methanol containing 3 g. anhydrous ammonia was sealed in a pressure-tube and heated for 18 hr. at 90°. The bomb was cooled and the contents transferred to a beaker. The tube was rinsed out with a little methanol and the combined methanol solution filtered free of ammonium chloride. The methanol and the excess ammonia were removed by evaporation and the residue dissolved in 50 ml. of 2-propanol. A further precipitate formed; this was removed by filtration. The solution was treated with dry hydrogen chloride. On addition of dry ether (about 150 ml.) a crystalline product formed; yield, 1.3 g. (40.5%), m.p. 231–232°.

Anal. Calcd. for $C_{28}H_{44}Cl_2N_4O_2$: N, 10.40; Cl, 13.15. Found: N, 10.71; Cl, 13.40.

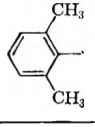
N,N-Bis[*N-methyl-N*(α,α-*dimethylphenethyl*)*aminoethyl*]-*2-hydroxyethylamine*. A solution of 9.4 g. (0.02 mole) of 2 - hydroxyethyliminobis[N - methyl - N(α,α - dimethylphenethyl)acetamide] in 150 ml. of anhydrous ether was added slowly to a stirred suspension of 1.8 g. (0.05 mole) of lithium aluminum hydride in 300 ml. of dry ether. After addition was complete the reaction was refluxed for 25 hr. The reaction mixture was decomposed by the cautious addition of 8 ml. of water. After filtration, the ethereal solution was dried over anhydrous sodium sulfate. The dried solution was treated with hydrogen chloride. An oil separated from the ether. The ether was removed by decantation and the oil, on trituration with acetone, solidified. After recrystallization from methanol-acetone 3.2 g. (29.3%) product, m.p. 229–230° dec. was obtained. The infrared spectra showed no indication of amide impurities.

Anal. Calcd for $C_{28}H_{48}Cl_3N_3O$: N, 7.66; Cl_3 19.40. Found: N, 7.70, Cl, 19.47.

TABLE III

HYDROXYALKYLIMINOBISACETAMIDES

R—N($CH_2CONR^1R^2$)$_2$

No.	R	R^1	R^2	M.P.	Formula	Carbon		Hydrogen		Nitrogen		Activity,	(%
						Calcd.	Found	Calcd.	Found	Calcd.	Found	Min.	Soln.)
1	$HOCH_2CH_2$	CH_3	$C_6H_5CH_2C(CH_3)_2$	104–104.5[a]	$C_{28}H_{41}N_3O_3$	71.9	71.93	8.80	8.92	9.0	8.73	25	0.0005
2	$HOCH(CH_3)CH_2$	CH_3	$C_6H_5CH_2C(CH_3)_2$	113–114[a]	$C_{29}H_{43}N_3O_3$	72.45	72.11	8.95	8.92	8.74	8.68	28	0.0001
3	$HOCH_2CH(C_2H_5)$	CH_3	$C_6H_5CH_2C(CH_3)_2$	144–145[b]	$C_{30}H_{46}ClN_3O_3$	67.72	67.15	8.70	8.36	7.88	7.61	37	0.0005
4	$HOCH_2CH_2CH_2$	CH_3	$C_6H_5CH_2C(CH_3)_2$	164–165[b]	$C_{29}H_4Cl_4N_3O_3$	[b,f]				8.13	8.30	82	0.1
5	$HO(CH_2)_5CH_2$	CH_3	$C_6H_5CH_2C(CH_3)_2$	[c]	$C_{32}H_{49}N_3O_3$	73.60	73.31	9.44	9.35			Neg.	0.1
6	$(HOCH_2)_3C$	CH_3	$C_6H_5CH_2C(CH_3)_2$	157–158[a]	$C_{30}H_{45}N_3O_6$	68.30	68.02	8.58	8.31	7.98	7.76	24	0.001
7		CH_3	$C_6H_5CH_2C(CH_3)_2$	108–108.5[a]	$C_{32}H_{47}N_3O_2$	73.75	74.0	9.06	9.01	8.05	8.00	75	0.0025
8	$C_6H_5CHOHCH_2$	CH_3	$C_6H_5CH_2C(CH_3)_2$	182–183[b]	$C_{34}H_{46}ClN_3O_3$	70.40	69.93	7.98	8.10	7.23	7.10	24	0.001
9	$C_6H_5CHOHC(CH_3)_2$	CH_3	$C_6H_5CH_2C(CH_3)_2$	203–204[b]	$C_{34}H_{46}ClN_3O_3$	[g]				6.91	6.93	Neg.	0.1
10	$HOCH_2CH_2$	CH_3	C_6H_{11}	[d]	$C_{20}H_{37}N_3O_3$	65.5	65.65	10.5	10.3	11.42	11.18	Neg.	0.1
11	$HOCH_2CH_2$	H	$C_6H_5CH_2CH_2$	72–73[b]	$C_{22}H_{29}N_3O_3$	69.0	69.15	7.64	7.60	10.95	10.87	Neg.	0.1
12	$HOCH_2CH_2$	$CH_3(CH_2)_2CH_2$	$C_6H_5CH_2$	118 [b]	$C_{25}H_{36}ClN_3O_3$	66.7	66.2	8.4	8.7	[h]		29	0.001
13	$HOCH(CH_3)CH_2$	$CH_3(CH_2)_4CH_2(CH_3)$	$C_6H_5CH_2$	[e]	$C_{35}H_{55}N_3O_3$	74.30	74.43	9.78	9.76	7.43	7.20	44	0.1
14	$HOCH(CH_3)CH_2$	H		193–194[b]	$C_{19}H_{24}ClN_3O_3$					9.72	9.49	Neg.	0.1

[a] Base. [b] Hydrochloride. [c] B.p. 250–260°/2 μ. [d] B.p. 190–195°/1 mm. [e] B.p. 195–200°/0.05 mm. [f] Cl, Calcd. 6.85; found, 6.87. [g] Cl, Calcd. 5.83; found, 5.93. [h] Cl, Calcd. 7.15; found, 7.38.

TABLE IV

UNSYMMETRIC HYDROXYALKYLIMINOBISACETAMIDES

$$R{-}N\begin{cases}CH_2CONR^1R^2\\CH_2CONR^3R^4\end{cases}$$

No.	R	R¹	R²	R³	R⁴	M.P.	Formula	Nitrogen Calcd.	Nitrogen Found	Duration Activity, Min.	(% Soln.)
1	$HOCH_2CH_2$	CH_3CH_2	CH_3CH_2	$CH_3(CH_2)_2CH_2$	$CH_3(CH_2)_2CH_2$	[a]	$C_{18}H_{37}N_3O_3$	12.2	11.9	29	0.1
2	$HOCH_2CH_2$	$CH_3CH_2CH_2$	$CH_3CH_2CH_2$	$CH_3(CH_2)_2CH_2$	$(CH_3)_2CHCH_2$	[b]	$C_{20}H_{37}N_3O_3$			21	0.1
3	$HOCH_2CH_2$	CH_3CH_2	CH_3CH_2	CH_3	$C_6H_5CH_2C(CH_3)_2$	121–122	$C_{21}H_{35}N_3O_3$	11.21	10.99	Neg.	0.1
4	$HOCH_2CH_2$	$CH_3(CH_2)_3CH_2$	$CH_3(CH_2)_3CH_2$	CH_3	$C_6H_5CH_2C(CH_3)_2$	92–93	$C_{27}H_{47}N_3O_3$	9.10	8.93	63	0.1
5	$HOCH_2CH_2CH_2$	$(CH_3)_2CHCH_2$	$(CH_3)_2CHCH_2$	CH_3	C_6H_{11}	[c]	$C_{22}H_{43}N_3O_3$	[f]		Neg.	0.1
6	$HOCH_2CH_2$	CH_3	$C_6H_5CH_2CH(CH_3)$	CH_3	$C_6H_5CH_2C(CH_3)_2$	(Hygro)	$C_{27}H_{40}N_3O_3Cl$	8.53	8.40	55	0.001
7	$HOCH_2CH_2$	H	$C_6H_5CH_2CH_2$	CH_3	$C_6H_5CH_2C(CH_3)_2$	158[d]	$C_{25}H_{36}N_3O_3Cl$	9.02	8.90	Neg.	0.1
8	$HOCH_2CH_2$	H	$HOCH_2CH_2$	CH_3	$C_6H_5CH_2C(CH_3)_2$	42[d]	$C_{19}H_{32}N_3O_4Cl$	[g]		Neg.	0.1
9	$HOCH_2CH_2$	H	$CH_3(CH_2)_4CH_2$	CH_3	$C_6H_5CH_2C(CH_3)_2$	[e]	$C_{24}H_{41}N_3O_3$	10.0	9.7	9	0.05

[a] B.p. 203–205/1 mm. (base). [b] B.p. 198–200/0.5 mm. (base). [c] B.p. 205–208/1 mm. (base). [d] Hydrochloride. [e] 260°/1 mm. (base). [f] *Anal.* Calcd.: C, 66.52; H, 10.91. Found: C, 66.57; H, 10.87. [g] Cl, Calcd. 8.8; found, 8.5.

TABLE V

ESTERS OF HYDROXYALKYLAMINOBISACETAMIDES

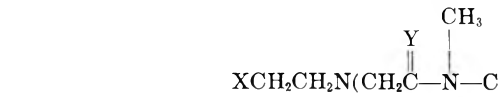
$$XCH_2CH_2N(CH_2CONR^1R^2)_2$$

No.	X	R¹	R²	M.P.[a]	Formula	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Duration of Activity, Min.	(% Soln.)
1	CH_3CO_2	CH_3	$C_6H_5CH_2C(CH_3)_2$	169–170	$C_{30}H_{44}N_3O_4Cl$	66.02	66.07	8.06	8.03	7.50	7.22	32	0.001
2	$CH_3(CH_2)_{10}CO_2$	CH_3	$C_6H_5CH_2C(CH_3)_2$	143–145	$C_{40}H_{64}N_3O_4Cl$	[b]				6.13	5.90	38	0.01
3	p-$CH_3C_6H_4CO_2$	CH_3	$C_6H_5CH_2C(CH_3)_2$	168–169	$C_{36}H_{47}N_3O_4Cl$	[c]				8.58	6.67	42	0.001
4	p-$NO_2C_6H_4CO_2$	CH_3	$C_6H_5CH_2C(CH_3)_2$	168–169	$C_{35}H_{45}N_4O_6Cl$	[d]				8.58	8.62	27	0.0005
5	CH_3CO_2	$CH_3(CH_2)_2CH_2$	$CH_3(CH_2)_2CH_2$	[e]	$C_{24}H_{47}N_3O_4$	65.0	64.8	10.7	10.5			32	0.01
6	m-$ClC_6H_4CO_2$	CH_3	$C_6H_5CH_2C(CH_3)_2$	87–88[f]	$C_{35}H_{44}N_3O_4Cl$	69.40	69.46	7.32	7.48	6.93	6.78	Active[g]	0.1
7	m-pyrCO_2	CH_3	$C_6H_5CH_2C(CH_3)_2$	158–159	$C_{34}H_{46}N_4O_4Cl_2$	[h]				8.68	8.52	35	0.0005
8	p-$CH_3OC_6H_4CO_2$	CH_3	$C_6H_5CH_2C(CH_3)_2$	126–127	$C_{36}H_{48}N_3O_5Cl$	67.70	67.73	7.58	7.90	6.58	6.80	Active[g]	0.1
9	p-$NH_2C_6H_4CO_2$	CH_3	$C_6H_5CH_2C(CH_3)_2$	199–200	$C_{35}H_{48}N_4O_4Cl_2$	63.90	63.80	7.34	7.53	8.51	8.25	Active[g]	0.1

[a] Hydrochloride. [b] Cl, Calcd., 5.20; found, 5.41. [c] Cl, Calcd., 5.71; found, 5.92. [d] Cl, Calcd., 5.44; found, 5.20. [e] B.p. 212–214°/0.05 mm. (base). [f] Base from 2-propanol-petroleum ether. [g] Tested only qualitatively. [h] Cl, Calcd., 11.05; found, 11.11.

TABLE VI

MISCELLANEOUS DERIVATIVES



No.	X	Y	M.P.	Formula	Chlorine Calcd.	Chlorine Found	Nitrogen Calcd.	Nitrogen Found	Duration of Activity, Min.	(% Soln.)
1	Cl	O	155–156[a]	$C_{28}H_{41}N_3O_2Cl_2$	13.50	13.16	8.04	7.75	43[b]	0.1
2	NH_2	O	231–232[a]	$C_{28}H_{44}N_4O_2Cl_2$	13.15	13.40	10.40	10.71	Neg.	0.1
3	HO(CH_3I)	O	122–123	$C_{29}H_{44}N_3O_3I$	20.85[c]	20.90	6.92	6.60	Neg.	0.1
4	HO	2H	239–240[a]	$C_{28}H_{48}N_3OCl_3$	19.40	19.47	7.66	7.70	Neg.	0.1

[a] Hydrochloride. [b] The compound *per se* may not be active; this degree of activity can be attributed to a trace of the highly active *N,N*-bis(*N*-methyl-*N*-ω-phenyl-*tert*-butylacetamido)-2-hydroxyethylamine present in the chloro compound either as an initial impurity or formed *in situ* by hydrolysis of the 2-chloroethylamine group. [c] Iodine.

A trimethiodide was prepared by heating the free base of the above trihydrochloride with methyl iodide in acetone. After crystallization from acetone it melted at 154–155°.

Anal. Calcd. for $C_{31}H_{54}IN_3O$: N, 4.85, I, 43.90. Found: N, 4.60; I, 43.82.

2-Hydroxyethyliminobis[N-methyl-N(α,α-dimethylphenethyl)acetamide methiodide. 2-Hydroxyethyliminobis[N-methyl-(α,α-dimethylphenethyl)acetamide], 5 g. (0.011 mole), was heated under reflux with 25 ml. of methyl iodide for 30 min. The solution was concentrated and the residue taken up in 30 ml. of ethyl acetate. On standing in the cold crystallization occurred and the product was collected on a filter, washed with ether, and dried; yield, 5.7 g. (86.4%), m.p. 122–123°.

Anal. Calcd. for $C_{29}H_{44}IN_3O_3$: N, 6.92, I, 20.85. Found: N, 6.60; I, 20.90.

PHILADELPHIA 1, PA.

[CONTRIBUTION FROM THE ORGANIC CHEMICAL RESEARCH SECTION, LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID CO.]

Tranquilizing Agents. Xanthen- and Thioxanthen-$\Delta^{9,\gamma}$-propylamines[1] and Related Compounds

GUIDO E. BONVICINO, HERBERT G. ARLT, JR., KARIN M. PEARSON, AND ROBERT A. HARDY, JR.

Received November 16, 1960

The Grignard reaction of a 3-chloro-*N,N*-dialkylpropylamine with xanthen-9-ones and thioxanthen-9-ones gave a series of 9-(3-dialkylaminopropyl)xanthen-9-ols and thioxanthen-9-ols. Dehydration of these compounds gave the corresponding xanthen- and thioxanthen-$\Delta^{9,\gamma}$-propylamines, some of which were potent tranquilizers. Substantial differences in dehydration of the xanthen-9-ols and thioxanthen-9-ols were observed and are explained. The characteristic changes in the ultraviolet spectra, used to follow these reactions, are described. Several open chain analogs were prepared to study structure-activity relationships.

The well known efficacy of chlorpromazine in the treatment of neuropsychiatric disorders has led to the syntheses of a great number of 10-phenothiazinepropylamines,[2] many of which are new tranquilizing drugs. We wish to report the chemistry of a series of xanthen- and thioxanthen-$\Delta^{9,\gamma}$-propylamines (III) (Table II) with potent tranquilizing activity. Our basic idea for these compounds originated from consideration of the structures of azacyclonol[3] and chlorpromazine.[4] This suggested the preparation of 9-(3-dialkylaminopropyl)xanthen-9-ol and thioxanthen-9-ol analogs (I) (Table I) for pharmacological investigation as potential tranquilizing agents. Dehydration of these compounds yielded the unsaturated analogs (III).

The general method for the preparation of the tertiary alcohols of type I was the Grignard reaction of a 3-chloro-*N,N*-dialkylpropylamine with a xanthen-9-one or thioxanthen-9-one. A modification of Marxer's procedure for 3-(dialkylaminopropyl)-diphenylcarbinols[5] was used. The reaction of the

(1) Since 1957, Chemical Abstracts numbering of the thioxanthene ring system has been changed to conform with that of the isosteric xanthene molecule. The current nomenclature is used throughout this paper.

(2) J.-P. Bourquin, G. Schwarb, G. Gamboni, R. Fischer, L. Ruesch, S. Guldimann, V. Theus, E. Schenker, and J. Renz, *Helv. Chim. Acta*, **41**, 1061, 1072 (1958); **42**, 259 (1959).

(3) (a) Frenquel is the trademark of Wm. S. Merril Co. for azacyclonol—*i.e.*, α-(4-piperidyl)diphenylcarbinol hydrochloride; (b) F. Rinaldi, L. H. Rudy and H. E. Himwich, *Am. J. Psychiatry*, **112**, 343 (1955).

(4) Thorazine is the trademark of Smith Kline and French Laboratories for chlorpromazine—*i.e.*, 2-chloro-10-(3-dimethylaminopropyl)phenothiazine hydrochloride.

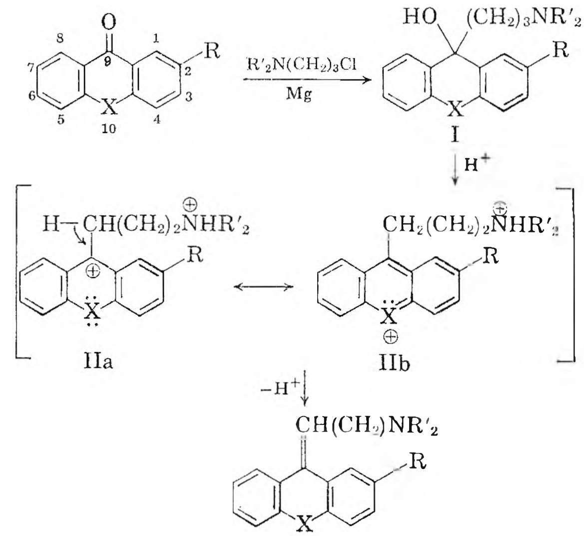
(5) A. Marxer, *Helv. Chim. Acta*, **24**, 209E (1941).

TABLE I. 9-(3-DIALKYLAMINOPROPYL)XANTHEN-9-OL AND -THIOXANTHEN-9-OL ANALOGS

No.	$N(R_2)$	R_1	R_2	X	Procedure[a]	M.P.[b]	Yield, %	Molecular Formula[b]	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Halogen Calcd.	Halogen Found	Nitrogen Calcd.	Nitrogen Found	Sulfur Calcd.	Sulfur Found
1	$(CH_3)_2$	H	H	O	A	109–111	70	$C_{18}H_{21}NO_2$	76.3	76.0	7.47	7.36			4.94	4.78		
2	$(CH_3)_2$	H	1-Cl	O	A	158–160	46	$C_{18}H_{20}ClNO_2$	68.0	68.0	6.34	6.50	11.2	11.0	4.41	4.52		
3	$(CH_3)_2$	H	2-OCH_3	O	A	103–104	92	$C_{19}H_{23}NO_3$	72.8	72.8	7.40	7.59			4.47	4.47		
4	$(CH_3)_2$	2-Cl	6-Cl	O	A	206–208[c]	55	$C_{18}H_{20}Cl_3NO_2$[c]	55.6	54.7	5.19	5.44	27.4	27.0	3.60	3.25		
5	$(CH_3)_2$	H	H	S	A	153–157	86	$C_{18}H_{21}NOS$	72.2	72.0	7.07	7.30			4.68	4.65	10.7	11.0
6	$(CH_3)_2$	H	2-Cl	S	A	152–153[d]	83	$C_{18}H_{20}ClNOS$	64.7	64.7	6.05	6.12	10.6	10.2	4.19	4.08	9.60	9.69
7	$(CH_3)_2$	H	2-OCH_3	S	A	123–125	89	$C_{19}H_{23}NO_2S$	69.3	69.1	7.04	7.09			4.25	4.16	9.74	9.72
8	$(CH_3)_2$	H[e]	4-CH_3	S	A	122–124	80	$C_{19}H_{24}NOS$	72.8	72.4	7.40	7.64	0.00	0.53[e]	4.47	4.50	10.2	10.4
9	$(CH_3)_2$	1-CH_3	4-Cl	S	A	162–166	55	$C_{19}H_{22}ClNOS$	66.5	66.4	6.38	6.13	10.2	11.1	4.02	3.99	9.20	9.26
10	$CH_3N\langle\rangle N$	H	H	S	C	171–173	60	$C_{21}H_{26}N_2OS$	71.2	71.0	7.39	7.40			7.89	7.60	9.05	9.22

[a] See Experimental. [b] Free bases, except as noted. [c] The hydrochloride salt separated from a N hydrochloric acid solution of the product in an effort to dehydrate it according to Procedure D. It was recrystallized from hot water. [d] Lit.,[11] m.p. 153–154°. [e] From 1-chloro-4-methylthioxanthen-9-one. The 1-chlorine atom was reduced apparently during the Grignard reaction.

ketones with two moles of 3-chloro-*N*,*N*-dimethylpropylamine and two moles of magnesium, in a benzene-ether mixture, usually required twelve to twenty-four hours of heating under reflux. However, up to eighty hours were needed for the reactions with 1-(3-chloropropyl)-4-methylpiperazine under the same conditions. The latter reactions required only three to seven hours in tetrahydrofuran (THF) when the ethylene bromide procedure of Pearson *et al.*,[6,7] was used.



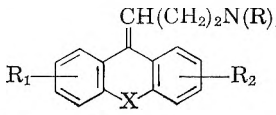
Generally, isolation of the desired tertiary alcohols (I) was dependent on whether or not mineral acids were used during the purification procedure. This was evident when 9-(3-dimethylaminopropyl)-xanthen-9-ol (Table I, No. 1) very readily dehydrated during its isolation on treatment with dilute hydrochloric acid. The isolated product was *N*,*N*-dimethylxanthen-$\Delta^{9,\gamma}$-propylamine, characterized as the hydrochloride, giving the first member of the xanthen-$\Delta^{9,\gamma}$-propylamine series (III. X = O). The desired alcohol (Table I, No. 1) was easily obtained as the free base, however, by decomposing the Grignard complex with ammonium chloride solution. Generally, the use of mineral acids must be assiduously avoided for the decomposition of this complex and for subsequent purification. This facile dehydration to the unsaturated series (III) was a general characteristic of the oxygen series (I. X = O). Dehydration in the sulfur series (I. X = S) required more drastic conditions. The *tert*-alcohols were insolable as mineral acid addition salts as well as the free bases. Furthermore, the use of dilute mineral acid was a distinct advantage for their purification.

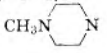
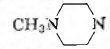
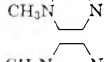
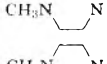
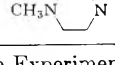
(6) D. E. Pearson, D. Cowan, and J. D. Beckler, *J. Org. Chem.*, 24, 504 (1959).

(7) The purpose of the ethylene bromide was to activate the magnesium surfaces and thus improve the formation of the Grignard reagent. The reaction of ethylene bromide and magnesium is: $Mg + BrCH_2CH_2Br \rightarrow CH_2{=}CH_2 + MgBr_2$ as described by Pearson *et al.*[6]

TABLE II

XANTHEN- AND THIOXANTHEN-$\Delta^{9,7}$-PROPYLAMINE ANALOGS



No.	N(R2)	R1	R2	X	Procedure[a]	M.P.[b]	Yield, %[c]	Molecular Formula[b]	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Chlorine Calcd.	Chlorine Found	Nitrogen Calcd.	Nitrogen Found	Sulfur Calcd.	Sulfur Found
1	$(CH_3)_2$	H	H	O	D	201.5–203	60	$C_{18}H_{20}ClNO$	71.6	71.4	6.68	6.65	11.8	11.6	4.64	4.63		
2	$(C_4H_9)_2$	H	H	O	D	203–205[d]	25	$C_{24}H_{32}ClNO$	74.7	74.2	8.36	8.47	9.19	9.27	3.63	3.57		
3		H	H	O	D	251–253	32	$C_{21}H_{26}Cl_2N_2O$	64.1	63.6	6.66	7.01	18.0	17.9	7.12	7.33		
4		H	H	O	D	213–214.5	20	$C_{21}H_{24}ClNO$	73.8	73.9	7.07	7.43	10.4	10.5	4.10	3.99		
5	$(CH_3)_2N$	H	1-Cl	O	D	173–177	21	$C_{18}H_{19}Cl_2NO$	64.3	64.3	5.70	5.87	21.1	21.1	4.17	4.43		
6	$(CH_3)_2N$	H	2-Cl	O	D	193–195	36	$C_{18}H_{19}Cl_2NO$	64.3	64.2	5.70	5.85	21.1	20.9	4.17	3.92		
7	$(CH_3)_2N$	H	2-Br	O	D	174–176	50	$C_{18}H_{19}BrClNO$	56.8	56.9	5.03	5.28	9.33	9.57[e]	3.68	3.95		
8	$(CH_3)_2N$	H	3-Cl	O	F[f]	170–172	30	$C_{18}H_{19}Cl_2NO$	64.3	64.0	5.70	5.39	21.1	20.7	4.17	4.23		
9	$(CH_3)_2N$	H	4-Cl	O	D	162–164	45	$C_{18}H_{19}Cl_2NO$	64.3	63.9	5.70	5.98	21.1	20.8	4.17	4.10		
10	$(CH_3)_2N$	2-Cl	6-Cl	O	E[f]	215–217	58	$C_{18}H_{18}Cl_3NO$	58.3	58.0	4.89	5.16	28.7	28.7	3.78	3.82		
11	$(CH_3)_2N$	2-Cl	4-CH_3	O	D	219–222	75	$C_{19}H_{21}Cl_2NO$	65.1	65.2	6.04	6.18	20.2	20.0	4.00	4.20		
12	$(CH_3)_2N$	2-Cl	7-OCH_3	O	D	170–172	50	$C_{19}H_{21}Cl_2NO_2$	62.3	62.0	5.80	6.09	19.4	19.3	3.83	3.93		
13	$(CH_3)_2N$	H	2-OCH_3	O	D	196–198	80	$C_{19}H_{22}ClNO_2$	68.8	68.8	6.68	6.84	10.7	10.6	4.22	4.13		
14	$(CH_3)_2N$	H	2-OCH_3	O	[g]	170–172[g]	15[g]	$C_{23}H_{25}NO_6$[g]	67.1	67.0	6.12	6.26			3.41	3.46		
15	$(CH_3)_2N$	H	2-OCH_3	O	[h]	151–153.5[h]	89[h]	$C_{23}H_{25}NO_6$[h]	67.1	66.9	6.12	6.46			3.41	3.46		
16	$(CH_3)_2N$	H	2-OH	O	[i]	219–221	57[j]	$C_{18}H_{20}ClNO_2$	68.0	67.6	6.34	6.26	11.2	11.2	4.41	4.41		
17		H	2-OCH_3	O	D	211–213	25	$C_{22}H_{28}Cl_2N_2O_2$	62.4	62.2	6.67	6.82	16.8	16.8	6.62	6.59		
18	$(CH_3)_2N$	H	H	S	F	181–183	48	$C_{18}H_{20}ClNS$	68.0	67.8	6.34	6.55	11.2	11.1	4.41	4.29	10.1	10.2
19	$(CH_3)_2N$	H	2-Cl	S	E	191–193[k]	89	$C_{18}H_{19}Cl_2NS$	61.4	61.3	5.44	5.67	20.1	19.8	3.98	4.33	9.10	9.01
20	$(CH_3)_2N$	H	2-OCH_3	S	F	168–170	61	$C_{19}H_{22}ClNOS$	65.6	65.4	6.37	6.68	10.2	10.2	4.03	3.86	9.21	9.17
21	$(CH_3)_2N$	H	4-CH_3	S	F	174–176	75	$C_{19}H_{22}ClNS$	68.7	68.3	6.69	6.82	10.7	10.3	4.22	4.22	9.64	9.40
22	$(CH_3)_2N$	1-CH_3	4-Cl	S	F	187–190	64	$C_{19}H_{21}Cl_2NS$	62.3	62.0	5.78	6.03	19.4	19.2	3.83	4.00	8.75	8.52
23		H	H	S	F	248–249	83	$C_{21}H_{26}Cl_2N_2S$	61.6	61.3	6.40	6.74	17.3	17.6	6.84	7.01	7.83	7.83
24		H	2-Cl	S	F	247–249	85	$C_{21}H_{25}Cl_3N_2S$	56.8	56.8	5.68	5.92	24.0	23.6	6.31	6.26	7.22	6.81
25		H	2-OCH_3	S	E	212–215[l]	44	$C_{22}H_{30}Cl_2N_2O_2S$[l]	57.8	57.6	6.61	6.92	15.5	15.4	6.12	6.39	7.01	6.58

[a] See Experimental. [b] Hydrochlorides except as noted. [c] Yields of the oxygen analogs were calculated from the xanthen-9-ones, except as noted. Yields of the sulfur analogs were calculated from the thioxanthen-9-ols (Table I), except as noted. [d] Lit.,[9] m.p. 204–205°. [e] Bromine: Calcd.: 21.0. Found: 21.4. [f] Procedure D was not satisfactory for these compounds. More drastic conditions were necessary for dehydration. [g] *cis* (or *trans*) fumarate (Va); see Experimental. [h] *trans* (or *cis*) fumarate (Vb); see Experimental. [i] Prepared by hydrolysis of compound No. 13; see Experimental. [j] From compound No. 13. [k] Lit.,[11] m.p. 189–190°. [l] Monohydrate, H_2O; Calcd.: 3.09. Found: 3.08. The anhydrous dihydrochloride, m.p. 225–226°, also gave a satisfactory analysis.

The dehydration appeared to be a two-step process. First, an acid-catalyzed dehydroxylation produced the "onium" salt (IIa, b), indicated by characteristic changes in the visible region of the absorption spectrum (*vide infra*). This was followed by a base-catalyzed deprotonization of the α-carbon (IIa → III). Dehydration of the oxygen-series *tert*-alcohols generally took place immediately at room temperature upon the addition of 0.5-1*N* aqueous hydrochloric acid as evidenced by the rapid development of a red color in the solution. The sulfur-series *tert*-alcohols were dehydrated by several procedures: treatment with (a) glacial acetic and concentrated hydrochloric acids, (b) anhydrous hydrogen chloride in benzene or ether, and (c) acetic anhydride–glacial acetic acid mixtures. Addition of base then gave the dehydrated products. The interesting differences in ease of dehydration between the oxygen and sulfur series may be explained by a greater resonance stabilization of the oxonium ion (IIb. X = O and its equivalent ions) compared to the sulfonium ion (IIb. X = S). This is due to the greater tendency of oxygen to "increase its covalency" described by Ingold.[8] 2,6-Dichloro-9-(3-dimethylaminopropyl)-xanthen-9-ol was an exception to the facile dehydration of the oxygen series, and required the more vigorous conditions used for the sulfur series.

The facile dehydration of a xanthen-9-ol derivative (I) was actually first observed by Perrine[9] in 1953. He obtained *N,N*-di-*n*-butylxanthen-$\Delta^{9,\gamma}$-propylamine hydrochloride (when he used hydrochloric acid to decompose the Grignard complex) instead of the desired *tert*-alcohol.

After our work was well underway it became evident that other laboratories were also investigating the tranquilizing activity of the xanthen- and thioxanthen-$\Delta^{9,\gamma}$-propylamines.[10-12] Other routes to these compounds have since been reported: (a) the Grignard reaction of allyl bromide with xanthen-9-ones and thioxanthen-9-ones followed by subsequent dehydration and ammation[13]; (b) 9-cyanoethylation of the xanthen-9-ols and thioxanthen-9-ols followed by reduction and dehydration[13]; (c) reaction of 3-dimethylaminopropyne-1 derivatives with xanthen-9-one and thioxanthen-9-one followed by reduction and dehydration.[14]

When unsymmetrically substituted ketones are used, stereoisomers are possible in both the *tert*-alcohol series (I) and the unsaturated series (III).

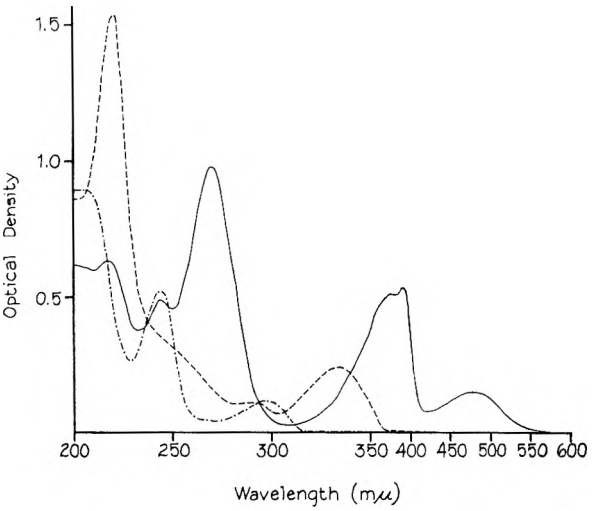
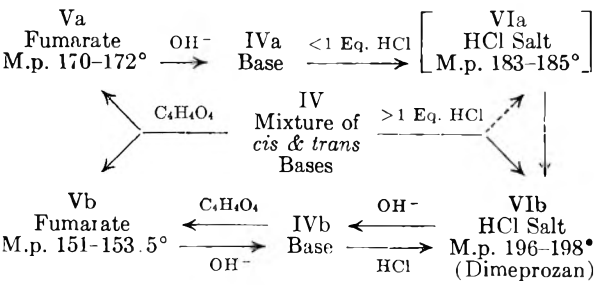


Fig. 1. Ultraviolet absorption spectra of oxygen series (concn. 10 μg./ml)
(a) -·—·—, 2-methoxy-9-[3-dimethylaminopropyl)xanthen-9-ol in methanol
(b) — — — —, 2-methoxy-*N,N*-dimethylxanthen-$\Delta^{9,\gamma}$-propylamine hydrochloride in methanol
(c) ————, the "onium" salt from (a) in 6*N* hydrochloric acid[15]

Separation of enantiomorphs in the *tert*-alcohol series was not attempted. Investigation of the geometrical isomers (*cis* and *trans*) in the unsaturated series was carried out with 2-methoxy-*N,N*-dimethylxanthen-$\Delta^{9,\gamma}$-propylamine. Neutralization of red oxonium salt (IIa, b; devoid of stereoisomers), formed when 2-methoxy-9-(3-dimethylaminopropyl)xanthen-9-ol was dissolved in hydrochloric acid, produced a mixture of *cis* and *trans* bases (IV). This was demonstrated by isolation of a mixture of fumarates (Va and Vb), m.p. 143–152°, from IV, and fumaric acid in ethanol. Repeated



fractional crystallization from ethanol afforded the less soluble fumarate (Va), m.p. 170–172°. The more soluble fumarate (Vb) could be isolated from the mother liquors, but was more readily obtained from VIb. The isomeric bases, IVa and IVb, liberated from the purified fumarates Va and Vb, respectively, gave different infrared absorption spectra. The spectrum of IV was consistent with its formulation as a mixture of IVa and IVb. When the mixture of bases (IV) was treated with slightly more than

(8) C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, Cornell University Press, Ithaca, N. Y., 1953, p. 75.
(9) T. D. Perrine, *J. Org. Chem.*, **18**, 1356 (1953).
(10) P. V. Petersen, N. Lassen, T. Holm, R. Kopf, and I. Møller Nielsen, *Arzneimittel Forsch.*, **8**, 395 (1958).
(11) J. M. Sprague and E. L. Engelhardt, U. S. Pat. 2,951,082 (1960).
(12) Hoffmann-La Roche AG, Belg. Pat. 558,171 (1957).
(13) Kefalas A/S, Belgian Pat. 585,338 (1960).
(14) W. Ried and J. Schönherr, *Ber.*, **93**, 1870 (1960).

(15) Before the spectrum was taken the solution was allowed to stand at room temperature for 1.75 hr. to insure complete transformation to the "onium" salt.

TABLE III

SUMMARY OF ULTRAVIOLET ABSORPTION MAXIMA

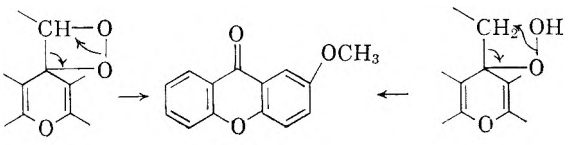
	Oxygen Series (X = O)		Sulfur Series (X = S)	
	$M\mu$	$\epsilon \times 10^{-3}$	$M\mu$	$\epsilon \times 10^{-3}$
Xanthen- and thioxanthen-9-ols (I)[a]; in methanol	208–212	28.3–33.4	210–214	26.7–28.7
	240–245	10.1–15.4	268–271	12.2–14.5
	280–290	2.50–3.50 broad band		
"Onium" forms (II); in 6*N* HCl	217	20.9[b]	212	24.5[c]
	244	17.3	229	20.6
	269	32.5	293	49.1
	375	16.9	395	9.74
	390	17.6	520	3.65
	480	4.81		
Xanthen- and thioxanthen-$\Delta^{9,\gamma}$-propylamines (III)[d]; in methanol	215–222	44.8–56.5	208–210	32.0–42.0[e]
	315–338	7.70–8.90	228–230	31.4–56.0
			268–270	13.1–24.5
			325–335	3.15–5.30

[a] Determined as bases. [b] 2-Methoxy-9-(3-dimethylaminopropyl)xanthen-9-ol was dissolved in 6*N* hydrochloric acid and allowed to stand at room temperature for 1.75 hr. to insure complete transformation before the spectrum was taken. [c] 2-Methoxy-*N*,*N*-dimethylthioxanthen-$\Delta^{9,\gamma}$-propylamine hydrochloride was dissolved in 6*N* hydrochloric acid and allowed to stand at room temperature for 1.75 hr. to ensure complete transformation before the spectrum was taken. [d] Determined as hydrochlorides. [e] The sulfur compounds (III. X = S) containing the methylpiperazine moiety lacked this maximum.

one equivalent of alcoholic hydrochloric acid, one isomeric salt (VIb) was isolated in excellent yield (80% or better), m.p. 196–198°. This was demonstrated by liberating the base IVb (from VIb) and converting it to the lower melting fumarate (Vb) in 89% yield, m.p. 151–153.5°. The base IVb was also reconverted to VIb. The isomeric base IVa, obtained from the higher-melting fumarate (Va), was treated with slightly less than one equivalent of alcoholic hydrochloric acid. The isolated salt (VIa) melted at 183–185° and was more soluble than VIb in ethanol. Characterization of this material (VIa) as the geometric isomer of VIb was difficult since it completely changed to VIb on standing for two weeks. Alternately, treatment of base IVa with more than one equivalent of alcoholic hydrochloric acid yielded VIb directly in 70% yield. These findings suggest that equilibration of the *cis* and *trans* forms occurs through the oxonium salt (IIa, b) in the presence of mineral acid. This allows preferential crystallization of the less soluble isomer in good yield.

The ultraviolet absorption spectra of these compounds show characteristic changes between the *tert*-alcohols (I), the "onium" forms (II) and the unsaturated derivatives (III). These changes are very useful for following the dehydration reactions and are summarized in Table III. Figures 1 and 2 illustrate these transformations (I → II → III) for a typical member of the oxygen and sulfur series, respectively. The development of low intensity maxima in the 315-340 mμ region was particularly characteristic for the formation of the unsaturated compounds (III. X = O or S). The corresponding *tert*-alcohols (I. X = O or S) were transparent in this region and this band was used for estimation of purity. Additionally, the unsaturated compounds (III. X = O) showed a particularly sharp and intense maximum in the 215–222 mμ region. The spectral bands particularly characteristic of the "onium" salts (II. X = O or S) were those above 350 mμ (red color).

In the course of working with 2-methoxy-*N*,*N*-dimethylxanthen-$\Delta^{9,\gamma}$-propylamine base over a period of several months, oxidative decomposition of this material was observed. After standing for two months at room temperature an ethereal solution deposited 13% of 2-methoxyxanthen-9-one (VII). This change was more rapid in air in the absence of solvent; about 65% of the ketone (VII) was obtained in three to five days. Suspecting that the decomposition in ether might be due to peroxides, an alcoholic solution of this base was treated with hydrogen peroxide. After nine days, 10–23% of the ketone (VII) was isolated. Dry air, aspirated through an alcoholic solution for twenty-four days did not appreciably affect the free base, as determined by infrared and ultraviolet spectra. The carbonyl absorption of 2-methoxy-xanthen-9-one at 6.03–6.05 μ was particularly diagnostic for the presence of this decomposition product in mixtures. The hydrochloride (VIb) was stable for extended periods, however. These air and peroxide oxidations may be considered as taking place through the intermediate states VIII or IX, respectively.



VIII VII IX

These oxidations may be surprising but are not without literature precedents.[16,17]

(16) R. Q. Brewster, *Organic Chemistry*, 2nd ed., Prentice-Hall, New York, 1953, p. 236.

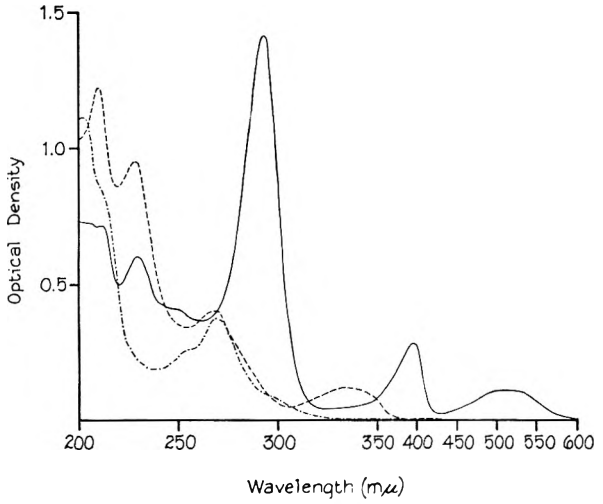
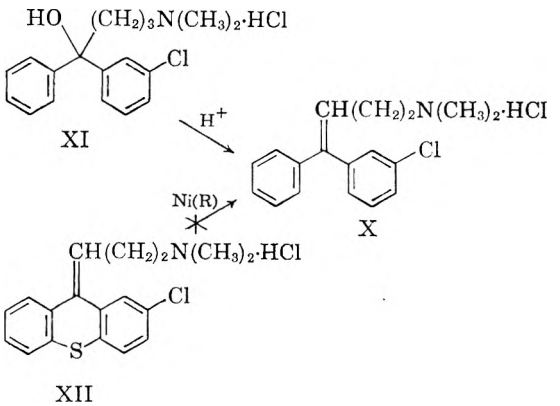


Fig. 2. Ultraviolet absorption spectra of sulfur series (concn. 10 μg./ml.)
(a) — · — · —, 2-methoxy-9-(3-dimethylaminopropyl)thioxanthen-9-ol in methanol
(b) — — — —, 2-methoxy-*N*,*N*-dimethylthioxanthen-$\Delta^{9,\gamma}$-propylamine hydrochloride in methanol
(c) ————, the "onium" salt from (b) in 6*N* hydrochloric acid[15]

Additional structural modifications were investigated to determine those features necessary for good tranquilizing activity. Catalytic hydrogenation of *N*,*N*-dimethylxanthen-$\Delta^{9,\gamma}$-propylamine hydrochloride saturated the $\Delta^{9,\gamma}$-double bond yielding *N*,*N*-dimethylxanthene-9-propylamine hydrochloride with markedly reduced tranquilizing activity. 4-(*m*-Chlorophenyl)-*N*,*N*-dimethyl-4-phenyl-3-butenylamine hydrochloride (X), an open chain analog of active xanthene or thioxanthene derivatives, was prepared. The Grignard reaction of 3-



chloro-*N*,*N*-dimethylpropylamine with *m*-chlorobenzophenone yielded 3-chloro-α-(3-dimethylaminopropyl)benzhydrol, isolated as the stable hydrochloride (XI). Dehydration of this *tert*-alcohol required the vigorous conditions necessary for the thioxanthen-9-ol analogs (I. X = S). An attempt to prepare X by Raney nickel desulfurization[18] of 2-chloro-*N*,*N*-dimethylthioxanthen-$\Delta^{9,\gamma}$-propylamine hydrochloride (XII)[10-13] was unsuccessful; only starting material was recovered. The corresponding open chain analog of chlorpromazine, *N*-*m*-chlorophenyl-*N'*,*N'*-dimethyl-*N* - phenyl - 1,3 - propanediamine hydrochloride (XIII), was also prepared for comparative testing. This was accomplished by treating *m*-chlorodiphenylamine with 3-chloro-*N*,*N*-dimethylpropylamine. As these derivatives lacked the hetero-atom, it seemed interesting to prepare an open chain analog containing an *o*-methoxyl group. This oxygen atom is situated in the same relative position as that occupied by the hetero-atom (O or S) of the "xanthene" or "thioxanthene" series, and at the same time the molecule retains the flexible characteristics of X. The preparation of 4-(*o* - methoxyphenyl) - *N*,*N* - dimethyl - 4 - phenyl-3-butenylamine was attempted but ether cleavage occurred during the Grignard reaction. *o*-Methoxybenzophenone treated with magnesium and 3-chloro-*N*,*N*-dimethylpropylamine gave α-(3-dimethylaminopropyl)-*o*-hydroxybenzhydrol (XIV) which required vigorous conditions for dehydration to *o*-(4-dimethylamino-1-phenyl-1-butenyl)phenol hydrochloride (XV). All of these open chain analogs were inactive indicating the need for maintaining the dibenzoheterocyclic system intact. The fluorene analog, *N*,*N*-dimethylaminofluoren-$\Delta^{9,\gamma}$-propylamine hydrochloride (XVI) was obtained from the vigorous dehydration of 9-(3-dimethylaminopropyl)-9-fluorenol (XVII) and had markedly reduced activity.

Preliminary evaluation of the tranquilizer activity of these compounds was carried out by determining the doses which produced ataxia, 50% reduction of spontaneous motor activity, loss of righting reflex and lethality in mice.[19] In these experiments, several of the xanthen- and thioxanthen-$\Delta^{9,\gamma}$-propylamines (III) showed activity qualitatively and quantitatively similar to chlorpromazine. Chlorine and methoxyl groups in the 2-position were particularly desirable. Dimethylamino or methylpiperazino groups were the basic moieties present in the active compounds. The structure-activity relationships in this series generally paralleled those of the phenothiazine series. The xanthen- and thioxanthen-9-ol precursors (I) showed no significant activity. 2-Methoxy-*N*,*N*-dimethyl-$\Delta^{9,\gamma}$-xanthenpropylamine hydrochloride (VIb), *dimeprozan*, is the same *cis*- or *trans*-isomer as the lower melting fumarate (Vb), and both of these were equally potent, active compounds comparing favorably with chlorpromazine. The higher melting fumarate (Va), on the other hand, was less

(17) (a) J. Fishman, *J. Am. Chem. Soc.*, **80**, 1213 (1958); (b) J. D. Loudon and J. A. Scott, *J. Chem. Soc.*, 265 (1953).

(18) R. Mozingo, D. E. Wolf, S. A. Harris, and K. Folkers, *J. Am. Chem. Soc.*, **65**, 1013 (1943).

(19) Pharmacological screening and evaluation studies were carried out by A. C. Osterberg *et al.*, of the Experimental Therapeutics Research Section of these laboratories. Details will be reported elsewhere.

than one-tenth as potent and about one-half as toxic. Dimeprozan was one of several compounds considered for trial in man. Preliminary clinical results suggest it is less effective than chlorpromazine as a tranquilizer for hospitalized psychotic patients. Pharmacological[10,20] and extensive clinical investigations[21] of 2-chloro-*N,N*-dimethylthioxanthen-$\Delta^{9,\gamma}$-propylamine hydrochloride, *chlorprothixene*, have been reported. It is interesting to note that the xanthen-$\Delta^{9,\gamma}$-propylamines (oxygen series; III. X = 0) cannot be oxidized to the 10-oxide in the fashion that phenothiazine tranquilizers have been reported to be partially metabolized.[22,23] 10-Oxide formation is a potential metabolic route for the thioxanthen-$\Delta^{9,\gamma}$-propylamines (sulfur series; III. X = S).

EXPERIMENTAL[24]

Preparation of salts. The hydrochloride salts were prepared by treating a weighed quantity of the bases, in the minimum volume of absolute alcohol, with the equivalent quantity of standardized alcoholic hydrogen chloride determined by the number of basic groups in the molecules.

Procedure A: 9-(3-Dialkylaminopropyl)xanthen-9-ol analogs (Table I). The preparation of 2-methoxy-9-(3-dimethylaminopropyl)xanthen-9-ol is an example of this general procedure. Magnesium metal, 43.7 g. (1.8 g.-atoms), in a 12-l. three-necked flask fitted with stirrer, condenser and a 1-l. addition funnel, was activated with a crystal of iodine and 2 ml. of methyl iodide. With gentle heating and stirring, a mixture of 1.8 moles of 3-chloro-*N,N*-dimethylpropylamine[5] in 900 ml. of anhydrous ether was added over a 45-min. period. The mixture was heated to reflux and 0.9 mole of 2-methoxyxanthen-9-one, dissolved in 3 l. of dry benzene, was added dropwise over 1.5 hr. The mixture was stirred and heated under reflux for 20 hr. (almost no magnesium metal remained). After cooling, the Grignard complex was decomposed by the addition of 2.2 l. of 10% ammonium chloride solution followed by 2.2 l. of water. The organic phase was separated and the aqueous phase was extracted with 2 l. of ether. The organic phases were combined and washed with water [Fraction (a)]. This ethereal solution was dried over magnesium sulfate and evaporated. Treatment of the residue with 2 parts of ethanol caused crystallization of the crude material as an almost white solid, m.p. 103–104°, 275 g. (92% yield). Recrystallization from alcohol did not change the melting point. For analysis see Table I, No. 3. The thioxanthen-9-ol analogs were isolated according to Procedure B. Dehydration of the xanthen-9-ol analogs was accomplished according to Procedure D, and the thioxanthen-9-ol analogs were dehydrated according to Procedure E or F.

Procedure B. 9-(3-Dialkylaminopropyl)thioxanthen-9-ol analogs (Table I). 2-Chloro-9-(3-dimethylaminopropyl)thioxanthen-9-ol is an example of this general method. 2-Chlorothioxanthen-9-one, 38 g. (0.15 mole) reacted with 38 g. (0.31 mole) of 3-chloro-*N,N*-dimethylpropylamine and 7.5 g. (0.31 g.-atom) of magnesium in an ether-benzene mixture as described in Procedure A. The combined organic phases corresponding to Fraction (a), (Procedure A), were extracted with three 200-ml. portions of *N* hydrochloric acid. The acidic aqueous extracts were combined and made alkaline with 20% sodium hydroxide, and extracted with several portions of ether. The combined ether extracts were washed free of alkali with water, dried over magnesium sulfate, and evaporated. The crude residue, on recrystallization from 3 A alcohol, afforded 43 g. (83% yield) of crystalline product, m.p. 152–153°, (lit.,[11] m.p. 153–154°). For analysis see Table I, No. 6.

Procedure C. 9-(3-Dialkylaminopropyl)xanthen-9-ol or -thioxanthen-9-ol analogs (Table I). *A modification of procedure A.* The preparation of 2-chloro-9-[3-(4-methyl-1-piperazinyl)propyl]thioxanthen-9-ol is an example of this general procedure. Freshly ground magnesium metal, 22.9 g. (0.94 g.-atom), and 250 ml. of anhydrous tetrahydrofuran,[25] in a 3-l. four-necked flask fitted with stirrer, condenser, 1-l. and 250-ml. addition funnels was treated with 1 ml. of ethylene bromide. The mixture was warmed to start the reaction. 1-(3-Chloropropyl)-4-methylpiperazine,[26] 82.7 g. (0.47 mole), was added in one portion, and a solution of 88.4 g. (0.47 mole) of ethylene bromide in 200 ml. of tetrahydrofuran was added dropwise until the reaction with magnesium was again evident. This generally required only a small portion of the ethylene bromide solution; the reaction may become vigorously exothermic at this point. Therefore, a cooling bath should be ready for use if necessary. When the exothermic reaction subsided, a suspension of 2-chlorothioxanthen-9-one, 57.9 g. (0.24 mole) in 700 ml. of tetrahydrofuran was added portionwise (15 min.). The reaction mixture was heated under reflux for 7 hr. while the remainder of the ethylene bromide was added dropwise. The reaction mixture was then decomposed as described in Procedure A. The crude product, 88.9 g. (97% yield), was isolated as described in Procedure B and was converted to 1-[3-(2-chlorothioxanthen-9-ylidene)propyl]-4-methylpiperazine dihydrochloride as described in Procedure F.

Procedure D. N,N-Dialkylxanthen-$\Delta^{9,\gamma}$-propylamine analogs (Table II). The preparation of 2-methoxy-*N,N*-dimethylxanthen-$\Delta^{9,\gamma}$ propylamine hydrochloride (VIb) is an example of this procedure generally used for the dehydration of the xanthen-9-ol analogs. A solution of 2-methoxy-9-(3-dimethylaminopropyl)xanthen-9-ol, prepared as described in Procedure A [Fraction (a)], was extracted with five 1-l. portions of *N* hydrochloric acid. The dark red, acidic extracts were combined and made alkaline with potassium carbonate under a layer of ether. The yellow aqueous layer and the ether layer were separated, and the aqueous layer was extracted with three 250-ml. portions of ether. The combined ether layers, after drying with magnesium sulfate, were concentrated *in vacuo* to a viscous oil on a steam bath; yield 250 g. (95% from xanthone). All efforts to crystallize this base were unsuccessful. It was dissolved in 675 ml. of ethanol and treated with anhydrous hydrogen chloride (with stirring) until a faint red tinge persisted. This solution was seeded and stirred for 16 hr. The heavy crystalline slurry was cooled to 10° and the product was collected by filtration. After vacuum drying (40°) 240 g. (80% yield, based on 2-methoxyxanthen-9-one) of product was obtained, m.p. 194–198°. Two recrystallizations from ethanol raised the melting point slightly, m.p. 196–198°, and gave analytically pure material (See Table II, No. 13).

(20) (a) I. Møller-Nielsen and K. Neuhold, *Acta Pharmacol. Toxicol.*, **15**, 335 (1959); (b) B. Pellmont, F. A. Steiner, H. Besendorf, H. P. Bächtold, and E. Läuppi, *Helv. Physiol. Acta*, **18**, 241 (1960).

(21) H. Hoffet and F. Cornu, *Schweiz. Med. Wochschr.*, **90**, 602 (1960); these authors also review earlier pertinent references.

(22) N. P. Salzman, N. C. Moran, and B. B. Brodie, *Nature*, **176**, 1122 (1955).

(23) L.-G. Allgén, B. Jönsson, A. Rappe, and R. Dahlbom, *Experientia*, **15**, 318 (1959).

(24) All melting points are uncorrected and were taken in a Hershberg melting point apparatus.

(25) Anhydrous tetrahydrofuran was prepared by drying commercially available material over sodium hydroxide pellets followed by distillation. The distilled product was then refluxed for 1 hr. in the presence of lithium aluminum hydride and finally redistilled.

(26) O. Hromatka, I. Grass, and F. Sauter, *Monatsh.*, **87**, 701 (1956); *Chem. Abstr.*, **51**, 8109h (1957).

Procedure E. N,N-Dialkylthioxanthen-$\Delta^{9,\gamma}$-propylamine analogs (Table II). The preparation of 2-chloro-*N,N*-dimethylthioxanthen-$\Delta^{9,\gamma}$-propylamine is an example of this general procedure for the dehydration of thioxanthen-9-ol analogs. Five grams (0.015 mole) of 2-chloro-9-(3-dimethylaminopropyl)thioxanthen-9-ol, isolated according to Procedure B, was dissolved in 100 ml. of anhydrous benzene, and hydrogen chloride was bubbled through the solution at room temperature for 15 min. During this time the solution turned dark red and a dark red gum separated (thioxanthonium salt). About 100 ml. of anhydrous ethanol was then added and the resultant, virtually colorless solution was evaporated on a steam bath *in vacuo*. The residue, a white glass, was dissolved in 25 ml. of absolute ethanol and diluted with anhydrous ether to the cloud point. On standing, the colorless hydrochloride crystallized and was collected, m.p. 181–193°. Recrystallization from ethanol by the addition of ether afforded 4.7 g. (89% yield) of product (Table II, No. 19), m.p. 191–193° (lit.,[11] m.p. 189–190°). No effort was made to separate the *cis* and *trans* isomers. The free base was obtained from the hydrochloride and distilled: b.p. 210–215°/0.5 mm.

Anal. Calcd. for $C_{18}H_{18}ClNS$ (315.86): C, 68.4; H, 5.74; Cl, 11.2; N, 4.43; S, 10.2 Found: C, 68.5; H, 5.91; Cl, 11.3; N, 4.26; S, 10.3.

Procedure F. N,N-Dialkylthioxanthen-$\Delta^{9,\gamma}$-propylamine analogs (Table II). The preparation of 1-[3-(2-chlorothioxanthen-9-yliden)propyl]-4-methylpiperazine dimaleate (and other salts) is an example of this general method. 2-Chloro-9-[3-(4-methyl-1-piperazinyl)propyl]thioxanthen-9-ol, 83.9 g. (0.22 mole) (Procedure C), in 250 ml. of concd. hydrochloric acid and 500 ml. of glacial acetic acid, was heated under reflux for 2 hr. The dark red solution (presumably the thioxanthonium cation) was made alkaline with 20% sodium hydroxide and extracted several times with ether. The combined ether extracts (yellow solution), after being washed free of alkali, were dried over magnesium sulfate and evaporated to dryness. The yield of the crude base[27] was 66.4 g. (76%) which could not be crystallized. This base, 61.4 g. (0.16 mole) in 300 ml. of ethanol, was treated with 38.2 g. (0.34 mole) of maleic acid in 300 ml. of ethanol. The crystalline salt was collected after 1 hr.; yield, 93 g. (94% from the crude base), m.p. 185–187° dec. Recrystallization from 85% alcohol yielded 80 g. (78% recovery) of pure dimaleate, m.p. 190–192°.

Anal. Calcd. for $C_{21}H_{23}ClN_2S \cdot 2C_4H_4O_4$ (603.09): C, 57.8; H, 5.18; Cl, 5.88; N, 4.65; S, 5.32. Found: C, 57.6; H, 5.53; Cl, 5.17; N, 4.91; S, 5.47.

Using the above procedure, from 5.0 g. (0.013 mole) of crude base in 30 ml. of ethanol and 3.1 g. (0.027 mole) of fumaric acid in 100 ml. of ethanol, 7.2 g. (92% yield) of the difumarate salt was isolated, m.p. 220–222° dec. Recrystallization from ethanol afforded 6.0 g (77% yield) of product, m.p. 219–221° dec.

Anal. Calcd. for $C_{21}H_{23}ClN_2S \cdot 2C_4H_4O_4$ (603.09): C, 57.8; H, 5.18; Cl, 5.88; N, 4.65; S, 5.32. Found: C, 57.1; H, 5.18; Cl, 5.68; N, 4.87; S, 5.68.

To 12.9 g. of crude base, in 15 ml. of ethanol, was added 50 ml. of 2.5*N* aqueous nitric acid and the mixture was allowed to stand for 0.5 hr. The precipitated dinitrate was collected, washed with water and dried. The yield was 14.9 g. (86% from crude base). A sample was recrystallized from boiling water, and the pure dinitrate decomposed instantly at 181°.

Anal. Calcd. for $C_{21}H_{23}ClN_2S \cdot 2HNO_3$ (496.97): C, 50.8; H, 5.07; Cl, 7.13; N, 11.3; S, 6.45. Found: C, 50.8; H, 5.02; Cl, 7.47; N, 11.2; S, 6.69.

The dinitrate, 13.5 g. (0.027 mole) was suspended in 100 ml. of water and 100 ml. of 20% aqueous sodium hydroxide was added. The mixture was extracted with three 100-ml. portions of ether, the combined ether extracts were washed free of alkali and dried over magnesium sulfate. Evaporation of the ether yielded 9.0 g. (0.024 mole) of the purified base. It was dissolved in 15 ml. of ethanol and treatment with 17 ml. of 2.9*N* alcoholic hydrogen chloride (two equivalents) precipitated the dihydrochloride. Approximately 100 ml. of ethanol was added, and the mixture heated until complete solution was attained. The hot solution was decolorized with charcoal, filtered and allowed to cool. The crystalline dihydrochloride hydrate, 8.7 g. (85% from purified base), melted with decomposition at 235–236°.

Anal. Calcd. for $C_{21}H_{23}ClN_2S \cdot 2HCl \cdot H_2O$ (461.89): C, 54.6; H, 5.89; Cl, 23.0; N, 6.06; S, 6.96. Found: C, 54.7; H, 6.05; Cl, 23.0; N, 6.07; S, 7.35.

This salt was hygroscopic. However the anhydrous dihydrochloride, m.p. 247–249° (Table II, No. 24), was obtained when the atmospheric humidity was low.

trans (or *cis*) *2-Methoxy-N,N-dimethylxanthen-$\Delta^{9,\gamma}$-propylamine fumarate* (Vb; Table II, No. 15). The hydrochloride (VIb) (Procedure D), 112 g. (0.34 mole), was added to a mixture of 700 ml. of water, 700 ml. of ether, and 70.5 g. (0.51 mole) of potassium carbonate. The mixture was shaken until two clear phases were present. The ether layer was removed and the aqueous layer extracted with three 100-ml. portions of ether. The combined ether layers were dried over magnesium sulfate and clarified. Fumaric acid, 39.5 g. (0.34 mole), was dissolved in 700 ml. of ethanol with heating. This solution, at 40–45°, was then poured into the ether solution above. An immediate precipitate appeared and was separated by filtration after cooling. The yield of the fumarate (dried in an oven at 45°) was 125 g. (89%), m.p. 151–153.5°. Recrystallization from 12 parts of ethanol gave 100 g. of analytically pure product, m.p. 151–153.5°. For analysis see Table II, No. 15.

This fumarate (Vb) was converted to its base (IVb) as described above. An alcoholic solution of this base, upon treatment with one equivalent of alcoholic hydrogen chloride, immediately deposited the hydrochloride (VIb) in 75–90% yield. The melting points, microanalyses, infrared and ultraviolet spectra were identical with those of this hydrochloride (VIb) from the mixture of *cis* and *trans* bases (IV).

cis (or *trans*) *2-Methoxy-N,N-dimethylxanthen-$\Delta^{9,\gamma}$-propylamine fumarate* (Va; Table II, No. 14). A sample of crude 2-methoxy-*N,N*-dimethylxanthen-$\Delta^{9,\gamma}$-propylamine (IV, base), obtained directly from the dehydration of the xanthen-9-ol analog (Procedure D), was treated with an equimolar amount of fumaric acid (as described for the preparation of the lower melting isomer Vb). A mixture of fumarates, m.p. 143–152°, was obtained (90% yield). Repeated fractional crystallization of this product from the minimum amount of ethanol afforded the higher-melting, less soluble fumarate (Va) in about 15% yield, m.p. 170–172° (for analysis see Table II, No. 14). The lower-melting fumarate isomer (Vb) could be isolated from the mother liquors but was best obtained from the hydrochloride (VIb).

A sample of the higher-melting fumarate (Va) was converted to its base (IVa) (see preparation of Vb from VIb). An alcoholic solution of this base was treated with slightly less than one equivalent of alcoholic hydrogen chloride, and concentration of the solution deposited the hydrochloride (VIa), m.p. 183–185° (precipitation of VIa did not begin immediately as VIb did from IVb).

(27) Generally, the analogous xanthen- and thioxanthen-$\Delta^{9,\gamma}$-propylamine bases were high boiling viscous oils. The dimethylaminopropyl derivatives were readily purified as the hydrochloride salts, since any residual 3-chloro-*N,N*-dimethylpropylamine or by-products from the Grignard reagent could be removed by washing an ethereal solution of the crude reaction product (Procedure A or C) with water. However, the (1-methyl-4-piperazino)propyl derivatives could not be purified this way. In these cases the excess Grignard reagent, or by-products derived from it, could not be removed by washing with water. Accordingly these compounds were isolated as dimaleates, difumarates or dinitrates which could be converted (*via* the free bases) to the desired hydrochlorides.

Anal. Calcd. for $C_{19}H_{21}NO_2 \cdot HCl$ (331.84): C, 68.8; H, 6.68; Cl, 10.7; N, 4.22. Found: C, 68.0; H, 6.81; Cl, 10.7; N, 4.45.

The melting point of this hydrochloride changed to 190–194° on standing for 2 weeks. A mixed melting point with a sample of VIb, prepared from Vb, was not depressed.

2-Methoxyxanthen-9-one (VII). *Isolation from the decomposition of 2-methoxy-N,N-dimethylxanthen-$\Delta^{9,\gamma}$-propylamine.* An ethereal solution of the free base (IV), 5.0 g. (00.017 mole), in a glass-stoppered flask, was allowed to stand for 2 months at room temperature. During the latter part of this period a large cluster of crystals formed, 0.6 g., m.p. 126–129°, which did not dissolve in 2*N* hydrochloric acid. Recrystallization from methanol yielded 0.5g. (13%) of 2-methoxyxanthen-9-one, m.p. 131–132° (lit.,[28] m.p. 130–131°). Its mixture melting point, infrared and ultraviolet spectra ($\lambda_{max}^{CH_3OH}$ 234 mμ, ε 39,100; 247 mμ, ε 33,200; 298 mμ, ε 4,290; 358 mμ, ε 6,550) were identical with those of an authentic sample.

Anal. Calcd. for $C_{14}H_{10}O_3$ (226.22): C, 74.4; H, 4.46. Found: C, 74.1; H, 4.54.

Hydrogen peroxide oxidation of 2-methoxy-N,N-dimethylxanthen-$\Delta^{9,\gamma}$-propylamine. A 50-ml. methanol solution of 4.0 g. (0.014 mole) of 2-methoxy-*N,N*-dimethylxanthen-$\Delta^{9,\gamma}$ propylamine (from VIb) was divided into two 25-ml. portions. Fraction A was treated with 1.0 ml. of 30% hydrogen peroxide (approx. 1 equivalent) and fraction B received 2.0 ml. of 30% hydrogen peroxide (approx. 2 equivalents). Both fractions were kept in glass-stoppered flasks at room temperature. After 48 hr. no changes in the ultraviolet spectra were noticed. Fraction A was then treated with an additional equivalent of hydrogen peroxide while fraction B received two additional equivalents. Fraction B, 24 hr. later, deposited 100 mg. (6.6% yield) of 2-methoxyxanthen-9-one, m.p. 131-132°. Nine days later, fraction A deposited 150 mg. (10% yield) of 2-methoxyxanthen-9-one, while fraction B deposited an additional 250 mg. (16.6% yield) of this compound.

Air-oxidation of 2-methoxy-N,N-dimethylxanthen-$\Delta^{9,\gamma}$-propylamine. A steady stream of air was passed through a solution of 4.0 g. (0.014 mole) of 2-methoxy-*N,N*-dimethylxanthen-$\Delta^{9,\gamma}$-propylamine in 40 ml. of ethanol for 12 days. A 10-ml. aliquot was removed and the solvent was evaporated. The residue, 1.0 g., was essentially unchanged starting material, shown by its infrared spectrum. A slight shoulder at 6.0 μ was apparent. 2-Methoxyxanthen-9-one shows a strong absorption peak at 6.03–6.05 μ, and 2-methoxy-*N,N*-dimethylxanthen-$\Delta^{9,\gamma}$-propylamine has no absorption in this region. After 12 more days of air oxidation, no further change in the infrared spectrum was observed. It may be concluded, therefore, that under the above conditions, 2-methoxy-*N,N*-dimethylxanthen-$\Delta^{9,\gamma}$-propylamine was not oxidized to any appreciable extent. On the other hand, when 1.0 g. (3.4 mmoles) of the oily base was streaked on a glass slide and allowed to stand for several days exposed to air, a solid product was formed. On recrystallization from methanol 0.5 g. (65% yield) of 2-methoxyxanthen-9-one, m.p. 130–131°, was obtained.

9-(3-Dimethylaminopropylidene)xanthen-2-ol hydrochloride. 2-Methoxy-*N,N*-dimethylxanthen-$\Delta^{9,\gamma}$-propylamine hydrochloride, 9.3 g. (0.028 mole) was heated under reflux for 18 hr. in 50 ml. of 48% hydrobromic acid. The resultant dark red solution was diluted with 100 ml. of water, and made slightly alkaline with potassium carbonate. The mixture was then extracted with three 75-ml. portions of ether, and the combined ether extracts were washed with water. The dried (magnesium sulfate) ethereal extract was treated with anhydrous hydrogen chloride and evaporated. The residue was dissolved in 300 ml. of hot ethanol, and decolorized with charcoal. On standing, the white crystalline product separated. It was collected by filtration and recrystallized from 200 ml. of 95% ethanol-dimethylformamide (3:1); yield, 3.5 g. (57%) of pure product, m.p. 219–221° dec. (for analysis see Table II, No. 16).

N,N-Dimethylxanthene-9-propylamine hydrochloride. N,N-Dimethylxanthen-$\Delta^{9,\gamma}$-propylamine hydrochloride, 4.83 g. (0.016 mole), was dissolved in 75 ml. of absolute ethanol and hydrogenated at room temperature and atmospheric pressure in the presence of 250 mg. of platinum oxide. The reduction proceeded very rapidly, and the theoretical amount of hydrogen was absorbed in about 15 min. At the end of 35 min. the reduction was discontinued. The actual uptake of hydrogen was 457 ml. (theoretical was 445 ml. including the 50 ml. taken up by the platinum oxide). The reaction mixture was filtered and the filtrate evaporated to dryness. The residue was a clear viscous oil. A sample was triturated in petroleum ether (b.p. 90–100°) and then in benzene. The semisolid gum was then dissolved in a few drops of hot acetone and cooled. The crystalline material, so obtained, was used to seed the crystallization of the rest of the product. When the oil had solidified, recrystallization from hot acetone yielded 4.35 g. (90% yield) of product, m.p. 108–110°. A second recrystallization raised the m.p. to 136–138°.

Anal. Calcd. for $C_{18}H_{21}NO \cdot HCl$ (303.83): C, 71.2; H, 7.30; Cl, 11.7; N, 4.61. Found: C, 70.7; H, 7.38; Cl, 11.5; N, 4.46.

3-Chloro-α-(3-dimethylaminopropyl)benzhydrol hydrochloride (XI). The Grignard reagent from 6.95 g. (0.286 g.-atom) of magnesium and 34.8 g. (0.286 mole) of 3-chloro-*N,N*-dimethylpropylamine in 250 ml. ether was prepared according to Procedure A. A solution of 31 g. (0.143 mole) of *m*-chlorobenzophenone[29] in 200 ml. of anhydrous benzene was added in portions and the reaction mixture was heated under reflux for 12 hr. The reaction mixture was decomposed with 20% aqueous ammonium chloride solution, and the organic phase separated. It was washed with water and extracted with two 150-ml. portions of *N* hydrochloric acid. On standing at room temperature for 3 hr. the crystalline product separated from the acidic extract. Recrystallization from alcohol-ether afforded 32 g. (66% yield) of product, m.p. 205–207°.

Anal. Calcd. for $C_{18}H_{22}ClNO \cdot HCl$ (340.28): C, 63.5; H, 6.81; Cl, 20.8; N, 4.12. Found: C, 63.4; H, 7.21; Cl, 20.9; N, 4.11.

4-(m-Chlorophenyl)-N,N-dimethyl-4-phenyl-3-butenylamine hydrochloride (X). Five grams (0.015 mole) of 3-chloro-α-(3-dimethylaminopropyl)benzhydrol hydrochloride (XI) was dehydrated with 10 ml. of concd. hydrochloric acid and 30 ml. of glacial acetic acid by heating under reflux for 3 hr. The reaction mixture was cooled, diluted with 100 ml. of water, and made alkaline with an excess of potassium carbonate. The free base was extracted with ether and converted to the hydrochloride in the usual way. Recrystallization of the crude product from 10 ml. alcohol and ether (to the cloud point) yielded 3.4 g. (70% yield) of product, m.p. 132–134°.

Anal. Calcd. for $C_{18}H_{20}ClN \cdot HCl$ (322.27): C, 67.1; H, 6.56; Cl, 22.0; N, 4.35. Found: C, 67.0; H, 6.83; Cl, 21.8; N, 4.28.

Attempted desulfurization of 2-chloro-N,N-dimethylthioxanthen-$\Delta^{9,\gamma}$-propylamine hydrochloride. 2-Chloro-*N,N*-dimethylthioxanthen-$\Delta^{9,\gamma}$-propylamine hydrochloride (prepared by Procedures A and E), 5.0 g. (0.014 mole), and 15 g. of Raney nickel were heated under reflux, with stirring, for 24 hr. The mixture was filtered, and the filtrate evaporated to dryness. The residue was recrystallized from alcohol-ether to give unchanged starting material, 4.0 g. (80% yield), m.p. 191–193°. A mixed melting point was unchanged.

N-m-Chlorophenyl-N',N'-dimethyl-N-phenyl-1,3-propanediamine hydrochloride (XIII). A mixture of 18.0 g. (0.09 mole of *m*-chlorodiphenylamine[30] and 5.9 g. (0.15 mole) of sodium

(28) F. Ullmann and H. Kipper, *Ber.*, **38**, 2120 (1905).

(29) (a) A. Hantzsch, *Ber.*, **24**, 51 (1891); (b) F. Smeets and J. Verhulst, *Bull. Soc. Chim. Belges*, **61**, 694 (1952).

(30) F. Ullmann, *Ann.*, **355**, 312 (1907).

amide in 300 ml. of anhydrous benzene was heated under reflux for 3 hr. 3-Chloro-*N*,*N*-dimethylpropylamine, 16.5 g. (0.13 mole), in 50 ml. of anhydrous benzene was added dropwise over a 30-min. period and the mixture was heated under reflux with stirring for an additional 5 hr. The excess sodium amide was decomposed with 25 ml. of ethanol followed by 50 ml. of water. The aqueous phase was separated and extracted with ether. The benzene and ether phases were combined, washed with water and then extracted with two 100-ml. portions of *N* hydrochloric acid. The acidic extracts were made alkaline with excess sodium carbonate, and extracted several times with ether. The ether extracts were dried and evaporated. Distillation of the residue yielded 21.0 g. (73% yield) of product, b.p. 152–155°/0.5 mm.

Anal. Calcd. for $C_{17}H_{21}ClN_2$ (288.82): C, 70.7; H, 7.33; Cl, 12.3; N, 9.70. Found: C, 69.9; H, 7.58; Cl, 12.3; N, 9.84.

The hydrochloride melted at 138–139°.

Anal. Calcd. for $C_{17}H_{21}ClN_2 \cdot HCl$ (325.28): C, 62.8; H, 6.81; Cl, 21.8; N, 8.61. Found: C, 62.4; H, 6.93; Cl, 22.1; N, 8.36.

α-(3-Dimethylaminopropyl)-o-hydroxybenzhydrol (XIV). The Grignard reagent was prepared according to Procedure A from 5.75 g. (0.236 g.-atom) of magnesium and 28.7 g. (0.236 mole) of 3-chloro-*N*,*N*-dimethylpropylamine in 250 ml of ether. *o*-Methoxybenzophenone,[31] 25 g. (0.118 mole), in 200 ml. of ether was added in small portions. The reaction mixture was heated under reflux for 16 hr., cooled and decomposed with 250 ml. of a cold 10% aqueous ammonium chloride solution. The organic phase was separated and extracted with 250 ml. of 0.5*N* hydrochloric acid. The acidic aqueous phase was made alkaline with potassium carbonate and extracted with ether. The dried ether extract was evaporated to a solid residue. Recrystallization from ethanol yielded 20 g. (56.5%) of product, m.p. 116–117°.

Anal. Calcd. for $C_{18}H_{23}NO_2$ (385.37): C, 75.8; H, 8.12; N, 4.91. Found: C, 75.0; H, 8.06; N, 4.90.

o-(4-Dimethylamino-1-phenyl-1-butenyl)phenol hydrochloride (XV). A mixture of 5 g. (0.018 mole) of α-(3-dimethylaminopropyl)-*o*-hydroxybenzhydrol (XIV), 10 ml. of concd. hydrochloric acid, and 30 ml. of glacial acetic acid was heated under reflux for 3 hr., cooled, diluted with 75 ml. of water, and made alkaline with an excess of potassium carbonate. The free base was extracted with ether and converted to the hydrochloride in the usual way. The yield of the hydrochloride was 4.0 g. (70%), m.p. 184–185°.

Anal. Calcd. for $C_{18}H_{21}NO \cdot HCl$ (303.83): C, 71.2; H, 7.30; Cl, 11.7; N, 4.61. Found: C, 71.0; H, 7.22; Cl, 12.2; N, 4.57.

9-(3-Dimethylaminopropyl)fluoren-9-ol (XVII). The Grignard reagent was prepared from 4.9 g. (0.2 g.-atom) of magnesium and 24.3 g. (0.2 mole) of 3-chloro-*N*,*N*-dimethylpropylamine in 150 ml. of ether as described in Procedure A. Fluoren-9-one, 18.1 g. (0.1 mole), in 150 ml. of benzene was added and the reaction mixture (a yellow suspension) was heated under reflux until all the magnesium was consumed (30 hr.). The reaction was worked up according to Procedure B, and the fluoren-9-ol derivative was isolated as the free base. Recrystallization from alcohol afforded 8.0 g. (30% yield) of product, m.p. 101–103°.

Anal. Calcd. for $C_{18}H_{21}NO$ (267.36): C, 80.9; H, 7.92; N, 5.24. Found: C, 80.6; H, 7.95; N, 5.37.

N,N - Dimethylfluoren - Δ⁹,γ - propylamine hydrochloride (XVI). Six grams (0.02 mole) of 9-(3-dimethylaminopropyl)-fluoren-9-ol in 100 ml. of ether was dehydrated by passing hydrogen chloride through the solution for 15 min. The reaction mixture was evaporated and the residue was dissolved in water. The aqueous solution was made alkaline with 10% sodium hydroxide and extracted with ether. The product was isolated as the hydrochloride from the ethereal solution by the addition of alcoholic hydrogen chloride. Recrystallization from alcohol-ether afforded 4.5 g. (71% yield) of product, m.p. 205–207°.

Anal. Calcd. for $C_{18}H_{19}N \cdot HCl$ (285.81): C, 75.6; H, 7.05; Cl, 12.4; N, 4.90. Found: C, 75.4; H, 7.35; Cl, 12.5; N, 5.18.

Acknowledgment. We are indebted to N. Q. Quinones, L. H. Yogodzinski, and Miss B. A. Carpentier for their technical assistance; J. H. Clark and his group for the preparation of some of the intermediates; L. Brancone and associates for the microanalyses; and W. Fulmor and associates for the spectral data.

PEARL RIVER, N. Y.

(31) T. Tasaki, *Acta Phytochim.*, 2, 49 (1925); *Chem. Abstr.*, 20, 1030 (1926).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF MICHIGAN]

Synthesis of Potential Anticancer Agents. IX. Lawsone Derivatives Containing an Alkylating Function[1,2]

W. R. VAUGHAN, M. S. HABIB, R. S. McELHINNEY, N. TAKAHASHI, AND J. A. WATERS

Received July 8, 1960

The Mannich reaction involving lawsone (2-hydroxy-1,4-naphthoquinone) and certain amines with formaldehyde and acetaldehyde has been carried out using modifications of a published procedure. In addition, the condensation product of lawsone with 4-bis(2-chloroethyl)aminobenzaldehyde is described.

It has been reported that lawsone (2-hydroxy-1,4-naphthoquinone) undergoes the Mannich reaction with a variety of primary and secondary amines including ethanolamine and morpholine, but not with diethylamine.[3] With the latter the reaction affords instead what appeared to be the diethylamine salt of 3,3′-methylenebis(2-hydroxy-1,4-naphthoquinone) (I).

(1) Previous paper in this series, P. Scheiner and W. R. Vaughan, *J. Org. Chem.*, 26, 1923 (1961).

(2) This work supported by Research Grant CY-2961 from the National Cancer Institute to the University of Michigan.

(3) M. T. Leffler and R. J. Hathaway, *J. Am. Chem. Soc.*, 70, 322 (1948).

Although the latter information would appear to be discouraging if one wished to use aziridine (ethylenimine), bis (2-chloroethyl)amine, or diethanolamine, it was believed that further exploration would reveal experimental conditions for satisfactory reaction. To this end the reaction of lawsone, formaldehyde, and morpholine was repeated with substantially the reported results[3] to give 4 - (4′ - morpholino)methyl - 2 - hydroxy - 1,4-naphthoquinone (II), but when exactly the same procedure was applied to diethanolamine, an orange precipitate was obtained which appeared to be the diethanolamine salt of I, since on treatment with dilute hydrochloric acid I was obtained. Thus it would appear that the course of the reaction was similar to that encountered by Leffler and Hathaway with diethylamine.[3]

Several modifications in the procedure were investigated, and finally it was found that addition of solid lawsone to a solution of diethanolamine[4] and formalin in absolute ethanol at 30–35° afforded an acid-soluble product which could be recovered from 5% hydrochloric acid by addition of sodium acetate. Microanalysis indicated that the product was a monohydrate of the expected 3- bis(2′ - hydroxyethyl)aminomethyl - 2 - hydroxy - 1,4 - naphthoquinone (III). However, any and all attempts to effect recrystallization resulted in decomposition with the apparent production of the diethanolamine salt of I originally encountered, for I was produced from it on treatment with 5% hydrochloric acid. Likewise, all attempts to convert II or III to 3-bis(2′-chloroethyl)aminomethyl-2- hydroxy - 1,4 - naphthoquinone (IV), the corresponding nitrogen mustard, resulted in production of a salt of I.

When ethylenimine was used in the Mannich reaction with lawsone and formaldehyde, it was found necessary to add the lawsone to the other reagents at 4–6°, whereupon a good yield of 3-aziridinomethyl - 2 - hydroxy - 1,4 - naphthoquinone (V) was obtained as a hydrate. The product was found to be slightly soluble in ice-cold 2% hydrochloric acid, from which it is recoverable if sodium acetate is added immediately. On standing the acidic solution deposits I, which is also obtained, presumably as the ethyleneimine salt, upon all attempts to effect recrystallization.

The possibility that azetidine derivatives might behave analogously to ethylenimine derivatives as "alkylating agents" has been suggested elsewhere.[5] With this in mind the reaction of lawsone, formaldehyde, and azetidine was carried out in a fashion similar to the ethylenimine reaction with satisfactory results. A 50% yield of 3-*N*-azetidinomethyl - 2 - hydroxy - 1,4 - naphthoquinone (VI) was obtained, and this substance proved to be comparatively stable. Indeed it was recrystallizable from methanol.

The reaction of lawsone and formaldehyde with nitrogen mustard (bis(2-chloroethyl)amine), proved very difficult, but it was finally found that the most satisfactory procedure for carrying out the Mannich reaction with lawsone and secondary amines of the type desired involved addition of an ethanol solution of lawsone to the amine and formaldehyde in absolute ethanol at low temperature. In this manner the condensation product constitutes the only solid present at any time in the reaction mixture; and by careful manipulation II, III, and IV can be obtained analytically pure.

As a check on the superior character of this technique for sensitive compounds, diethylamine was similarly condensed, and a satisfactory yield of the previously unavailable[3] 3-diethylaminomethyl-2-hydroxy-1,4-naphthoquinone (VII) was obtained.

The behavior of compounds III—V with dilute hydrochloric acid and with glacial acetic acid deserves some comment. Compound III is apparently soluble and stable in dilute hydrochloric acid; V with ice-cold 2% hydrochloric acid appears to form a semihydrochloride (VIII) which is rather insoluble and which decomposes on standing in contact with the acid; and both IV and V decompose at once with more concentrated hydrochloric acid even at 0°. In all hydrochloric acid decompositions I is precipitated, and the change is readily observed, since the red Mannich products rapidly become bright yellow as I is produced from them.

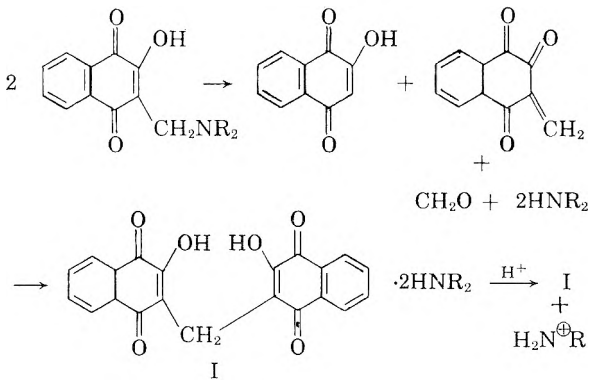
With glacial acetic acid IV immediately decomposes to give I while the others do so more slowly, the relative rates being in the order: IV > V > VIII > III < VII. Furthermore, each of these substances affords the diacetate of I[6] when treated with acetic anhydride containing a drop of concentrated sulfuric acid.

In the absence of acids the same type of decomposition is encountered, though more slowly, and appears to be heat-induced, although the acidic character of the lawsone hydroxyl may provide a weak autocatalysis. For example, when only one equivalent of sodium acetate is used to "neutralize" a hydrochloric acid solution of III, the decomposition is rapid, whereas an excess of sodium acetate regenerates III smoothly. It would appear that this decomposition involves a reversal of the Mannich reaction to produce 3-methylene-1,2,4-trioxotetralin and lawsone which then react by addition to give I. Where an acid is present I precipitates directly; otherwise, the corresponding amine salt is formed.

(4) The procedure developed herein differs from that of C. L. Dalgliesh, *J. Am. Chem. Soc.*, 71, 1697 (1949), in that the amine is always present in excess and thus the medium is always alkaline. Consequently, the *free* amine is available, and this is what is required for the production of the C—N bond.

(5) W. R. Vaughan, R. S. Klonowski, R. S. McElhinney, and B. B. Millward, *J. Org. Chem.*, 26, 138 (1961).

(6) L. F. Fieser, M. T. Leffler, *et al.*, *J. Am. Chem. Soc.*, 70, 3212 (1948).



Inasmuch as lawsone condenses readily with aldehydes other than formaldehyde to give analogs of I[4,6], *e.g.*, with 4-dimethylaminobenzaldehyde, the procedure for condensation of the latter was applied to 4-bis(2-chloroethyl)aminobenzaldehyde,[7] with some modification, and there was obtained in fair yield di(2 - hydroxy - 1,4 - naphthoquinon - 3-yl) - 4 - bis(2 - chloroethyl)aminophenylmethane (IX). Considerable difficulty was encountered in purifying this substance, substantial decomposition to unidentified materials occurring in most cases, but recrystallization was finally effected by dissolving the crude product in dimethylformamide at room temperature and then adding the solution dropwise to a large excess of ethanol.

Acetaldehyde has been rarely used in Mannich reactions, but a search of the literature revealed that open chain compounds from a Mannich-type reaction when acetaldehyde was employed were available with Lawsone.[4]

When aldehydes other than formaldehyde enter into a Mannich-type reaction, the amines are generally limited to ammonia or primary amines and their salts. It was therefore interesting to note that we encountered no difficulty using secondary amines, as well as primary amines. The compounds were generally obtained from the reaction mixture in pure form. If the reaction mixture required working up, room temperature to moderate temperatures were employed without subsequent recrystallization. As for the formaldehyde reactions, the yields were low in certain instances, as the reaction was often accompanied by dark, intractable tars.

Eight compounds derived from acetaldehyde have been prepared, two of which were derived from primary amines and the others from secondary amines. It is interesting to note that the nitrogen mustard compound was chromophorically different from the others, in that it was obtained as a bright yellow compound, while the others were consistently orange, red, or reddish brown.

(7) R. C. Elderfield, I. S. Covey, J. B. Geiduschek, W. L. Meyer, A. B. Ross, and J. H. Ross, *J. Org. Chem.*, **23**, 1749 (1958).

EXPERIMENTAL[8,9]

3,3'-Methylene-bis(2-hydroxy-1,4-naphthoquinone) (I). This substance was prepared essentially as described by Fieser.[5]

3-Bis(2'-hydroxyethyl)aminomethyl-2-hydroxy-1,4-naphthoquinone (III). (A) *Using solid lawsone.* To a solution of 2.8 ml. of 37% formalin and 3.8 g. (0.036 mole) of redistilled diethanolamine in 50 ml. of absolute ethanol was added with mechanical stirring 5.8 g. (0.033 mole) of lawsone in portions over 45 min., the temperature being maintained at 30–35° by a water bath. Stirring was continued for 4 hr. at the same temperature during which time golden red needles slowly precipitated. The mixture was filtered, washed with 25 ml. of absolute ethanol and then with water, after which the precipitate was dissolved in *ca.* 100 ml. of 2% hydrochloric acid, filtered from a trace of residue, and then treated with a solution of 10 g. of anhydrous sodium acetate in 25 ml. of water. After overnight standing in the refrigerator the product was filtered off and dried in air at 50°: 8.2 g. (85%), m.p. 111.5° (softens), gradually darkening above 150° and liquefying at 192–198°.

Anal. Calcd. for $C_{15}H_{17}NO_5 \cdot H_2O$: C, 58.24; H, 6.19; N, 4.53. Found[10]: C, 58.47; H, 6.10; N, 4.26, 4.31.

(b) *Using lawsone solution.* To 2.8 ml. of 37% formalin and 3.8 g. (0.036 mole) of diethanolamine there was added with efficient stirring over a 4-hr. period a filtered solution of 4.9 g. (0.028 mole) of lawsone in 450 ml. of absolute ethanol. The temperature was maintained at 23–25° by a water bath. At the end of the addition there was added 50 ml. of absolute ethanol, and stirring was continued for 30 min. The orange-red precipitate, which appeared in the initial stages of the reaction, was filtered off and washed with two 50-ml. portions of absolute ethanol: 5.5 g. (68%), slow decomposition from 158–172°. The analytical sample was dried *in vacuo* at room temperature over phosphorus pentoxide.

Anal. Calcd. for $C_{15}H_{17}NO_5$: C, 61.86; H, 5.87; N, 4.81. Found: C, 61.89; H, 5.85; N, 4.78.

Purification of this product by solution in 2% hydrochloric acid with reprecipitation by sodium acetate as in the previous experiment produced no change after the product was dried *in vacuo* over phosphorus pentoxide. When the reprecipitation was effected by using but one equivalent of sodium acetate, only I was recoverable, as shown by melting point and mixed melting point.

3-Bis(2'-chloroethyl)aminomethyl-2-hydroxy-1,4-naphthoquinone (IV). To a suspension of 1.5 g. (0.0084 mole) of bis(2-chloroethyl)amine hydrochloride in 20 ml. of ether was added 0.75 g. (0.0090 mole) of sodium bicarbonate in 15 ml. of water. The mixture was shaken and separated, and the aqueous layer was extracted with two 20-ml. portions of ether. The combined ethereal solutions were placed in the reaction vessel and the ether removed at reduced pressure, and to the free nitrogen mustard was added 25 ml. of absolute ethanol containing 0.4 ml. of 37% formalin. The mixture was cooled and maintained at 14–16° while a filtered solution of 0.8 g. (0.0046 mole) of lawsone in 80 ml. of absolute ethanol was added over 1 hr., with magnetic stirring. During the addition an orange solid separated, and stirring was continued for 45 min. after completion of the addition—until the mixture reached room temperature (after removal of the cooling bath). The product was filtered with suction and repeatedly washed with ethanol: 0.70 g. (46%), darkens slowly above 125°. The analytical sample was dried as for III (B).

Anal. Calcd. for $C_{15}H_{15}Cl_2NO_3$: C, 54.89; H, 4.60; Cl, 21.61; N, 4.27. Found: C, 55.16; H, 4.78; Cl, 21.73; N, 4.19.

(8) Melting points, taken in open capillaries, are uncorrected.

(9) Microanalyses by Spang Microanalytical Laboratories, Ann Arbor, Mich., unless otherwise indicated.

(10) Carbon and hydrogen analysis by Mrs. Anna Griffen, University of Michigan.

TABLE I

3-AMINOETHYLIDENE-2-HYDROXY-1,4-NAPHTHOQUINONES[a,s]

R_1	R_2	Reaction Temp.	Notes	Yield, %	Dec.[b]	Calcd. for	C	H	N	Cl
C_2H_5[c]	H	5	[d]	36.6	148	$C_{14}H_{15}NO_3$	68.55	6.16	5.71	
						Found	68.53	6.25	5.73	
$HOCH_2CH_2$	H	40	[e]	12.8	124	$C_{14}H_{15}NO_4$	64.35	5.78	5.36	
						Found	64.18	5.68	5.27	
C_2H_5	C_2H_5	25[f]	[g]	4.8	185	$C_{16}H_{19}NO_3$	70.30	7.02	5.12	
						Found	70.36	6.85	4.91	
$HOCH_2CH_2$	$HOCH_2CH_2$	5–10	[h]	21.7	121–122	$C_{16}H_{19}NO_5$	62.93	6.29	4.58	
						Found	63.06	6.47	4.68	
$ClCH_2CH_2$	$ClCH_2CH_2$[i]	5–10	[j]	15.6	156–157[k]	$C_{16}H_{17}Cl_2NO_3$	56.16	5.00	4.09	20.72
						Found	56.41	5.28	3.53	20.56
—$(CH_2)_5$—		20–25[l]	[m]	30.0	169[n]	$C_{17}H_{19}NO_3$	71.55	6.73	4.91	
						Found	71.67	6.97	4.92	
—$(CH_2)_2O(CH_2)$—		20–25	[o]	5.8	154	$C_{16}H_{17}NO_4$	66.89	5.95	4.87	
						Found	66.89	6.09	4.59	
—$(CH_2)_2$—		20–25[p]	[q]	0.2 g.[r]	164	$C_{14}H_{13}NO_3 \cdot {}^1/_2H_2O \cdot {}^1/_4C_2H_5N$	66.45	5.50	6.67	
						Found	66.23	5.55	6.50	

[a] See general procedure immediately preceding. [b] Where no range is reported, product decomposes slowly above recorded temperature. [c] A 70% aqueous solution of ethylamine was used. [d] After the reaction 50 ml. of dry ether was added and the solution filtered after 3 days refrigeration. [e] The reaction was stirred at 40° overnight, then refrigerated. Product washed with ethanol also. [f] Only 80 ml. of absolute ethanol used for lawsone. [g] After reaction, the solution was air-evaporated to 40 ml.; then diluted with 40 ml. of ether and cooled. [h] After reaction, the solvent was removed *in vacuo* at 40–50°. Then 40 ml. of dry ether was added and the solution refrigerated. [i] The mustard hydrochloride (1.5 g.) was suspended in ether and extracted with 0.75 g. of sodium bicarbonate in 15 ml. of water. Aldehyde in 10 ml. absolute ethanol was added to ether solution of free mustard. [j] After the reaction was stirred for 30 min. at room temperature, the product was washed with ethanol alone. [k] Product bright yellow. [l] Amine and aldehyde in 15 ml. absolute ethanol, lawsone in 75 ml. [m] After the reaction, the solvent was evaporated in air stream to 10 ml. [n] Original product recrystallized from ethanol-ether and washed with ether. [o] After the reaction was refrigerated, it was filtered and washed with ethanol alone. [p] Amine and aldehyde in 15 ml. absolute ethanol. [q] After the reaction was stirred for 30 min., it was refrigerated for several hours, filtered, and washed with ethanol alone. [r] Product was not the expected pure 3-aziridinoethylidene-2-hydroxy-1,4-naphthoquinone. [s] These data added to original manuscript: received December 2, 1960.

3-Aziridinomethyl-2-hydroxy-1,4-naphthoquinone (V). Using essentially the procedure described above (for III (A)) with 2.8 ml. of 37% formalin, 1.6 g. (1.9 ml.) of ethylenimine (aziridine), 50 ml. of absolute methanol, and 5.8 g. (0.033 mole) of lawsone (30 min. portionwise addition at 4–6°), there was obtained 7.2 g. (98%) of bright red product which chars slowly above 162°.

Anal. Calcd. for $C_{13}H_{11}NO_3 \cdot H_2O$: C, 63.15; H, 5.30; N, 5.67. Found: C, 62.68; H, 5.40; N, 5.42.

No satisfactory recrystallization could be effected, but an unaltered product is recoverable from cold 2% hydrochloric acid, in which it is not appreciably soluble, by treatment with sodium acetate. Upon shaking a 0.5-g. sample in 75 ml. of ice-cold 2% hydrochloric acid for 5 min. and filtering off the residual solid and washing it with water, there was obtained 0.49 g. of a substance which darkens slowly above 140° (VIII).

Anal. Calcd. for $C_{13}H_{11}NO_3 \cdot H_2O.1/2HCl$: C, 58.81; H, 5.13; Cl, 6.68; N, 5.27. Found: C, 58.70; H, 5.19; Cl, 6.35; N, 5.37.

From the acidic filtrate from VIII, upon addition of sodium acetate there was recovered a small amount of V, identified by infrared spectrum. A small sample of VIII was treated with 5% sodium bicarbonate, and the red precipitate was filtered from the dark red solution (not observed on similar treatment of V), which was then treated with dilute nitric acid and centrifuged from an orange precipitate (I) and treated with silver nitrate to give silver chloride.

3-N-Azetidinomethyl-2-hydroxy-1,4-naphthoquinone (VI). This substance was prepared essentially as for V (A) using 2.8 ml. of 37% formalin, 2.0 g. (0.035 mole) of azetidine[5] (in 50 ml. of absolute ethanol), and 5.8 g. (0.033 mole) of solid lawsone, added over 30 min. at 4–6°. After complete addition, 25 ml. more absolute ethanol was added and stirring was continued for 5 hr. while the temperature was allowed to rise slowly to 25°. Filtration and drying afforded 4.05 g. (50%) of brick-red product: after recrystallization from methanol, dull red needles, indefinite decomposition above 160°.

Anal. Calcd. for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.14; H, 5.42; N, 5.34 (0.40% ash).

3-Diethylaminomethyl-2-hydroxy-1,4-naphthoquinone (VII). To a stirred solution of 0.5 ml. of 37% formalin and 0.6 g. (0.008 mole) of diethylamine in 15 ml. of absolute ethanol was added a filtered solution of 1.0 g. (0.006 mole) of lawsone in 100 ml. of absolute ethanol (1 hr. 50 min. at 10–15°). No separation of solid was observed, even after cooling to 0°. Consequently the solvent was evaporated at room temperature in an air stream, whereupon a deep red (almost violet) precipitate was obtained. After suction filtration and several washings with small amounts of cold ethanol there was obtained 1.3 g. (83%): m.p., 145.0–147.5° dec.

Anal. Calcd. for $C_{15}H_{17}NO_3$: C, 69.49; H, 6.59; N, 5.40. Found[11]: C, 69.31; H, 6.79; N, 5.52.

This substance dissolved in hot acetic acid with the immediate precipitation of I.

Di(2-hydroxy-1,4-naphthoquinon-3-yl)-4-bis(2-chloroethyl)-aminophenylmethane (IX). A solution of 9.1 g. (0.051 mole) of lawsone in 125 ml. of ethanol and a filtered solution of 6.2 g. (0.025 mole) of 4-bis(2-chloroethyl) aminobenzaldehyde[7] in 100 ml. of ethanol were mixed and heated under reflux for 4 hr. after which time the solution was concentrated under reduced pressure to 100 ml. and filtered hot. The brick-

(11) Microanalysis by Galbraith Laboratories, Knoxville, Tenn.

red residue (6.0 g.) was dissolved in *ca.* 8 ml. of dimethylformamide at room temperature, and the resultant solution was allowed to drop slowly into 300 ml. of ethanol. The red solution thus produced deposited crimson leaflets. Repetition of the solution-precipitation process afforded 4.0 g. (36%): m.p., 142° dec.

Anal. Calcd. for $C_{21}H_{23}Cl_2NO_6$: C, 64.59; H, 4.02; Cl, 12.32; N, 2.43. Found: C, 64.25; H, 4.29; Cl, 12.61, 12.72; N, 2.48.

Attempts to use several of the more conventional recrystallization techniques were unsuccessful, either achieving no purification or producing tar.

Reactions of Mannich products with acetic acid. In one experiment 0.10-g. samples of III, IV, V, and VIII were added to 2.5 ml. of glacial acetic acid and allowed to stand at room temperature. From III and IV there was obtained 0.05 g. (each), and from V and VIII there was obtained 0.06 g. (each) of I, which was identified by infrared spectrum and melting point. The order in which the original color was replaced by the yellow of I was IV > V > VIII > III. In a separate experiment VII was shown to change color more rapidly than III.

Reactions of Mannich products with acetic anhydride. In a typical experiment a small sample of the substituted aminomethyllawsone was added to 1 ml. of acetic anhydride containing 2 drops of concd. sulfuric acid. Upon being allowed to stand overnight a yellow precipitate appeared. This was identified by infrared spectrum and m.p. (235–237° dec.) as the diacetate of I. The authentic sample for comparison was prepared according to the directions of Fieser[6]: m.p. 235–237° dec., reported m.p., 132–133°.[12]

Anal. Calcd. for $C_{25}H_{16}O_8$: C, 67.57; H, 3.63. Found: C, 67.63; H, 3.72.

Reactions with acetaldehyde. A slight excess of the amine (0.007–0.008 mole) and 0.5 ml. of acetaldehyde was dissolved in 10 ml. of absolute ethanol and treated dropwise with a filtered solution of 1.0 g. (0.006 mole) of lawsone in 100 ml. of absolute ethanol by means of a Hershberg (slow addition) dropping funnel. Addition required 1 hr. The initial precipitate was suction filtered and washed well with 1:1 ethanol-ether and then vacuum dried. Data are collected in Table I. Appreciable additional quantities of less pure products were obtained in every case by evaporation or further dilution of mother-liquors with ether and/or petroleum ether.

ANN ARBOR, MICH.

(12) This value is apparently erroneous and should be 232–233°. In order to confirm this, our synthetic product was analyzed.

[CONTRIBUTION FROM THE KETTERING-MEYER LABORATORY, SOUTHERN RESEARCH INSTITUTE]

Synthesis of Potential Anticancer Agents. XXIX. 5-Diazoimidazole-4-carboxamide and 5-Diazo-*v*-triazole-4-carboxamide[1,2]

Y. FULMER SHEALY, ROBERT F. STRUCK, LEE B. HOLUM, AND JOHN A. MONTGOMERY

Received October 19, 1960

The initial product of the diazotization of 5(or 4)-aminoimidazole-4-(or 5)-carboxamide has been isolated and shown to be 5-diazoimidazole-4-carboxamide. The diazo derivative, stable in the absence of moisture, cyclizes in aqueous solutions to the fused-ring isomer, 2-azahypoxanthine. 5-Diazo-*v*-triazole-4-carboxamide and 2,8-diazahypoxanthine have likewise been obtained from 5-amino-*v*-triazole-4-carboxamide. 5-Diazoimidazole-4-carboxamide has anticancer activity *in vitro* and *in vivo*. The structure of the diazoheterocycles is discussed.

The 2-azapurines (imidazo[4,5-*d*]-*v*-triazines) belong to the group of heterocyclic analogs of purines that have shown activity as inhibitors of neoplastic cells[3,4] and of microorganisms.[5] The few known 2-azapurines have been obtained by diazotization of the appropriate aminoimidazoles.[5–8] The reaction of 5(or 4)-aminoimidazole-4(or 5)-carboxamide (I) hydrochloride with sodium nitrite in aqueous solution has been reported to furnish 2-azahypoxanthine (imidazo[4,5-*d*]-*v*-triazin-4-(3*H*)-one) (III) directly in 85% yield.[5]

In the present work, a compound different from 2-azahypoxanthine has been obtained as the initial product of diazotization of 5(or 4)-aminoimidazole-4(or 5)-carboxamide (I) (AIC). The new compound forms, in yields of 70-94%, as a crystalline precipitate when a solution of AIC hydrochloride in 1*N* hydrochloric acid is added to an aqueous solution of sodium nitrite. The nature of the precipitate was first revealed by a positive Bratton-Marshall test,[9] indicative of an aromatic diazo group; by a sharp, intense infrared band—at 2190 cm.$^{-1}$—in the region characteristic of triple-bond and cumulative double-bond structures; and by analytical data in accord with the empirical formula $C_4H_3N_5O$. These and subsequent observations show that the initial product of the diazotization of AIC (I) is 5-diazoimidazole-4-carboxamide, which is represented here by the dipolar structure of

(1) The work described in this paper was presented before the Division of Medicinal Chemistry, 137th Meeting of the American Chemical Society, Cleveland, Ohio, April 5–14, 1960.

(2) This investigation was supported by the C. F. Kettering Foundation and the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Contract No. Sa-43-ph-1740.

(3) A. Fjelde, *Z. Krebsforsch.*, **61**, 364 (1956).

(4) J. J. Biesele, *Cancer*, **5**, 787 (1952).

(5) D. W. Woolley and E. Shaw, *J. Biol. Chem.*, **189**, 401 (1951).

(6) M. R. Stetten and C. L. Fox, Jr., *J. Biol. Chem.*, **161**, 333 (1945).

(7) E. Shaw and D. W. Woolley, *J. Biol. Chem.*, **194**, 641 (1952).

(8) M. A. Stevens, H. W. Smith, and G. B. Brown, *J. Am. Chem. Soc.*, **82**, 3189 (1960).

(9) A. C. Bratton and E. K. Marshall, Jr., *J. Biol. Chem.*, **128**, 537 (1939).

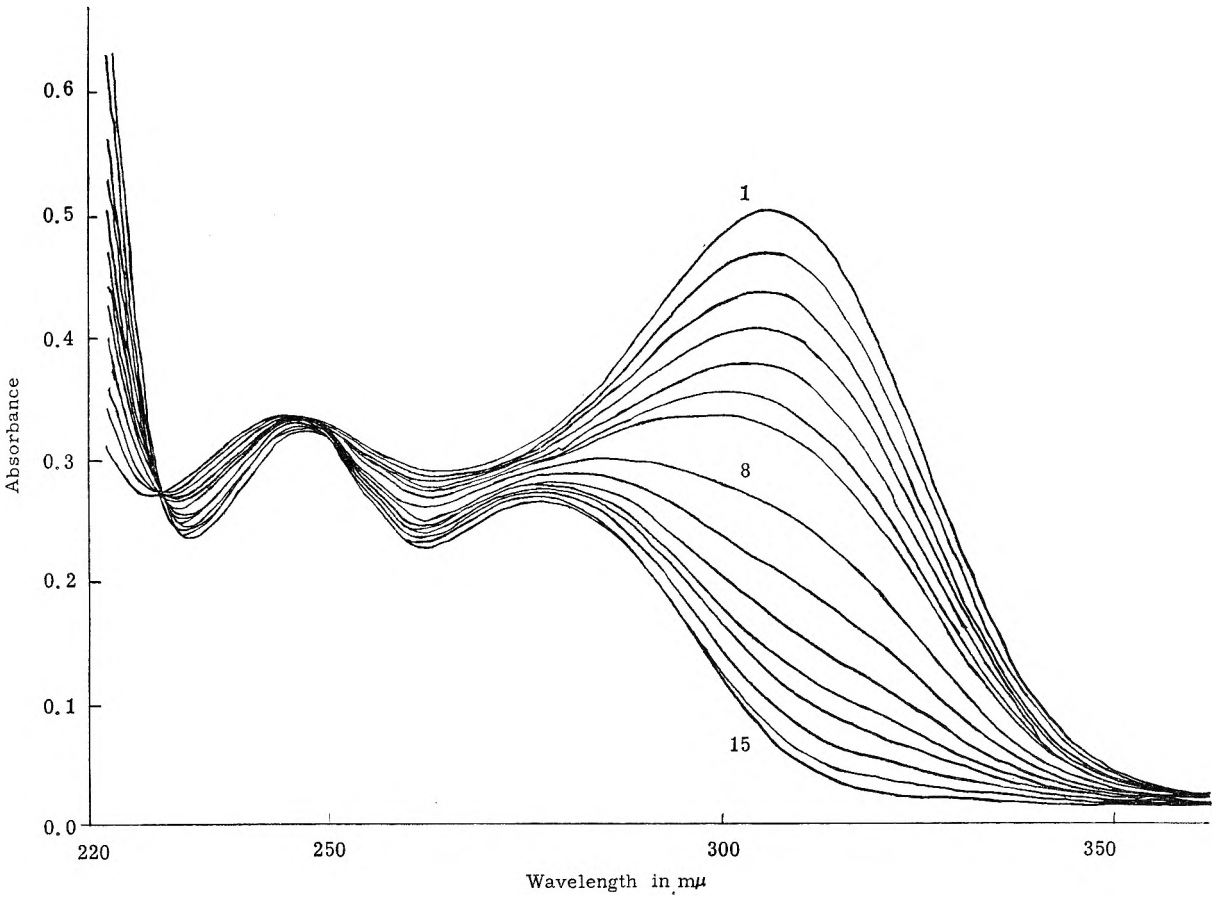
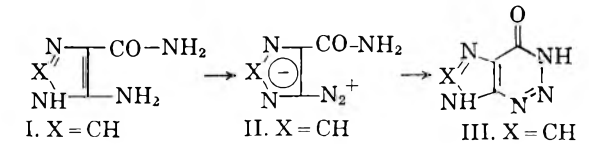


Fig. 1. Ultraviolet spectra showing the cyclization of II to III in 0.1 *N* hydrochloric acid. Curves 1–7 were traced at five-minute intervals after the addition of the solvent to II; curves 8–12, at fifteen-minute intervals after No. 7; and curves 13–15, at thirty-minute intervals after No. 12

an internal diazonium salt (II). The diazo derivative decomposes explosively near 210°; its infrared



I. X = CH
IV. X = N

II. X = CH
V. X = N

III. X = CH
VI. X = N

spectrum clearly distinguishes it from 2-azahypoxanthine. A specimen of II stored for two and one-half years in a stoppered, clear-glass vial under ordinary laboratory conditions had darkened somewhat, but its infrared spectrum was practically identical with that of freshly prepared, analytically pure material.

5-Diazoimidazole-4-carboxamide was readily converted to 2-azahypoxanthine in yields up to 96% by 1*N* aqueous ammonia. In contrast to the diazo intermediate, 2-azahypoxanthine does not give a positive Bratton-Marshall test, displays no distinct absorption in the 2300–2000 cm.$^{-1}$ region of its infrared spectrum, and crystallizes from aqueous solution as a monohydrate. 2-Azahypoxanthine was first isolated as a monohydrate by Stetten and Fox[6] when they diazotized an amine, later[10] shown to be 5(or 4)-aminoimidazole-4(or 5)-carboxamide, which they had isolated from biological sources. The crystallization of 2-azahypoxanthine from aqueous solutions as a monohydrate is in agreement with the original observation of Stetten and Fox rather than that reported later.[5] The strong carbonyl band at 1690 cm.$^{-1}$ indicates that it exists in the keto, rather than the enol, form.

Subsequently, ultraviolet absorption studies revealed that 5-diazoimidazole-4-carboxamide (II) cyclizes to 2-azahypoxanthine in acidic solutions as well as in basic solutions. The course of the cyclization at one level of acidity (0.1*N* hydrochloric acid) is depicted in Fig. 1. Similar families of curves traced at various time intervals were obtained from solutions of II in 6*N* hydrochloric acid, *p*H 3 buffer solution, distilled water (*p*H 5.9), *p*H 7 buffer solution, and 0.1*N* sodium hydroxide. In each of the six solutions the spectrum eventually became identical with that given by 2-azahypoxanthine at the same *p*H. Some of the data obtained in these studies[11] are summarized in Table I and in Fig. 2.

Diazotization of 5-amino-*v*-triazole-4-carboxamide (IV) gave results paralleling those of the

(10) W. Shive, W. W. Ackermann, M. Gordon, M. E. Getzendaner, and R. E. Eakin, *J. Am. Chem. Soc.*, 69, 725 (1947).

TABLE I

ABSORPTION MAXIMA OF 2-AZAHYPOXANTHINE AND 5-DIAZOIMIDAZOLE-4-CARBOXAMIDE

	2-Azahypoxanthine (III)		Solutions of II	
Solvent	λ_{max} (mμ)	$\epsilon \times 10^{-3}$	ΔT (min.)[a]	λ_{max} (mμ)
0.1*N* NaOH	296, 256	6.19, 4.82	2.5	296, 256[b]
*p*H 7	286, 250	4.23, 5.04	3	304,[c] 249
			33	285, 250
Water (*p*H 5.9)	275–277, 249	4.22, 5.1	7	312, 246
			1190[d]	278, 248
*p*H 3			4	312, 246
			1440[e]	278, 248
0.1*N* HCl	277, 248	4.03, 4.98	5[f]	308,[g] 243
			170	277, 248
6*N* HCl	273–274, 245	3.66, 5.01	3.5	293,[g] 232–242
			129	273–274, 245

[a] ΔT as defined in Figure 2. [b] Absorption by II could not be observed because cyclization to III was complete within 2.5 min. [c] Evidently the resultant, due to the rapid rate of cyclization, of the long-wavelength maxima of II and III; therefore, curve E (Fig. 2) was plotted from absorbancies at 312 mμ. [d] Cyclization essentially complete within 3 hr. [e] Cyclization essentially complete within 4–6 hr. [f] λ_{max} same at ΔT = 3.5 min. [g] The hypsochromic shifts in the strongly acidic media may result from protonation of the imidazole ring to a "normal" diazonium salt. The fact that the spectra eventually become identical with those of III in the same media is evidence that replacement of the diazo group by chlorine did not occur.

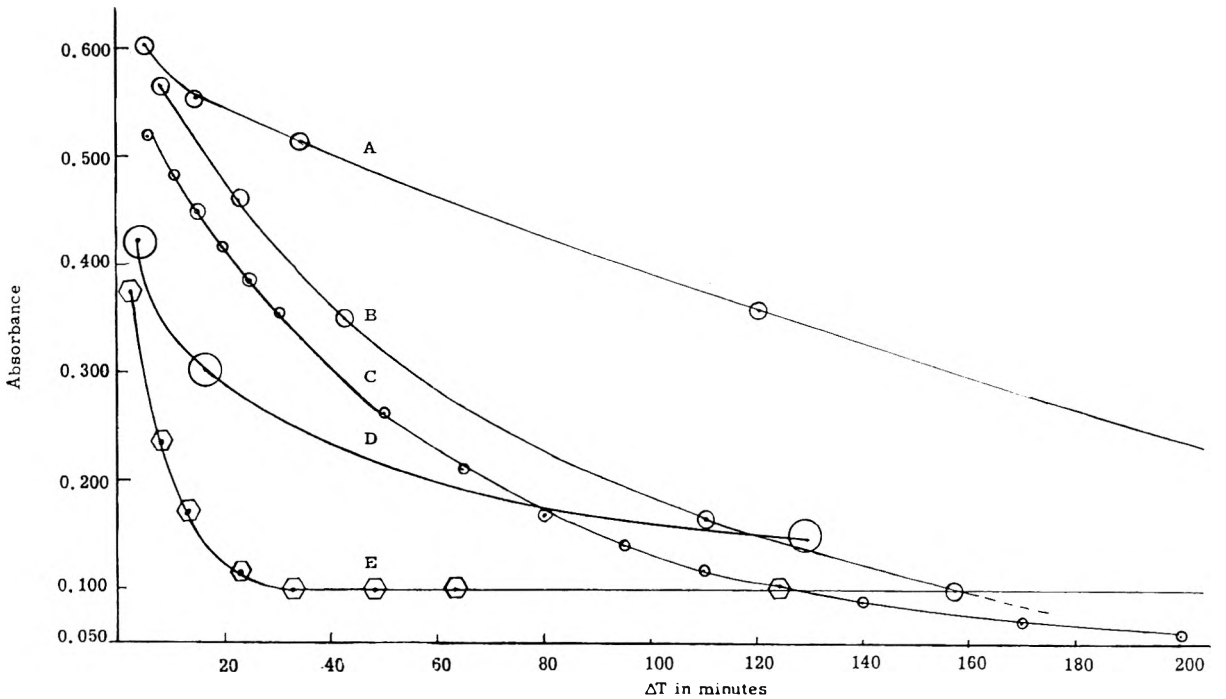


Fig. 2. Cyclization of II to III. A—*p*H 3, A_s at 312 mμ; B—*p*H 5.9, A_s at 312 mμ; C—0.1 *N* hydrochloric acid, A_s at 308 mμ; D—6 *N* hydrochloric acid, A_s at 293 mμ; E—*p*H 7, A_s at 312 mμ (footnote c, Table I). ΔT is the difference between the time at which solvent was added to II and the time at which the recording of a spectrum was begun

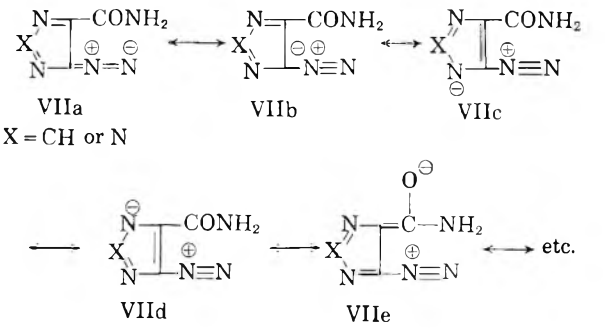
imidazole series. 5-Diazo-*v*-triazole-4-carboxamide (V) was isolated in 52% yield as a crystalline solid which decomposed explosively near 175°, gave a positive Bratton-Marshall test, and exhibited very strong absorption at 2210 cm.$^{-1}$ Ring closure to 2,8-diazahypoxanthine (*v*- triazolo[4,5-*d*]-*v*-triazin-7(6*H*)-one) (VI) was effected in alkaline solution. The diazotriazole is easily distinguished from its fused-ring isomer (isolated as the dihydrate) by the infrared spectra, the diazo frequencies being absent from the spectrum of 2,8-diazahypoxanthine. The keto structure VI is assigned to 2,8-diazahypoxanthine on the basis of a very strong band at 1740 cm.$^{-1}$

An examination of the infrared spectra of the two diazoheterocycles suggests further details of their structures. The broad doublets in the 3300–3100 cm.$^{-1}$ region are typical of the NH-stretching

(11) All of these cyclization studies were made with solutions protected from light. A solution of II at *p*H 5.9 prepared without excluding light and then exposed continuously in the spectrophotometer cell to light at 312 mμ displayed a faster rate of cyclization than a solution of the same *p*H kept in the dark.

vibrations of primary amides.[12] The most prominent bands in the spectra are those of the diazo group[13] near 2200 cm.$^{-1}$ The frequencies of the diazo bands of II (2190 cm.$^{-1}$) and V (2210 cm.$^{-1}$) lie approximately between those of typical aryldiazonium salts[14,15] and those of diazophenols,[15,16] *p*-diazoanilines,[15] and the more complex diazocarbonyl compounds.[17,18,19] Aroney, LeFèvre, and Werner[14] and Whetsel, Hawkins, and Johnson[15] have found that the diazonium group absorbs in the region 2310–2235 cm.$^{-1}$ with only slight shifts due to variation of the anion. More recently, frequency ranges extending to those of II and V have been reported[20]; some typical aryldiazonium cations in the form of triiodides produced bands in the region 2260–2200 cm.$^{-1}$ A strong band in the 1430–1330 cm.$^{-1}$ region of the spectra of certain diazocarbonyl compounds has been observed by Yates, Shapiro, Yoda, and Fugger[17] and by Fahr.[18] The spectrum of the diazoimidazole (II) shows a strong band at 1380 cm.$^{-1}$, and that of the diazotriazole (V) has a band at 1390 cm.$^{-1}$ comparable in intensity to the band at 2210 cm.$^{-1}$

The close similarity of these diazoheterocycles to aromatic diazonium compounds is suggested by the diazo band near 2200 cm.$^{-1}$ and by the formation of coupling products[21,22] typical of those of aryldiazonium salts. Some of the possible contributing forms to a resonance hybrid are represented by VIIa–e. Structures VIIa and VIIb correspond to the two major forms contributing to the structure of diazomethane.[23] Forms VIIc and VIId may be viewed formally and arbitrarily as being formed by ionization of the acidic ring hydrogen atom during the diazotization process. If the contributions of forms having a triply bonded diazo group (-N$^+$≡N) can be correlated with the infrared absorption



frequency, as suggested by Whetsel *et al.*,[15] then the importance of forms such as VIIb–d would appear to be greater in these two heterocyclic systems than similar forms are in the carbocyclic series where diazocyclopentadiene[24] absorbs at 2082 cm.$^{-1}$ The localized electron pair of forms VIIb, VIIc, VIId, and other canonical forms is potentially capable of being incorporated into the π-electron system of the ring, the negative charge then becoming associated with the π-electron sextet (II and V). Such diazoheterocycles may be regarded as diazonium salts in which the ring system serves as the anionic component, the degree of aromaticity varying with the magnitude of charge localization on the heteroatoms. This representation may be considered analogous to the formulation of mesoionic compounds as ring structures bearing a negatively charged substituent and having a positive charge associated with the π-electron sextet.[25] These considerations suggested that other heterocycles having an easily ionizable hydrogen and a suitably placed amino group will form stable diazo (or diazonium) derivatives. It is probable that earlier workers[26] were dealing with derivatives of this type in the pyrazole, pyrrole, 1,2,4-triazole, and tetrazole series. Stable diazo derivatives of one of these ring systems have recently been isolated; subsequent to our preliminary report,[21] a note recording the preparation and characterization of diazopyrazoles has appeared.[27]

Biological activity. 5-Diazoimidazole-4-carboxamide and 5-diazo-*v*-triazole-4-carboxamide are of interest as potential anticancer agents. Both are analogs of 5(or 4)-aminoimidazole-4(or 5)-carboxamide, whose ribonucleotide is a precursor of nu-

(12) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley & Sons, Inc., N. Y., 1958.

(13) A detailed tabulation of wavelengths of the diazo group in other types of diazo compounds is presented in reference 18, p. 18.

(14) M. Aroney, R. J. W. Le Fèvre, and R. L. Werner, *J. Chem. Soc.*, 276 (1955).

(15) K. B. Whetsel, G. F. Hawkins, and F. E. Johnson, *J. Am. Chem. Soc.*, **78**, 3360 (1956).

(16) R. J. W. Le Fèvre, J. B. Sousa, and R. L. Werner, *J. Chem. Soc.*, 4686 (1954).

(17) P. Yates, B. L. Shapiro, N. Yoda, and J. Fugger, *J. Am. Chem. Soc.*, **79**, 5756 (1957); spectra determined in solution.

(18) E. Fahr, *Ann.*, **617**, 11 (1958).

(19) J. H. Looker and D. N. Thatcher, *J. Org. Chem.*, **22**, 1233 (1957).

(20) J. G. Carey and I. T. Millar, *Chem. and Ind.*, 97 (1960); J. G. Carey, G. Jones, and I. T. Millar, *Chem. and Ind.*, 1018 (1959).

(21) Y. F. Shealy, R. F. Struck, L. B. Holum, and J. A. Montgomery, Abstracts of Papers, 137th Meeting of the American Chemical Society, Cleveland, Ohio, April 5–14, 1960, p. 4N.

(22) Y. F. Shealy, C. A. Krauth, C. A. O'Dell, and J. A. Montgomery, unpublished.

(23) G. W. Wheland, *Resonance in Organic Chemistry*, John Wiley & Sons, Inc., N. Y., 1955, p. 181.

(24) W. von E. Doering and C. H. DePuy, *J. Am. Chem. Soc.*, **75**, 5955 (1953); solution and vapor-phase spectra.

(25) W. Baker and W. D. Ollis, *Quart. Revs.*, **11**, 15 (1957).

(26) *E.g.*, L. Knorr, *Ber.*, **37**, 3520 (1904); J. Thiele and W. Manchot, *Ann.*, **303**, 33 (1898); J. Reilly and D. Madden, *J. Chem. Soc.*, 815 (1929); J. Thiele and J. T. Marais, *Ann.*, **273**, 144 (1893); F. Angelico, *Atti. Accad. Lincei*, [V], **14II**, 167 (1905) [Beilstein's *Handbuch Der Organischen Chemie*, XXII, pp. 468, 479].

(27) D. G. Farnum and P. Yates, *Chem. and Ind.* 659 (1960). More recently the isolation of diazopurines has been reported: J. W. Jones and R. K. Robins, *J. Am. Chem. Soc.*, **82**, 3773 (1960).

oleic acids[28]; and, like certain other anticancer agents such as azaserine[29] and 6-diazo-5-oxo-L-norleucine,[30] they possess a reactive function. The information on the stability of 5-diazoimidazole-4-carboxamide gained from the ultraviolet absorption studies was essential to the demonstration of biological activity. With suitable precautions in administration, the diazoimidazole (II) inhibits the growth of Human Epidermoid Carcinoma (H. Ep. -2) cells in tissue culture, the Ehrlich Ascites Carcinoma in mice, and the Walker 256 Carcinoma in rats.[31] The distinction between 5-diazoimidazole-4-carboxamide and 2-azahypoxanthine shown spectroscopically and chemically is further confirmed by the biological data. 2-Azahypoxanthine was not inhibitory to H. Ep.-2 cells in tissue culture at 5×10^{-4} g./ml. and was nontoxic at 125 mg./kg./day in mice bearing Sarcoma 180 or Adenocarcinoma 755. In these same tests in mice, 5-diazoimidazole-4-carboxamide was toxic at 2.5–10 mg./kg./day.[31]

EXPERIMENTAL

5-Diazoimidazole-4-carboxamide. A stirred solution of 4.7 g. (68 mmoles) of sodium nitrite in 120 ml. of water was maintained at 0–5° while a solution of 10 g. (61.5 mmoles) of 5(or 4)-aminoimidazole-4(or 5)-carboxamide hydrochloride[32] in 80 ml. of cold 1 *N* hydrochloric acid was introduced dropwise. A crystalline precipitate began to form after a small portion of the aminoimidazole solution had been added; after about 90% of the aminoimidazole solution had been added, the reaction mixture began to assume a pink color. The addition was discontinued, and the precipitate was removed by filtration, washed three times with 20-ml. portions of water, and dried *in vacuo* over phosphorus pentoxide. The small crystalline needles of 5-diazoimidazole-4-carboxamide weighed 5.9 g. (70% yield), decomposed explosively[33] at 205–210°, gave a positive Bratton-Marshall test,[9] and produced a diazo absorption band at 2190 cm.$^{-1}$ A sample of the diazo derivative that had been dried at 55° *in vacuo* over phosphorus pentoxide was submitted for analysis.

Anal. Calcd. for $C_4H_3N_5O$: C, 35.04; H 2.21; N, 51.09. Found: C, 34.99; H, 2.35; N, 51.10.

The total yield was brought to 73.5% by refiltering the filtrate, introducing additional sodium nitrite, and continuing the addition of the solution of 5(or 4)-aminoimidazole-4 (or 5)-carboxamide.

5-Diazoimidazole-4-carboxamide can be obtained as a crystalline solid ranging in color from ivory to faintly yellow. It is evident from the ultraviolet data that pure specimens can be isolated from aqueous media only if the reaction is conducted in such a way that the product precipitates. Unless the reaction conditions are closely controlled, intense red or purple reaction mixtures are formed; the colored products probably result from coupling of II with unreacted 5(or 4)-aminoimidazole-4(or 5)-carboxamide.

2-Azahypoxanthine monohydrate. A mixture of 2.30 g. of 5-diazoimidazole-4-carboxamide, 70 ml. of 1*N* ammonia, and a small quantity of decolorizing carbon was allowed to stand overnight. The mixture was filtered, the colorless filtrate was evaporated to dryness under diminished pressure, and the residual white solid was dried *in vacuo* over phosphorus pentoxide at 55° for 2 hr.: weight, 2.43 g. (93% yield); explosive decomposition, 210°; negative Bratton-Marshall test. A specimen was recrystallized from water and dried under the same conditions. In agreement with the statements of Stetten and Fox,[6] 2-azahydroxanthine monohydrate darkened near 150° when the temperature was raised gradually and, then, did not melt below 260°. It explodes when placed on the Kofler Heizbank at 210°.

Anal. Calcd. for $C_4H_3N_5O \cdot H_2O$: C, 30.95; H, 3.25; N, 45.12. Found: C, 31.10; H, 3.02; N, 44.99.

5-Diazo-v-triazole-4-carboxamide. A solution prepared from 1 g. of 5-amino-*v*-triazole-4-carboxamide, 7 ml. of water, and 43 ml. of 2:1 acetic acid–water was cooled to 5°. To the cold, stirred triazole solution 1.3 ml. of isoamyl nitrite was added dropwise, and stirring was continued at 5° for 1 hr. and at room temperature for 2 hr. The reaction solution was allowed to stand overnight, concentrated to 10 ml. under reduced pressure at room temperature, and chilled. The cold solution deposited 470 mg. of a crystalline product. This material gave a positive Bratton-Marshall test,[9] decomposed explosively near 175°, and showed the intense infrared absorption of the diazo group at 2210 cm.$^{-1}$ The filtrate furnished a second crop (100 mg.) of the diazotriazole: total yield, 570 mg. (52%). Two recrystallizations from water gave 5-diazo-*v*-triazole-4-carboxamide as white crystals which decomposed explosively near 175°.

Anal. Calcd. for $C_3H_2N_6O$: C, 26.09; H, 1.46; N, 60.85. Found: C, 26.06; H, 1.56; N, 60.87.

2,8-Diazahypoxanthine (v-triazolo[4,5-d]-v-triazin-7(6H)-one). a. *From 5-amino-v-triazole-4-carboxamide.* A solution of 0.69 g. (10 mmoles) of sodium nitrite in 6 ml. of water was added to a cold (0–5°) stirred solution composed of 1.0 g. (7.9 mmoles) of 5-amino-*v*-triazole-4-carboxamide, 2.4 ml. of glacial acetic acid, and 220 ml. of water. The nitrite solution was added dropwise over a period of 1 hr. The colorless reaction solution was allowed to warm to room temperature, stirred at room temperature for 4 hr., and then allowed to stand at room temperature overnight. The *p*H of the solution was raised with 1.0 *N* sodium hydroxide to *p*H 9.2. After the basic solution had been allowed to stand overnight, it was passed through a column (3.5 cm. × 13 cm.) of the cation exchange resin IRC-50 (acid form). The effluent was evaporated to dryness *in vacuo* at room temperature. Recrystallization of the residue from ethanol-water furnished 0.7 g. (51% yield) of crystalline 2,8-diazahypoxanthine dihydrate. This product did not give a positive Bratton-Marshall test, had no distinct absorption bands in the 2300–2000 cm.$^{-1}$ region of its infrared spectrum, and decomposed explosively at 270°. When the compound was heated gradually, it began to darken near 200° and did not melt below 290°. Recrystallization from water gave colorless needles of 2,8-diazahypoxanthine dihydrate: explosive decomposition, 270°.

Spectral data. λ_{max} in mμ ($\epsilon \times 10^{-3}$): 264 (6.44) in 0.1 *N* hydrochloric acid; 278 (5.15) at *p*H 7; 259 (4.37) and 294 (7.92) in 0.1 *N* sodium hydroxide.

Anal. Calcd. for $C_3H_2N_6O \cdot 2H_2O$: C, 20.67; H, 3.47; N, 48.29. Found: C, 20.90; H, 3.25; N, 48.46.

b. *From 5-diazo-v-triazole-4-carboxamide.* 5-Diazo-*v*-triazole-4-carboxamide isolated from the reaction of 5-amino-*v*-triazole-4-carboxamide with isoamyl nitrite in aqueous acetic acid cyclized during the following operations. A specimen of 5-diazo-*v*-triazole-4-carboxamide was stirred in aqueous

(28) H. E. Skipper and L. L. Bennett, Jr., *Annual Review of Biochemistry*, Annual Reviews, Inc., Palo Alto, Calif., 1958, Vol. 27, p. 137.

(29) S. A. Fusari, T. H. Haskell, R. P. Frohardt, and Q. R. Bartz, *J. Am. Chem. Soc.*, 76, 2881 (1954).

(30) H. W. Dion, S. A. Fusari, Z. L. Jakubowski, J. G. Zora, and Q. R. Bartz, *Abstrs. of Papers* 129th Meeting of the American Chemical Society, Dallas, Tex., April 8–13, 1956, p. 13M.

(31) Biological evaluations were carried out by Drs. F. M. Schabel, Jr., W. R. Laster, and associates of the Chemotherapy Division, Southern Research Institute.

(32) E. Shaw and D. W. Woolley, *J. Biol. Chem.*, 181, 89 (1949); J. A. Montgomery, K. Hewson, R. F. Struck, and Y. F. Shealy, *J. Org. Chem.*, 24, 256 (1959).

(33) Explosion temperatures and melting points were determined on a Kofler Heizbank melting-point apparatus.

acetic acid at *p*H 3–4 for approximately 1 day, and the solvent was evaporated in a stream of nitrogen. The solid residue was redissolved in aqueous solution and stirred at *p*H 6.4 for 3 hr. Evaporation of the water left a solid residue that gave a weakly positive Bratton-Marshall test. The solid was, therefore, redissolved in water, treated with activated carbon, and recrystallized from water. The colorless needles that separated gave ultraviolet and infrared spectra identical with those of 2,8-diazahypozanthine dihydrate prepared from 5-amino-*v*-triazole-4-carboxamide without isolation of the diazo derivative.

Spectroscopic determinations. Stock solutions of 5-diazoimidazole-4-carboxamide for the ultraviolet studies were prepared by adding the solvent in the dark to a specimen weighed to the nearest microgram. Each stock solution was stored in the dark during the determination of stability at a given *p*H. Initial concentrations of the diazoimidazole (II) were near 10 mg./l.

All ultraviolet spectra were recorded with a Beckman Model DK-2 spectrophotometer or with a Cary Model 14 spectrophotometer. The infrared spectra were determined in pressed potassium bromide disks with a Perkin-Elmer Model 21 spectrophotometer.

Acknowledgment. The authors are indebted to Mr. C. A. O'Dell for technical assistance; to Dr. W. J. Barrett, Dr. W. C. Coburn, Jr., and associates of the Analytical Section for spectral determinations; and to Mr. W. F. Fitzgibbon and associates of the Organic Preparations Section for large quantities of starting materials. Microanalyses were performed by the Galbraith Microanalytical Laboratories, Knoxville, Tenn.

BIRMINGHAM, ALA.

[CONTRIBUTION FROM THE RADIUM INSTITUTE, UNIVERSITY OF PARIS]

Compounds with Potential Activity Against Lethal Radiations. VIII. Synthesis of Phenolic Ketones by Means of Boron Trifluoride

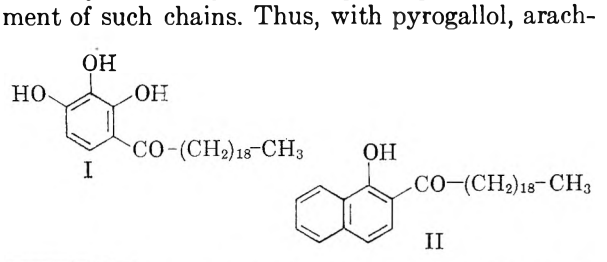
N. P. BUU-HOÏ AND N. D. XUONG

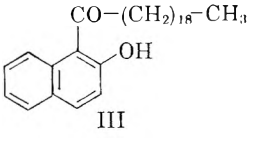
Received September 1, 1960

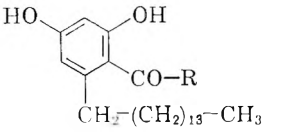
Boron trifluoride in the presence of hydrogen fluoride proved an excellent catalyst for the synthesis of phenolic ketones, prepared for evaluation of their protective action against lethal radiations. The naphthols and pyrogallol gave monoketones, while hydroquinone was disubstituted. 4-Acylcatechols were best prepared by acylation of guaiacol and subsequent demethylation.

In earlier papers,[1] we described how a number of phenolic ketones, especially those bearing a long-chain acyl group, possess significant protective properties against whole-body x-ray irradiation in mice. Continuing this research, we have now synthesized phenolic ketones derived from di- and triphenols and from α- and β-naphthol.

The most convenient method for these syntheses was the condensation of carboxylic acids with the phenols in presence of boron trifluoride mixed with some hydrogen fluoride (*i.e.*, the gas produced by the reaction of oleum on potassium fluorborate), the hydrogen fluoride enhancing the condensing qualities of boron trifluoride. In these conditions, a temperature of 70° was sufficient to complete the condensation. The procedure is particularly useful for preparing ketones with long chains, as the Nencki, Friedel-Crafts, or Fries reactions customarily used may lead to splitting or rearrangement of such chains. Thus, with pyrogallol, arachidic acid gave 4-arachidoylpyrogallol (I), and with α- and β-naphthol, 2-arachidoyl-1-naphthol (II) and 1-arachidoyl-2-naphthol (III), all in excellent yields and without by-products. Similarly, 5-pentadecylresorcinol was easily converted with the appropriate acids, into 5-pentadecyl-4-resacetophenone (IV), 5-pentadecyl-4-respropiophenone







IV. R = CH_3
V. R = C_2H_5
VI. R = CH_2—C_6H_5

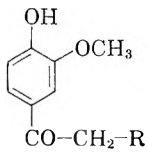
(V), and 5-pentadecyl-4-phenacetylresorcinol (VI), where in similar conditions the Nencki reaction gave but poor results.[2]

The acylation of catechol was far less easy to achieve (this lack of reactivity had already been noted in Nencki reactions[3]), and 4-acylcatechols were more readily accessible by boron trifluoride-catalyzed acylation of guaiacol and demethylation of the resulting 2-methoxy-4-acylphenols by means

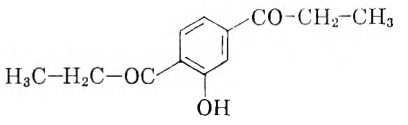
(1) A. Lacassagne, J. F. Duplan, and N. P. Buu-Hoï, *J. Natl. Cancer Inst.*, 15, 915 (1955).

(2) *Cf.* R. D. Haworth and D. Woodcock, *J. Chem. Soc.*, 999 (1946).

(3) N. P. Buu-Hoï, *J. Org. Chem.*, 19, 1770 (1954).



VII. R = CH_3
VIII. R = C_2H_5



IX

of pyridine hydrochloride.[4] 4-Propionylcatechol and 4-butyrylcatechol were thus obtained in good yields *via* 2-methoxy-4-propionylphenol (VII) and 2-methoxy-4-butyrylphenol (VIII) respectively. This method also provides a convenient route to the 3-ethers of acylcatechols which otherwise are not easily accessible.[5]

Whereas in all the above instances only monoacylation was observed, in the case of hydroquinone propionylation gave 2,5-dipropionylhydroquinone (IX).

In biological tests of these ketones for their protective action against the lethal effects of whole-body x-ray irradiation in mice, 4-arachidoylpyrogallol, 2-arachidoyl-1-naphthol, and 1-arachidoyl-2-naphthol showed significant activity.

EXPERIMENTAL

4-Arachidoylpyrogallol (I). The catalytic mixture of boron trifluoride and hydrogen chloride was produced by the reaction of oleum on potassium fluoroborate in a proportion of 8 l. of oleum to 7 kg. fluorborate; a mixture of 48 g. of arachidic acid, 30 g. of pyrogallol, and 30 ml. of anhydrous xylene was saturated, during 20 min., with the gas thus generated, and during the last 5 min. the flask was heated on a water bath at 70° to complete the condensation. After cooling, the product was treated with water and xylene was added; the xylene layer was washed first with aqueous sodium carbonate, then with water, and dried over sodium sulfate, and the solvent evaporated *in vacuo*. The solid remaining was recrystallized first from cyclohexane, then from acetone, giving fine colorless needles, m.p. 99°. Yield: 90%. The product was readily soluble in lipids and showed pronounced antioxidant activity (substrate, linseed oil). Its solution in ethanol gave a bright yellow coloration with sodium hydroxide.

Anal. Calcd. for $C_{26}H_{44}O_4$: C, 74.3; H, 10.6. Found: C, 74.3; H, 10.7.

2-Arachidoyl-1-naphthol (II). A mixture of 10 g. of α-naphthol, 15 g. of arachidic acid, and 15 ml. of anhydrous xylene was treated with boron trifluoride–hydrogen fluoride and the product worked up as above. After two recrystallizations from cyclohexane, the ketone was obtained in 70% yield as shiny pale yellow needles, m.p. 93°, very soluble in lipids and giving a yellow coloration in a solution of sodium hydroxide in ethanol.

Anal. Calcd. for $C_{30}H_{46}O_2$: C, 81.3; H, 10.6. Found: C, 81.6; H, 10.4.

1-Arachidoyl-2-naphthol (*III*). Prepared in 80% yield from 10 g. of β-naphthol and 15 g. of arachidic acid in 15 ml. of xylene, this ketone crystallized from cyclohexane in shiny yellowish needles, m.p. 76°, with properties similar to its isomer.

Anal. Calcd. for $C_{30}H_{46}O_2$: C, 81.3; H, 10.6. Found: C, 81.5; H, 10.5.

5-Pentadecyl-4-resacetophenone (IV). The 5-pentadecylresorcinol[6] used in this work (m.p. 95°) was prepared by catalytic hydrogenation of cardol. A mixture of 20 g. of this phenol, 30 ml. of xylene, and 30 ml. of acetic acid was saturated with the catalyst for 1 hr. at 50–60°, and the reaction product left to stand overnight. After decomposition with ice and neutralization with sodium carbonate, the solid obtained was recrystallized twice from ethanol, giving fine colorless needles, m.p. 63°. Yield: 75%.

Anal. Calcd. for $C_{23}H_{38}O_3$: C, 76.2; H, 10.6. Found: C, 76.0; H, 10.8.

5-Pentadecyl-4-respropiophenone (V). Prepared as above, and in similar yield, from propionic acid, this ketone crystallized from ethanol in fine colorless prisms, m.p. 76°.

Anal. Calcd. for $C_{24}H_{40}O_3$: C, 76.6; H, 10.7. Found: C, 76.4; H, 10.5.

5-Pentadecyl-4-phenacetylresorcinol (VI). Prepared with a 15% excess of phenylacetic acid, the product of the condensation was purified by treatment with a hot aqueous solution of sodium carbonate. Crystallization from ethanol gave yellowish needles, m.p. 105°. In this as in the two previous cases, the Nencki reaction (heating of 5-pentadecylresorcinol with the corresponding acid in presence of anhydrous zinc chloride) furnished several unidentified by-products.

Anal. Calcd. for $C_{29}H_{42}O_4$: C, 79.4; H, 9.6. Found: C, 79.1; H, 9.8.

Preparation of 4-propionylcatechol. A mixture of 20 g. of freshly redistilled guaiacol, 15 g. of glacial acetic acid, and 30 ml. of xylene was saturated with the catalyst at 60–70°, and the product kept overnight at room temperature. After the usual treatment and vacuum-distillation of the reaction product, *2-methoxy-4-propionylphenone* (VII) was obtained in almost theoretical yield as a pale yellow oil, b.p. 182°/12 mm., which readily solidified; recrystallization from hexane gave shiny colorless leaflets, m.p. 54°.

Anal. Calcd. for $C_{10}H_{12}O_3$: C, 66.7; H, 6.7. Found: C, 66.5; H, 6.7.

A mixture of 5 g. of the foregoing ketone and 10 g. of redistilled pyridine hydrochloride was gently refluxed for 10 min.; after cooling and addition of dilute hydrochloric acid, the precipitate formed was washed with water, and recrystallized from aqueous ethanol, giving *4-propionylcatechol* in 80% yield, as shiny colorless prisms, m.p. 142°.

Preparation of 4-butyrylcatechol. 2-Methoxy-4-butyrylphenol (VIII), prepared from guaiacol and butyric acid as for the lower homolog, was purified by vacuum distillation; the pale yellow oil obtained, b.p. 202°/12 mm., readily solidified in hexane, to give fine colorless prisms, m.p. 45°.

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.0; H, 7.3. Found: C, 67.7; H, 7.5.

Demethylation of 5 g. of this ketone with 10 g. of pyridine hydrochloride afforded *4-butyrylcatechol*, crystallizing from aqueous ethanol in fine colorless prisms m.p. 149°.

2,5-Dipropionylhydroquinone (IX). The condensation of hydroquinone with propionic acid in xylene was difficult to achieve and necessitated heating on a boiling water bath. Repeated crystallization of the reaction product from aqueous methanol afforded a 7% yield of this *diketone* as large yellowish prisms, m.p. 151–152°. This compound was sublimable and gave a yellow solution in sulfuric acid.

Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64.8; H, 6.3; O, 28.8. Found: C, 64.5; H, 6.0; O, 29.0.

PARIS Ve, FRANCE

(4) *Cf.* N. P. Buu-Hoï, *Rec. trav. chim.*, **68**, 759 (1949).
(5) T. Reichstein, *Helv. chim. Acta*, **10**, 394 (1927).
(6) For further derivatives of this diphenol, see R. N. Chakravarti and N. P. Buu-Hoï, *Bull. Soc. chim. France*, 1498 (1959).

[CONTRIBUTION FROM THE DIVISION OF CHEMICAL RESEARCH, G. D. SEARLE & CO.]

The C-16 Halides of Estrone Methyl Ester

GEORGE P. MUELLER AND WILLIAM F. JOHNS

Received July 5, 1960

Epimeric forms of four C-16 halides of estrone methyl ether are reported. Chemical reactions are presented which include proof of structure, isomerization, interconversion and reduction. Two C-17 halides of 16-estrone methyl ether are similarly discussed.

Noteworthy and often valuable alterations of clinical activity accompany the exchange of halogen for hydrogen at various points in the steroid nucleus. Progestational, cortical, and androgenic-anabolic steroids have received most attention in structure-activity studies.[1] Our interest in halogenated estrone derivatives was prompted by the possibility that we could retain the favorable lipid-shifting activity of this hormone while depressing its characteristic feminizing activity to the point that a useful clinical agent would evolve. Biological and clinical tests have been encouraging and have been published.[2] We wish to present the experimental work and additional compounds necessarily omitted from our earlier communication.

Direct halogenation of androstan-17-ones leads to substitution at C-16.[3] The necessary reaction conditions, however, may induce concomittant ring-A substitution of estrone derivatives.[4] We therefore chose to extend the use of 17-enol acetates to the synthesis of a variety of halides. This route has been used to prepare 16-bromoestratrienes[5,6] and androstanes[7,8,9] where in each example only the 16α-bromide was formed.

Our experience accords with the literature in that enol acetate bromination produced only 16α-bromo ketones. However, chlorination of IIa yielded, besides IIIf, 3.7% of IV, illustrative of 16β-substitution. The structure was assigned on the basis of analytical and spectral data, the assumption of *trans* halogen addition to a double bond and acid hydrolysis to the 16β-chloro ketone, Vc. The latter occurred under conditions which do not epimerize 16α-chloro ketones. The stability of IV is undoubtedly due to its structure in which the 17β-acetoxyl is shielded by adjacent β-methyl and β-chlorine substituents. This structure arises through β-attack of chloronium ion at C-16, leading to a *trans* adduct. Similar intermediates to the 16α-chloro ketone, initiated by the favored rearside of α route of attack, are presumably unstable and decomposed as formed or during extraction.

Also, from the reaction of IIa with *N*-iodosuccinimide, we isolated both 16α- and 16β-iodides, IIId and Va. Direct iodination, with or without mercuric acetate catalysis, gave the 16α-isomer. Inferential evidence for structure of the 16α-iodide was derived from analogy between its formation and that of the favored 16α-chlorides and 16α-bromides, *i.e.*, by "attack from the rear," and by its position in the molecular rotation sequence of the haloketones, (see the following paragraph). The 16β-iodide Va received its formulation from the latter criterion.

Two epimeric fluoroketones were prepared, the 16β-isomer Vd by silver fluoride displacement of the 16α-iodide IIId, and the 16α-fluoride[10] by electrophilic attack at C-16 with perchloryl fluoride. Presumptive evidence for the configurations assigned is based on the following considerations: fluoride displacement of 16α-iodide could reasonably occur with inversion while attack of the perchloryl fluoride reagent at an unsubstituted 16 carbon atom "from the rear" would be the favored assumption; either epimer, on treatment with alkali, yielded the same mixture of the two as characterized by infrared absorption; molecular rotatory dispersion curves (Table I) show Δa values in accord with the structures assigned and with the known "opposite" behavior of α-fluoro ketones (*cf.* reference, footnote 28); the molecular

(1) (a) G. Pincus, *Vitamins and Hormones*, New York, Academic Press, 1959, p. 307; (b) L. H. Sarett, *Annals of the New York Academy of Sciences*, **82**, 802 (1959).

(2) (a) G. P. Mueller, W. F. Johns, D. L. Cook, and R. A. Edgren, *J. Am. Chem. Soc.*, **80**, 1769 (1958); (b) A. U. Rivin, *Metabolism*, **8**, 704 (1959); (c) V. A. Drill, D. L. Cook, and R. A. Edgren, *Hormones and Atherosclerosis*, New York, Academic Press, Inc., 1959, p. 247; (d) H. Spencer, B. Kabakow, J. Samachson, and D. Laszlo, *J. Endocrinol. and Metabolism*, **19**, 1581 (1959); (e) G. Annoni, *Minerva med.*, **50**, 3084 (1959).

(3) J. Fajkos, *Coll. Czech. Chem. Comm.*, **20**, 312 (1955).

(4) R. B. Woodward, *J. Am. Chem. Soc.*, **62**, 1625 (1940).

(5) W. S. Johnson and W. F. Johns, *J. Am. Chem. Soc.*, **79**, 2005 (1957).

(6) J. Fishman and W. R. Biggerstaff, *J. Org. Chem.*, **23**, 1190 (1958).

(7) R. Pappo, B. M. Bloom, and W. S. Johnson, *J. Am. Chem. Soc.*, **78**, 6347 (1956).

(8) J. Fajkos and F. Sorm, *Coll. Czech. Chem. Comm.*, **24**, 766 (1959).

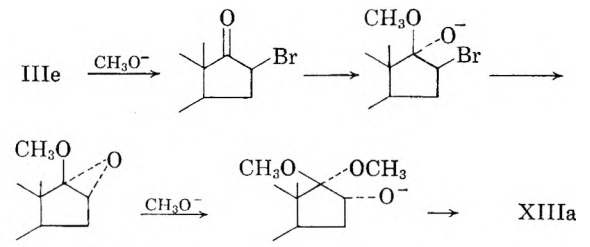
(9) C. W. Shoppee, R. H. Jenkins, and G. H. R. Summers, *J. Chem. Soc.*, 3048 (1958).

(10) Synthesis and equilibration of this compound was part of an independent study by our colleague, Dr. Arthur Goldkamp. He has graciously permitted us to describe the compound: it melted at 155.5–164.5°, $[\alpha]_D$ + 176.5°; $\nu_{max}^{CHCl_3}$ 1760 cm.$^{-1}$

rotation of each falls respectively in the straight-line relationships of the 16α- and 16β-halides, as explained below, where again the "opposite" effect of α-fluorine contributes to this interesting linear progression of molecular rotations.

Epimerization of 16α-bromide IIIe to 16β-bromide Vb in methanolic sulfuric acid led to a mixture containing about 62% of the latter, a result similar to those recently published.[11] Epimerization also resulted from treatment of the 16α-bromide at room temperature with lithium bromide in dimethylformamide. Inversion accompanied by exchange occurred when IIIe was treated instead with lithium chloride, and the 16β-chloride Vc was conveniently obtained. The latter could also be prepared by isomerizing the 16α-chloride with alkaline alumina in benzene.[12] The 16α-chloride, however, was not epimerized in the presence of lithium chloride.

Attempts to effect epimerization of IIIe with alkali led to loss of bromide. Following this approach, treatment of the 16α-bromo ketone with sodium methoxide in methanol generated the dimethylketal XIIIa. Its structure was suggested by analysis and by acid hydrolysis, which gave rise to the ketol XIVa, identical with an authentic sample.[13] Previous work with ring-D ketols[14] showed acid hydrolysis of a 16β-hydroxy-17-ketone to proceed with rearrangement to a 17β-hydroxy-16-ketone, whereas a system involving the 16α-hydroxy-17-ketone is stable. This provided strong presumptive evidence in favor of formulation XIIIa. However, in order to establish the presence of 16-hydroxyl in the latter and to preclude rearrangement of some other structure to the acid-stable XIVa, the tosylate XIIIb was prepared, hydrolyzed to XIVb and treated with lithium chloride, generating the 16β-chloro ketone Vc. With the structure XIIIa established in two ways, we were led to the following mechanism which, despite obvious objections, logically explains the experimental results:



As illustrated previously,[15] epoxide formation has supervened here where Faworskii rearrangement was precluded. Moreover opening of the epoxide intermediate was assumed to proceed at C-17 with inversion.[16] Finally, similar behavior of α-halocyclohexanones has been noted, although the configuration of the products was not completely defined.[17]

Reduction of the α-halo ketones IIIe and IIIf with lithium aluminum hydride produced a mixture of *cis*- and *trans*-halohydrins VII and VIII whose structures were confirmed by standard methods.[3,8,9,11,18] Thus, the bromo ketone yielded *cis*-bromohydrin VIIa which was oxidized again to the parent bromo ketone IIIe, converted with alkali to estrone methyl ether, Ia, and reduced with zinc to the olefin X; the *trans*-bromohydrin VIIIa also formed was reoxidized to IIIe and converted with alkali to the 16β,17β-epoxide IX. A similar sequence of reactions was applied to the bromohydrins VIIb and VIIIb, prepared but not isolated by Fishman and Biggerstaff,[6] as well as the chlorohydrins, VIIc and VIIIc.

Lithium aluminum hydride reduction of 16β-chloro ketone Vc gave VI, a *cis*-chlorohydrin that could be reoxidized to Vc or converted with alkali into estrone methyl ether Ia. No *trans*-chlorohydrin was found in the reduction products.

Both *cis*- and *trans*-bromohydrins have been shown to undergo elimination with zinc in acetic acid[19] and by such treatment the crude mixture of bromohydrins VIIa and VIIIa obtained by reduction was converted in good yield to the olefin X.[9,13] Conversion of the latter to the 16α,17α-epoxide[13] XI and treatment with hydrochloric acid afforded the *trans*-chlorohydrin XII, which was oxidized to Vc.

The singular conversion of 16α-bromoandrostan-17β-ol by alkali exclusively to androstan-17-one[9] has been challenged by Fajkos[11] on the basis of his own androstane work and is also contrary to our experience in the methoxyestratriene series. The *trans*-bromohydrin VIIIa is the more difficultly isolable product of reduction and must be purified; however, alkaline treatment of it produced 3-methoxy-16β,17β-epoxyestra-1,3,5(10)-triene, IX, in good yield.

Fajkos had obtained 3β-acetoxy-17α-bromoan-

(11) J. Fajkos, *J. Chem. Soc.*, 3966 (1959). For additional infrared data see M. Horak and J. Fajkos, *Coll. Czech. Chem. Comm.*, 24, 1515 (1959).

(12) *Cf.* J. Fajkos, *Coll. Czech. Chem. Comm.*, **23**, 1559 (1958).

(13) We wish to acknowledge with thanks the cooperation of Dr. D. A. Tyner, G. D. Searle & Co., in providing us with physical data and samples of compounds from his own investigations.

(14) W. S. Johnson, B. Gastambide, and R. Pappo, *J. Am. Chem. Soc.*, 79, 199 (1957).

(15) *Cf.* R. B. Loftfield, *J. Am. Chem. Soc.*, **73**, 4707 (1951).

(16) *Cf. Ionic Organic Reactions*, E. R. Alexander, John Wiley & Sons, Inc., New York, N. Y., 1950, p. 219; C. L. Stevens and T. H. Coffield, *J. Am. Chem. Soc.*, 80, 1919 (1958); *J. Org. Chem.*, **23**, 336 (1958).

(17) C. L. Stevens, J. J. Beereboom, Jr., and K. G. Rutherford, *J. Am. Chem. Soc.*, **77**, 4590 (1955); C. L. Stevens and A. J. Weinheimer, *J. Am. Chem. Soc.*, 80, 4072 (1958); D. A. Prins and C. W. Shoppee, *J. Chem. Soc.*, 494 (1946).

(18) B. Ellis, D. Patel, and V. Petrow, *J. Chem. Soc.*, 800 (1958).

(19) L. F. Fieser and R. Ettorre, *J. Am. Chem. Soc.*, 75, 1700 (1953).

TABLE I

3-Methoxyestra-1,3,5(10)-triene	Rotation Differences				Rotatory Dispersions					
	$[\alpha]_D$	M_D	$\Delta(\beta-\alpha)$	Δ(Halogen-H)	ϕPeak	λ (mμ)	ϕTrough	λ (mμ)	Amplitude (10^{-2})	$10^{-2}\Delta a$[a]
17-one	+157	+446			+ 6900	315			+142	
16α-fluoro-17-one	+177	+534	− 59	+ 88	+13200	338	−10550	292	+238	+100
16β-fluoro-17-one	+157	+475		+ 29	+ 5860	338	− 3320	295	+ 92	− 50
16α-chloro-17-one	+161	+512	0	+ 66	+ 7650	330	− 4840[c]	290	+125	− 20
16β-chloro-17-one	+161	+512		+ 66	+ 9570	340	− 7170	295	+167	+ 30
16α-bromo-17-one	+127	+461	+134	+ 15	+ 5450	335	− 5400[c]	287	+109	− 30
16β-bromo-17-one	+164	+595		+149	+ 8450	340	− 5750	300	+142	0
16α-iodo-17-one	+ 89	+366	+350	− 80	+ 7540	348	− 5870	300	+134	− 10
16β-iodo-17-one	+175	+716		+270	+ 7650	348	− 5740	305	+134	− 10
16-one	−103	−293					−10800	312	−260	
17α-chloro-16-one	− 49	−156	−154	+137	+6320[c]	295	− 5170	340	−115	+150
17β-chloro-16-one	− 92	−310		− 17	+5470[c]	290	−10500	318	−160	+100
17α-bromo-16-one	− 5	− 18	−345	+275	+2060[c]	305	− 2200	342	− 43	+220
17β-bromo-16-one	−100	−363		− 70	+9750[c]	290	− 8900	322	−187	+ 70
17α-hydroxy[b]	+ 60	+172								
16α-chloro-17α-hydroxy	+ 68	+218	−64	+ 46						
16β-chloro-17α-hydroxy	+ 48	+154		− 18						
16α-bromo-17α-hydroxy	+ 75	+274		+102						
17β-hydroxy[d]	+ 77	+222								
16α-chloro-17β-hydroxy	+ 69	+222	0	0						
16β-chloro-17β-hydroxy	+ 69	+222		0						
16α-bromo-17β-hydroxy	+ 79	+288		+ 66						
16α-hydroxy	+ 80	+228								
16α-hydroxy-17α-bromo	+ 8	+ 29		−199						
16β-hydroxy[a]	+ 70	+199								
16β-hydroxy-17β-bromo	+ 70	+256		+ 57						

[a] Δa is the difference in amplitude from the unsubstituted 16- or 17-ketone (the androstanes were used for reference because aromatic absorption of the parent estratrienes obscured ketone absorption at second extremum); it may be regarded as the contribution of the halogen atom. Values are rounded off to the nearest 10 units. [b] See footnote 13. [c] The second extremum was not reached; the true amplitude may therefore be greater than that stated. The Δa value in each case would be subject to change, accordingly. [d] A. L. Wilds and N. A. Nelson, *J. Am. Chem. Soc.*, 75, 5366 (1953).

drostan-16β-ol from 3β-acetoxy-16β,17β-epoxyandrostane.[20] We extended these studies with epoxide IX. Ring opening with hydrobromic acid yielded the *trans*-bromohydrin XVa as an oil containing about 20% of VIIIa, as shown by oxidation of the mixture of bromohydrins followed by fractional crystallization or chromatography to separate 17α-bromo ketone XVIa from the contaminating 16α-bromo ketone IIIe. The 17α-chloro ketone XVIb prepared in a similar sequence from IX and hydrochloric acid.

Lithium aluminum hydride reduction of the new 17α-bromo ketone yielded the *cis*-bromohydrin XVIII which could be reoxidized to the original bromoketone. The *cis* configuration of the bromohydrin was evident from its conversion in alkali to the ketone XIX, and the α,α-orientation of the substituents was confirmed by hydrogenolysis to 3-methoxyestra-1,3,5(10)-trien-16α-ol.

Acid-catalyzed epimerization[21] of XVIa and XVIb afforded the 17β-isomers XXa and XXb. The structure of the 17β-bromide was confirmed by hydride reduction to a new bromohydrin XXI, of *cis* configuration by infrared criteria (see below) and conversion to the C-16 ketone, which was in turn converted into 3-methoxyestra-1,3,5(10),-16-tetraene, X, by reduction with zinc.

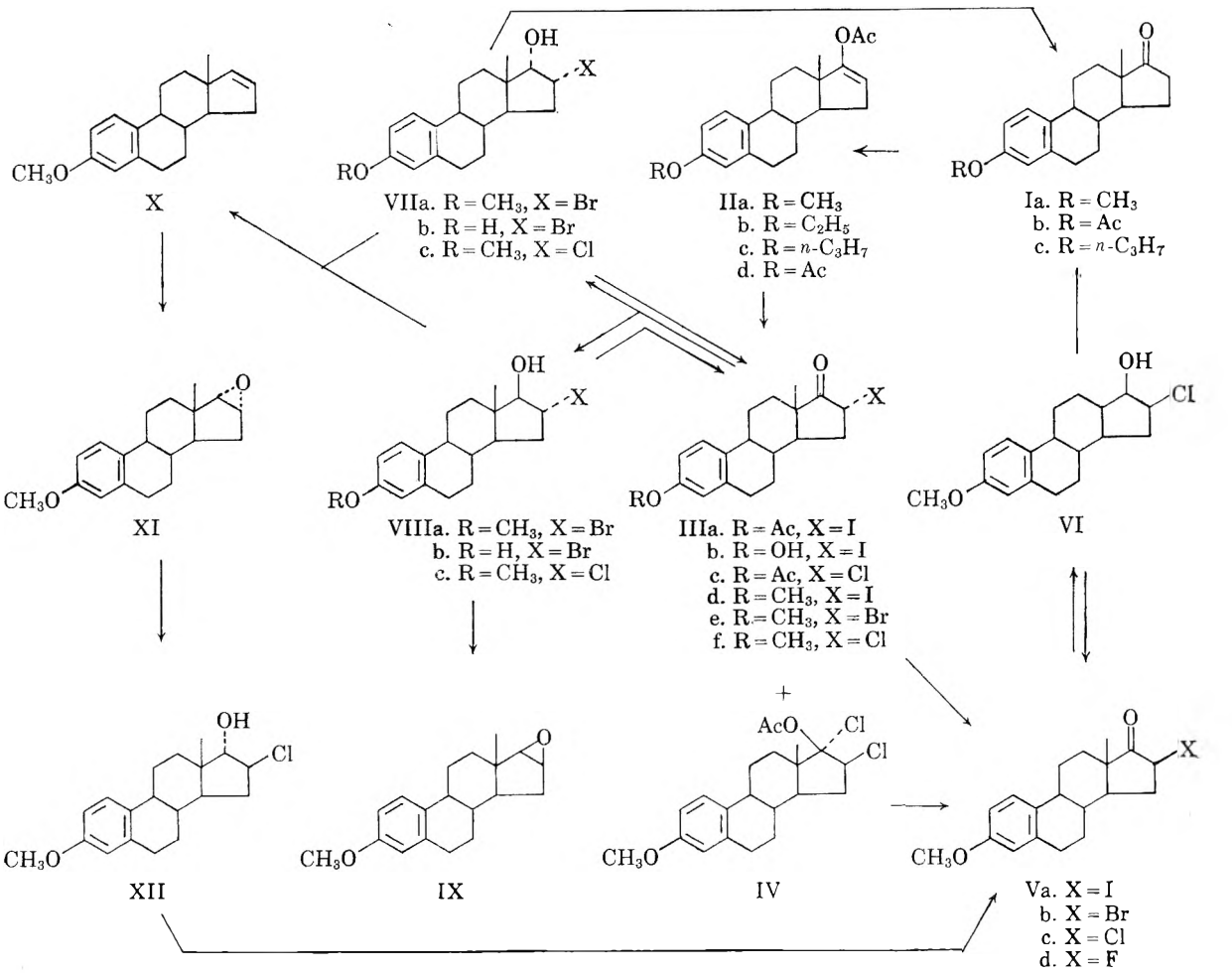
16,16-Dibromo ketones have been prepared through direct halogenation of saturated C-17 ketones.[3] We were unsuccessful, however, in obtaining dihalides through enol acetylation of the monohalo ketones. For example, enol-acetylating conditions applied for periods as long as sixty-four hours to 16α- and 16β-chloro ketones, IIIf and Vc, or the 16α-bromo ketone IIIe yielded only starting materials.[22]

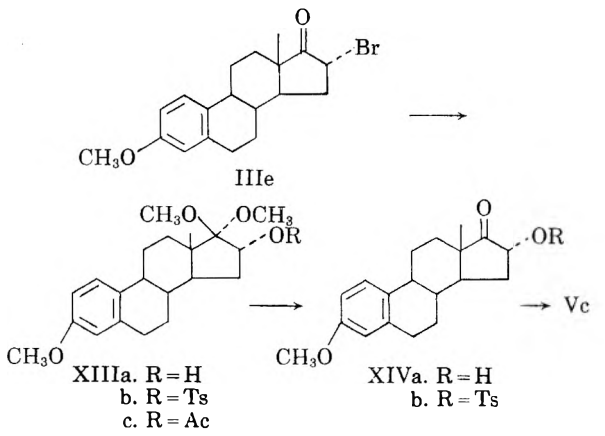
Infrared spectra were recorded routinely, using a sodium-chloride prism, with no attempt at high resolution analysis. Bands of principal interest are recorded here. Within our limits of accuracy and in agreement with Shoppee's observations,[9] there were no apparent shifts in carbonyl maxima as between 16α- and 16β-isomers, III and V, in any

(20) J. Fajkos, *Coll. Czech. Chem. Comm.*, 20, 1478 (1955).

(21) *Cf.* J. Fishman, Abstracts Organic Section, American Chemical Society, Cleveland, Ohio, April 5, 1960, p. 84-O.

(22) Enol acetates of α-halocyclohexanones have been prepared by treatment in the cold with sodium methoxide followed by acetyl chloride. *Cf.* K. G. Rutherford and C. L. Stevens, *J. Am. Chem. Soc.*, 77, 3278 (1955).



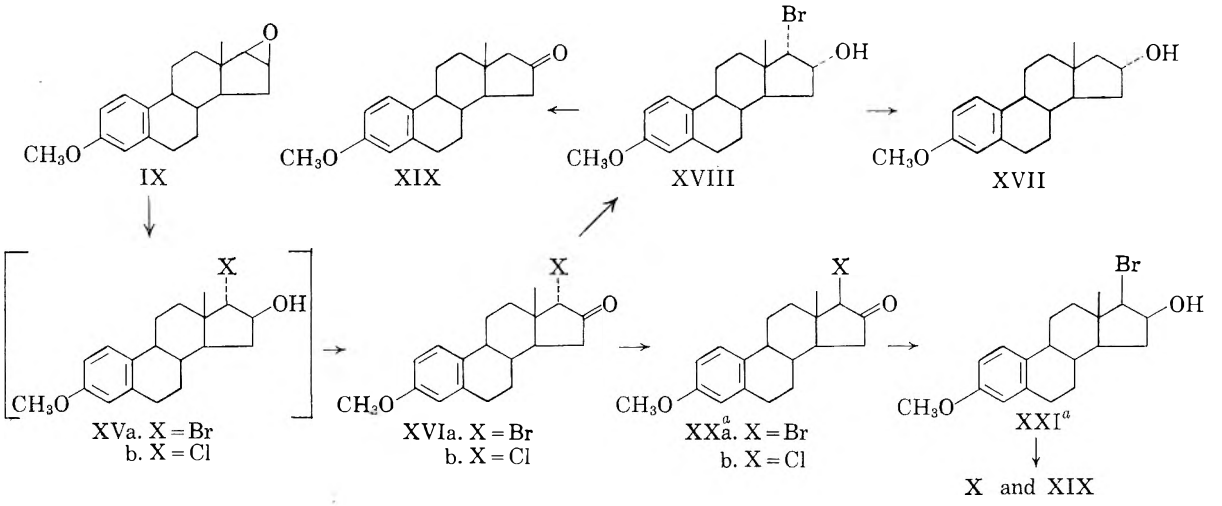


of the halides. However, relative to estrone methyl ether, absorbing at 1742 cm.$^{-1}$, maxima appeared at 1742, 1754, 1761, and 1766 cm.$^{-1}$, respectively, for the C-16 iodides, bromides, chlorides, and fluorides.[23,24]

Shoppee, Jenkins, and Summers[3] introduced Nickon's[25] relationship between conformation and infrared absorption in 1,2 chlorohydrins and bromohydrins without applying the concept to their own compounds. Fajkos[11] presented data affirming that the frequency of O—H stretching is indeed a sensitive indication of halohydrin configuration in the D ring. Our data, as expected from the foregoing, show no shift of the *trans* chlorohydrin XII absorption from that of the parent 17α-hydroxy steroid at 3642 cm.$^{-1}$ The *cis*-α-halohydrins exhibit shifts, where $\Delta\nu$ of VIIc and VIIa is -45 and -58 cm.$^{-1}$, respectively. Estradiol methyl ether absorbs at 3650 cm.$^{-1}$ and the *trans* halohydrins likewise. The *cis* isomer VI shows $\Delta\nu$ of -66 cm.$^{-1}$ Finally, the *cis* bromohydrin XXI has $\Delta\nu$ -70 cm.$^{-1}$ relative to 3-methoxyestra-1,3,5(10)-trien-16β-ol, 3680 cm.$^{-1}$[13]

Optical rotations and ancillary data are summarized in Table I. Some interesting correlations may be found here and comparison made with a similar summary of the data of Fajkos[11] and of Shoppee[9] in the androstane series. In particular we found that when molecular rotations were plotted linearly against molecular weight the four 16β-halo-17-ketones formed a straight line of positive slope intersecting almost perpendicularly a similar straight line containing the 16α-isomers. Intersection occurs at the value +512, common to

(23) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, London, Methuen and Co. Ltd., 1954, p. 121.
(24) F. V. Brutcher, Jr., T. Roberts, S. J. Barr, and N. Pearson, *J. Am. Chem. Soc.*, **78**, 1507 (1956).
(25) A. Nickon, *J. Am. Chem. Soc.*, **79**, 243 (1957).



[a] The compounds XX and XXI, including preparation, reactions and physical data, were appended to the manuscript on November 15, 1960.

both chlorides. This relationship proved useful, as mentioned earlier, in relating configurations of the 16-fluoro- and 16-iodo ketones to the corresponding chlorides and bromides.

Optical rotatory dispersion curves were obtained for all of the halogenated ketones.[26,27] The curves of the 16-halo 17-ketones showed the expected strong, positive Cotton effect[28] while those of 17-halo 16-ketones showed a negative Cotton effect. The amplitude and position of extrema appear to offer no definitive assignment of configuration in the ring-D halo ketones.

(26) We wish to thank Miss Jane Jackson, Postgraduate Medical School, London, for obtaining these curves, and Dr. W. Klyne for generously making the arrangements and interpreting the curves. His comments are as follows: The Δa values (Table I) may be interpreted according to the octant rule in its simplest form: (1) both 16-fluoro ketones have values of the expected sign; (2) the remaining 16α-halo ketones have negative values smaller than expected, indicating some ring distortion; (3) the remaining 16β-halo ketones are expected to have positive values and the fact that two have low or negative values probably indicates major distortion of ring D, presumably due to interaction of the β-halogen with the C-13 methyl group; (4) the 17α-halides have values of the expected sign and magnitude, indicating the halogens are occupying almost truly axial positions, although the 17β-halides show quasi-equatorial character with their small (but uncertain) $+\Delta a$ values. Perhaps most interesting here is the small $\Delta\lambda$ (6–10°, compared with the unsubstituted ketone) of the latter compared with a 20 to 30 mμ shift for the quasi-axial 17α- and bisectional 16α- and 16β-halides (see p. 290 and reference 27a).

(27) For discussions of this subject and the octant rule see, *Optical Rotatory Dispersion*, C. Djerassi, McGraw-Hill Book Co., Inc., New York, N. Y., 1960, and W. Klyne in "Advances in Organic Chemistry," vol. I, T. A. Raphael, E. C. Taylor, and H. Wynberg, editors, Interscience Publishers, Inc., New York, N. Y., 1960, p. 335.

(28) The similarity in dispersion curves of 16α- and 16β-bromo-17-ketosteroids has been described earlier by C. Djerassi, J. Osiecki, R. Riniker, and B. Riniker, *J. Am. Chem. Soc.*, **80**, 1216 (1958).

EXPERIMENTAL

All rotations were run at about 1% concentration in chloroform, and infrared spectra were recorded in chloroform. The term petroleum ether refers to the fraction boiling at 63–69°. Melting points are uncorrected.

Estrone n-propyl ether (Ic). Alkylation of 18.2 g. of estrone in 500 ml. of ethanol with 100 ml. of *n*-propyl iodide and 4 g. of potassium carbonate was carried out at reflux for 4 hr. Concentration to one-half volume, filtration from salts and further concentration gave 18.0 g. of product, m.p. 96–100°, which was recrystallized from methanol, yielding 14.2 g. of flat prisms, m.p. 98–99°, $[\alpha]_D$ + 143°.

Anal. Calcd. for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.88; H, 9.24.

Enol acetates of estrone alkyl ethers (IIb), (IIc). The enol-acetylation procedure used has been described.[5] We found it convenient to dissolve the crude enol acetate in hot petroleum ether or cyclohexane and pour the warm solution quickly through a short column (*ca.* 1–2″ deep) of Florisil. This is quicker than conventional chromatography, tar absorption is complete, and there is less danger of decomposition of the enol acetate which sometimes occurs during chromatography.

3-Ethoxy-17-acetoxyestra-1,3,5(10),16-tetraene crystallized from pentane in flat, elongated plates, m.p. 107–108°.

Anal. Calcd. for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29. Found: C, 77.46; H, 8.24.

3-*n*-Propoxy-17-acetoxyestra-1,3,5(10),16-tetraene crystallized from petroleum ether, m.p. 98–99°.

Anal. Calcd. for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 78.02; H, 8.52.

3-Acetoxy-16α-iodoestra-1,3,5(10)-trien-17-one (IIIa). 3,17-Diacetoxyestra-1,3,5(10),16-tetraene,[29] 6.52 g., in 20 ml. of warm dioxane was covered with nitrogen, treated with 5 g. of *N*-iodosuccinimide, warmed in a stoppered flask at 65° for 3 hr., chilled and treated successively with concentrated solutions of 3.3 g. of potassium iodide and 5 g. of sodium thiosulfate. Dilution with water, extraction with chloroform and evaporation of the washed and dried chloroform extracts gave an oil which crystallized overnight from 30 ml. of ether; the yield was 3.50 g., m.p. 135–140°. Recrystallization from methanol, benzene-cyclohexane and finally pure ether yielded bundles of small, flat needles, m.p. 142.0–143.6°, $[\alpha]_D$ + 82°, ν_{max} 1742 cm.$^{-1}$

(29) N. S. Leeds, D. K. Fukushima, and T. F. Gallagher, *J. Am. Chem. Soc.*, **76**, 2943 (1954).

Anal. Calcd. for $C_{20}H_{23}IO_3$: C, 54.80; H, 5.29; I, 28.96. Found: C, 54.57; H, 5.54; I, 28.64.

3-Acetoxy-16α-chloroestra-1,3,5(10)-trien-17-one (IIIc). The enol diacetate, 3.54 g., and 25 g. of anhydrous potassium carbonate in 125 ml. of carbon tetrachloride were treated at 12° with 15.2 ml. of 0.727*M* chlorine in carbon tetrachloride. The addition required 0.5 hr.; 20 g. of sodium thiosulfate in water was added, the layers separated, and the extraction completed with chloroform. The dried, evaporated organic solution yielded a clear glass, crystallizing as plates, m.p. 163–168°, 1.38 g. Recrystallization from methanol furnished long needles, m.p. 163–166°, $[\alpha]_D$ + 150°, ν_{max} 1761 cm.$^{-1}$

Anal. Calcd. for $C_{20}H_{23}ClO_3$: C, 69.25; H, 6.68; Cl, 10.22. Found: C, 69.62; H, 7.19; Cl, 10.27.

16α-Iodoestrone (IIIb). About 6 g. of crude acetate IIIa was dissolved in 125 ml. of methanol, treated with 5 ml. of concd. hydrochloric acid, warmed briefly to clear the solution, and set aside at room temperature overnight. A crop of 3.5 g. of crystals, m.p. (violet color at 185°, sweating at 200°) 210–211° (violent dec.), was collected. Two recrystallizations with decolorization from methanol yielded 1.21 g., m.p. 213.0–213.5° (violent dec., with violet color), $[\alpha]_D$ +137°.

Anal. Calcd. for $C_{18}H_{21}IO_2$: C, 54.55; H, 5.34; I, 32.03. Found: C, 54.83; H, 5.08; I, 32.21.

Reacetylation overnight of 0.1 g. in 5 ml. of pyridine with 5 ml. of acetic anhydride gave 0.12 g. of crude, oily product. This was recrystallized twice from ether-pentane, affording plates, m.p. 140–142°, $[\alpha]_D$ +87°. These showed infrared absorption identical with that of IIIa, suggesting the absence of inversion during the preceding hydrolysis. However, this conclusion may be open to question for want of a high yield in reacetylation.

16α-Chloroestrone. Hydrolysis of 1.1 g. of the acetate IIIc was accomplished by heating overnight at 100° with 20 ml. of 50% acetic acid. The product, 0.63 g., m.p. 233–239°, separated on cooling. It was recrystallized three times from acetone-pentane and melted at 238.5–240.5°, $[\alpha]_D$ +166°.

Anal. Calcd. for $C_{18}H_{21}ClO_3$: C, 70.92; H, 6.95; Cl, 11.63. Found: C, 70.93; H, 6.96; Cl, 11.70.

Assurance of configurational retention at C-16 was supplied by acetylating this phenol. The product, obtained in nearly quantitative yield and recrystallized from methanol, m.p. 164–169°, $[\alpha]_D$ +148°, was identical in all respects to IIIc.

The 3-methoxy-16-iodoestra-1,3,5(10)-trien-17-ones, (IIId) *and* (Va). A solution of 1.0 g. of 3-methoxy-17-acetoxyestra-1,3,5(10)-triene in 25 ml. of carbon tetrachloride, with 2 g. of anhydrous potassium carbonate, was treated with 0.8 g. of iodine in 25 ml. of carbon tetrachloride at 30° for 0.5 hr. The mixture was worked up with chloroform and aqueous sodium bisulfite and the residue remaining after evaporation of the solvent crystallized from methanol as rods, m.p. 161–167°, $[\alpha]_D$ +90.5°, of 3-methoxy-16α-iodoestra-1,3,5(10)-trien-17-one, IIId.

A more suitable preparation of this isomer resulted from treating 16.30 g. of the enol acetate, dissolved in 750 ml. of acetic acid, with 8.0 g. of mercuric acetate, stirring, cooling to 15°, and adding 13.0 g. of iodine dissolved in 750 ml. of acetic acid. The product was precipitated with water and washed several times by decantation. It was then extracted from the aqueous slurry with chloroform; this solution was washed successively with potassium iodide and sodium thiosulfate solutions and water, dried over magnesium sulfate and distilled *in vacuo*. Crystallization from 500 ml. of isopropyl alcohol, and from 400 ml. of methanol provided 7.8 g. of needles, m.p. 163–165.5°, with sweating at 148°. One further recrystallization from methanol gave 6.06 g. of IIId, m.p. 165–166° (sweating at 155°), $[\alpha]_D$ + 89.3°, ν_{max} 1742 cm.$^{-1}$

Anal. Calcd. for $C_{19}H_{23}IO_2$: I, 30.93. Found: I, 30.27.

Both 16-iodo-epimers were obtained by heating 6.52 g. of the enol acetate at 70° with 5.0 g. of *N*-iodosuccinimide in 20 ml. of purified dioxane for 1.5 hr. This was done in a stoppered flask from which air had been displaced by nitrogen. The colored solution was treated successively with saturated aqueous solutions of 3.3 g. of potassium iodide, 5 g. of sodium thiosulfate, diluted with 200 ml. of water and extracted with three 50-ml. portions of chloroform, the extracts being washed, dried and evaporated. Direct recrystallization of the crude residue yielded 5.94 g. (71.5%) of the 16α-isomer. Slow evaporation of the mother liquors at room temperature yielded a mixture of elongated plates (16α-isomer) and rosettes of stout hexagonal staffs (16β-isomer). Manual separation and recrystallization of the latter from methanol-chloroform afforded 3-methoxy-16β-iodoestra-1,3,5(10)-trien-17-one (Va) m.p. 164–166° (with sweating at 157°), $[\alpha]_D$ + 175°, ν_{max} 1745 cm.$^{-1}$

Anal. Found: I, 30.42.

An alternate method of separating isomers depended on the greater solubility of the 16β-iodide in ether. Thus, the total iodination product was crystallized once from ether, and the mother-liquor material was crystallized carefully from ether, benzene or ethyl acetate to produce the β-isomer.

3-Ethoxy-16α-iodoestro-1,3,5(10)-trien-17-one. This was prepared from IIb and *N*-iodosuccinimide as described for the methyl ether above. The crude product was recrystallized from methanol, twice from ether, and again from methanol; m.p. 156–160°, $[\alpha]_D$ +91.5°.

Anal. Calcd. for $C_{20}H_{25}IO_2$: C, 56.61; H, 5.94; I, 29.91. Found: C, 56.78; H, 5.79; I, 29.90.

3-Methoxy-16α-bromoestra-1,3,5(10)-trien-17-one (IIIe). *A. By bromination of the enol acetate* IIa. This procedure was described by Johnson and Johns;[6] the product gave the constants: m.p. 179–182°, $[\alpha]_D$ +127°.

B. By oxidation of 3-methoxy-16α-bromoestra-1,3,5(10)-trien-17α-ol (VIIa). Oxidation of 0.11 g. of VIIa was accomplished by adding its pyridine solution to a slurry of 0.5 g. of chromic anhydride in 10 ml. of pyridine at 25°. After 18 hr. the mixture was diluted, worked up with water and ether and the dried ether solution concentrated. Crystallization from methanol afforded 65 mg. of bromoketone IIIe, m.p. 176–178°, $[\alpha]_D$ +124°, ν_{max} 1754 cm.$^{-1}$

C. By oxidation of 3-methoxy-16α-bromoestra-1,3,5(10)-trien-17β-ol (VIIIa). Similar treatment of the *trans*-bromohydrin, 0.30 g., in 10 ml. of pyridine with 0.50 g. of chromic anhydride overnight at 25°, yielded an ether-extractable product. This was recrystallized from methanol and proved to be the bromo ketone IIIe, 0.25 g., m.p. 178–181°, identical in infrared absorption to the above samples.

3-Methoxy-16α-chloroestra-1,3,5(10)-trien-17-one (IIIf). A. *By chlorination of the enol acetate* IIa. A solution of chlorine in carbon tetrachloride was prepared by scrubbing commercial chlorine with saturated copper sulfate followed by concentrated sulfuric acid, finally passing it through anhydrous potassium carbonate and into the solvent; in this experiment the chlorine concentration was 0.869*M*.

The 3-methoxy-17-acetoxyestra-1,3,5(10),16-tetraene (IIa), 32.68 g., was dissolved in 1200 ml. of carbon tetrachloride, treated with 35 g. of powdered anhydrous potassium carbonate suspended by powerful stirring, and cooled to 10°. Chlorine solution was added dropwise over a 15-min. period at 9–12°, an additional 35 g. of potassium carbonate being added near the half-way point. After another 30 min. stirring at 12–15°, 35 g. of sodium bisulfite in concentrated solution was added slowly. Gas evolution soon subsided; sufficient water was added to dissolve all salts and the layers were separated. The organic layer was washed twice with water and distilled (drying was unnecessary) to about 200-ml. volume, adding 500 ml. of methanol, concentrating, adding 500 ml. of methanol and concentrating finally to 200 ml. After standing 2 days at room temperature, the mixture was filtered to yield 26.67 g. of high-quality product appearing as elongated plates, m.p. 174–182° (with sweating, beginning at 150° and becoming heavy in the 160–165° region).

Recrystallization twice from methyl alcohol by dissolving, concentrating the solution to half volume and allowing it to stand at room temperature, gave heavy needles, m.p. 175–

179° (with slight sweating at 158°), $[\alpha]_D$ + 161°, ν_{max}1761 cm.$^{-1}$

Anal. Calcd. for $C_{19}H_{23}ClO_2$: C, 71.57; H, 7.27; Cl, 11.12. Found: C, 71.34; H, 7.52; Cl, 11.13.

Crystallization from concentrated solutions in methanol-chloroform, methanol-acetone, and acetone was also satisfactory.

B. By oxidation of 3-methoxy-16α-chloroestra-1,3,5(10)-trien-17α-ol (VIIc). A solution of 0.80 g. of VIIc in 15 ml. of pyridine was added to 1.0 g. of chromic anhydride in 10 ml. of pyridine. After 16 hr. stirring at room temperature, the mixture was diluted with water and extracted with ether. After the usual treatment with dilute hydrochloric acid, sodium bicarbonate, and solid sodium sulfate, the extract was evaporated. Recrystallization from acetone-methanol yielded the chloro ketone IIIf, m.p. 174–181°, identical in all other respects with the above.

C. By oxidation of 3-methoxy-16α-chloroestra-1,3,5(10)-trien-17β-ol (VIIIc). Compound VIIIc, 0.64 g., in 20 ml. of pyridine was oxidized for 20 hr. with 1 g. of oxidant in 10 ml. of pyridine as just described. Recrystallization of the crude product from acetone–petroleum ether, and from methanol, yielded 0.42 g. of IIIf, m.p. 177–180°, having infrared absorption identical with the foregoing preparation.

3-Methoxy-17β-acetoxy-16β,17α-dichloroestra-1,3,5(10)-triene (IV). In another preparation of IIIf by procedure A, special consideration was given the mother liquors remaining after removal of first and second crops of desired product. These liquors were evaporated *in vacuo* leaving a dark, oily semicrystalline mixture. Chromatography of 21.8 g. on 1800 g. of silica, with benzene elution and automatic collection of eluates, yielded an initial peak of 2.38 g., on which a molar yield of 3.74% was calculable from the weight of enol acetate chlorinated. Recrystallization of this fraction from acetone, acetone–petroleum ether, or methanol yielded IV as small rosettes of heavy needles, m.p. 135–136°, $[\alpha]_D$ +62.6°.

Anal. Calcd. for $C_{21}H_{26}Cl_2O_3$: C, 63.47; H, 6.60; Cl, 17.85. Found: C, 63.83; H, 6.14; Cl, 17.95.

3-Ethoxy-16α-chloroestra-1,3,5(10)-trien-17-one. Using the procedure outlined for the methyl ether, 3.40 g. of enol acetate, IIb, in 100 ml. of carbon tetrachloride, 20 g. of potassium carbonate, and 15.7 ml. of 0.727*M* chlorine solution yielded a colorless glass which crystallized from 175 ml. of methanol giving 1.92 g. of flat needles, m.p. 158–166°. Recrystallization from acetone-methanol gave analytical quality material, m.p. 164.5–166.8°, $[\alpha]_D$ +153.5°.

Anal. Calcd. for $C_{20}H_{25}ClO_2$: C, 72.16; H, 7.57; Cl, 10.65. Found: C, 71.95; H, 7.47; Cl, 10.46.

3-n-Propoxy-16α-chloroestra-1,3,5(10)-trien-17-one. The preparation from IIc was like that of the ethers described above. Recrystallization from acetone–petroleum ether gave pure material, m.p. 138–140°, $[\alpha]_D$ +149°.

Anal. Calcd. for $C_{21}H_{27}ClO_2$: C, 72.71; H, 7.85. Found: C, 72.71; H, 7.54.

3-Methoxy-16β-bromoestra-1,3,5(10)-trien-17-one (Vb). *A. By acid-catalyzed epimerization of 16α-bromide* IIIe. A solution of 1.0 g. of IIIe in 45 ml. of ethanol, 2 ml. of water, and 2 ml. of concd. sulfuric acid was refluxed for 18 hr., cooled, diluted with water, and filtered. The total solid showed the rotation, $[\alpha]_D$ +133°. Retreatment of this solid in the same way changed the rotation to $[\alpha]_D$ +142°. This value rose to +150° and remained constant after 72- and 144-hr. treatments. Careful crystallization from methanol of the product of a 144-hr. reflux period led to pure Vb, m.p. 145–148°, $[\alpha]_D$ +164°.

Anal. Calcd. for $C_{19}H_{23}BrO_2$: C, 62.81; H, 6.38. Found: C, 62.54; H, 6.12.

B. By epimerization of 16α-bromide IIIe *with lithium bromide.* A solution containing 5.0 g. of lithium bromide in 40 ml. of dimethylformamide was added to 2.0 g. of IIIe and the mixture stirred at room temperature for 24 hr., diluted with hot water, and filtered. The precipitate was extracted with benzene and this solution washed, dried, and evaporated *in vacuo*. Crystallization from methanol yielded 1.85 g. of impure 16β-bromide, m.p. 128–140°, $[\alpha]_D$ +147°. A similar product was obtained after 4.5-hr. reaction time. Rotational data suggest these products to be mixtures of isomers although infrared absorption in each case was nearly identical with the pure 16β-isomer Vb.

3-Methoxy-16β-chloroestra-1,3,5(10)-trien-17-one (Vc). *A. By displacement with the 16α-bromide* IIIe. Lithium chloride, 30 g., was dissolved in 200 ml. of warm dimethylformamide and 10.0 g. of 3-methoxy-16α-bromoestra-1,3,5(10)-trien-17-one was added at room temperature. The solution became homogeneous after stirring 2 hr., and after 6 hr. it was diluted with water and filtered. Recrystallization afforded 8.15 g. of crystals, m.p. 128–133°. Careful recrystallization from methylene chloride-methanol and from acetone–petroleum ether gave the pure 16β-chloro-ketone, m.p. 138–140°, $[\alpha]_D$ +161°, ν_{max} 1758 cm.$^{-1}$

Anal. Calcd. for $C_{19}H_{23}ClO_2$: C, 71.57; H, 7.27; Cl, 11.12. Found: C, 71.49; H, 7.58; Cl, 11.08.

By quenching aliquots at 0.5- and 3-hr. periods and determining the chloride and bromide content of the whole, precipitated samples, the reaction was estimated to be 31% and 98% complete at these times.

B. By isomerization of the 16α-chloro ketone IIIf. A solution of 0.5 g. of IIIf in 50 ml. of benzene was stirred 16 hr. with 10 g. of Woehlm alkaline alumina at room temperature. The solution was then filtered and chromatographed quickly on silica gel. Elution with 5% ethyl acetate yielded 0.37 g. of semicrystalline material separable by fractional crystallization from aqueous methanol and acetone–petroleum ether into IIIf, m.p. 163–172° and Vc, m.p. 133–138°. Infrared correlations of these preparations with those reported above were confirmatory.

C. By oxidation of the trans-chlorohydrin XII. A solution containing 0.90 g. of chlorohydrin in 30 ml. of pyridine was added to the complex from 2 g. of chromic anhydride in 50 ml. of pyridine. After stirring overnight at room temperature the reactants were diluted with water and processed with ether as described above. The ethereal residue crystallized from methanol, giving 0.40 g. of Vc, m.p. 132–134°, having an infrared pattern identical with an authentic sample.

D. By oxidation of the cis-chlorohydrin VI. Similar oxidation of 0.50 g. of *cis*-chlorohydrin in 10 ml. of pyridine with 1.0 g. of chromic anhydride in 10 ml. of pyridine and recrystallization of the product from methanol gave 0.33 g. of pure 3-methoxy-16β-chloroestra-1,3,5(10)-trien-17-one, m.p. 138–140°, whose identity was again confirmed by the infrared spectrum.

E. By hydrolysis of the adduct IV. A solution of the enol acetate dichloride IV, 0.10 g., in 50 ml. of methanol, containing 1.0 ml. of concd. hydrochloric acid, was stirred at room temperature for 18 hr., diluted with water, and filtered. Recrystallization of the precipitate from methanol yielded 55 mg. of pure 16β-chloride, m.p. 140–142°, again having an infrared curve identical with that of Vc.

F. By displacement of the 16α-p-toluenesulfonoxy group of XIVb. A solution of 2.0 g. of lithium chloride and 0.88 g. of the ketol tosylate XIVb in 100 ml. of dimethylformamide was stirred at room temperature for 28 hr. The mixture was diluted with water and filtered, yielding 0.75 g. of crystals, m.p. 126–132°. Recrystallization gave 0.50 g. of pure Vc, m.p. 137–139°, characterized by the correct infrared spectrum. The recrystallization liquors afforded a second crop, 0.15 g., m.p. 120–125°, which appeared to consist mainly of 16β-chloride contaminated with a small amount of 16α-chloride IIIf.

3-Methoxy-16β-fluoroestra-1,3,5(10)trien-17-one (Vd). Five grams of 3-methoxy-16α-iodoestra-1,3,5(10)-trien-17-one, IIId, was refluxed in 130 ml. of acetonitrile for 16 hr. under a Soxhlet extractor containing 25 g. of commercial silver fluoride. The solution was cooled, filtered, diluted with two volumes of chloroform, washed, dried over magnesium sulfate, and evaporated to a dark oil. This, in 20 ml. of benzene and 40 ml. of petroleum ether, was passed over 25 g. of 60-

mesh Florisil and eluted with 250, 200, and 200 ml. of 25%, 50%, and 100% benzene in petroleum ether, respectively. The heavy color remained adsorbed and the collected eluates were evaporated to leave 4.02 g. of oily plates. Chromatography on 100 g. of silica and elution with 75% benzene in petroleum ether brought down 2.35 g. of material which was crystallized from methanol, twice from benzene–petroleum ether, and from ethanol. The desired product formed irregular, heavy needles, m.p. 166–168°, $[\alpha]_D$ + 157°, ν_{max} 1766 cm.$^{-1}$

Anal. Calcd. for $C_{19}H_{23}FO_2$: C, 75.47; H, 7.67; F, 6.28. Found: C, 74.88; H, 7.58; F, 6.04.

3-Acetoxy-16β-fluoroestra-1,3,5(10)-trien-17-one A saturated solution was prepared by heating 25 g. of purified acetonitrile with 10 g. of commercial silver fluoride and filtering the hot mixture. To the filtrate 3.5 g. of 3-acetoxy-16α-iodoestra-1,3,5(10)-trien-17-one, IIIa, was added and the mixture heated on the steam bath for 1.5 hr., treated with an additional 10 g. of silver fluoride, heated for a like period and set aside for 3 days. It was again heated to boiling, filtered, and the cooled filtrate diluted with ether, washed, dried, and evaporated. The resulting brown gum was reacetylated for 30 min. in 20 ml. of refluxing acetic anhydride, the excess being removed *in vacuo*. This residue in 50 ml. of benzene and 30 ml. of petroleum ether was passed over 100 g. of silica and eluted with mixtures of benzene–petroleum ether through pure benzene. The crude product, 1.05 g., was removed with 5% ethyl acetate in benzene. It was recrystallized twice from ether and three times from benzene-pentane. The pure product melted at 182–184°, $[\alpha]_D$ +145°.

Anal. Calcd. for $C_{20}H_{23}FO_3$: C, 72.70; H, 7.02; F, 5.75. Found: C, 72.80; H, 6.72; F, 6.2.

3-Methoxy-16β-chloroestra-1,3,5(10)-trien-17β-ol (VI). The ketone Vc was reduced by adding 5.15 g., dissolved in 40 ml. of tetrahydrofuran, to a stirred solution of 0.80 g. of lithium aluminum hydride in 100 ml. of ether at 0° during 10 min. After careful dilution with water, acidification with dilute hydrochloric acid, extraction with benzene and washing the benzene solution with aqueous sodium bicarbonate, drying, and concentrating to dryness *in vacuo*, the chlorohydrin was obtained. This crystallized nicely from acetone–petroleum ether as fine, felted rods, 3.05 g., m.p. 116–118°. Further crystallization from aqueous methanol raised the melting point to 118–120°, $[\alpha]_D$ +69°, ν_{max} 3584 cm.$^{-1}$ The sample appeared to be homogeneous by column and paper chromatography.

Anal. Calcd. for $C_{19}H_{25}ClO_2$: C, 71.12; H, 7.85. Found: C, 71.16; H, 7.85.

The acetate was prepared by heating 0.33 g. of chlorohydrin with 4 ml. of acetic anhydride in 8 ml. of pyridine at 100° for 20 min., diluting with water and extracting with benzene. The usual washing, drying, and concentration gave 0.15 g. of 3-methoxy-16β-chlorestra-1,3,5(10)-trien-17β-ol acetate, m.p. 116–120°, crystallizing from methanol. Further recrystallization gave the sample for analysis, m.p. 126–127°, $[\alpha]_D$ +101°.

Anal. Calcd. for $C_{21}H_{27}ClO_3$: C, 69.50; H, 7.50. Found: C, 69.64; H, 7.59.

The structure of chlorohydrin VI was confirmed by refluxing 0.64 g. of the substance under nitrogen with 1.0 g. of potassium hydroxide in 50 ml. of methanol for 48 hr., cooling, diluting, and filtering the mixture. The precipitate was recrystallized from aqueous acetone, affording 0.52 g. of estrone methyl ether, m.p. 168–171°, identical to an authentic sample.

3,17-17-Trimethoxyestra-1,3,5(10)-trien-16α-ol (XIIIa). Sixty-three grams of 16α-bromo ketone IIIe was dissolved in 700 ml. of anhydrous methanol, containing 20 g. of dissolved sodium metal, and stirred at room temperature in a stoppered flask for 65 hr. Dilution with 2 l. of water followed by filtration and washing yielded 57.3 g. of XIIIa, m.p. 132–134°. Recrystallization of a portion of this from petroleum ether gave analytical material, m.p. 136–138°, $[\alpha]_D$ +11.5°, ν_{max} 3542 cm.$^{-1}$

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73; OCH_3, 26.87. Found: C, 73.09; H, 8.83; OCH_3, 25.80.

The acetate XIIIc was prepared by treating 0.10 g. of hydroxyketal with 2 ml. of pyridine and 1 ml. of acetic anhydride for 18 hr. at room temperature, diluting with water, collecting, and recrystallizing the crude product from petroleum ether. The purified 3,17,17-trimethoxyestra-1,3,5(10)-trien-16α-ol acetate melted at 124–125°.

Anal. Calcd. for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 71.17; H, 8.28.

3,17,17-Trimethoxyestra-1,3,5(10)-trien-16α-ol p-toluenesulfonate (XIIIb). A solution containing 2.0 g. of XIIIa and 2.0 g. of *p*-toluenesulfonyl chloride in 30 ml. of pyridine was set aside overnight, stirred for 10 min. with aqueous potassium bicarbonate and finally precipitated completely with an excess of water. The crude product, washed and dried, weighed 2.50 g., m.p. 158–165°. Recrystallization of a portion from methylene chloride-methanol afforded pure material, m.p. 166–167°, $[\alpha]_D$ +12°.

Anal. Calcd. for $C_{28}H_{36}O_6S$: C, 67.17; H, 7.25. Found: C, 67.00; H, 7.35.

3-Methoxy-16α-hydroxyestra-1,3,5(10)-trien-17-one (XIVa). Hydrolysis of 0.20 g. of the dimethylketal XIIIa was achieved by treating with 150 ml. of *t*-butyl alcohol, 30 ml. of water, and 0.40 g. of *p*-toluenesulfonic acid, distilling slowly for 45 min., cooling, diluting with water, and filtering. The precipitate, dried and recrystallized from acetone–petroleum ether, amounted to 85 mg. of pure product, m.p. 156–157°, $[\alpha]_D$ +176°.

Anal. Calcd. for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 75.81; H, 8.22.

The identity of this product was shown by comparing with an authentic sample.[13]

3-Methoxy-16α-hydroxyestra-1,3,5(10)-trien-17-one p-toluenesulfonate (XIVb). The dimethylketal XIIIb, 2.50 g., was boiled for 4 min. with 200 ml. of ethanol containing 5 ml. of concd. hydrochloric acid. The precipitate, which had appeared shortly upon heating, was collected from the chilled mixture and washed generously with water. The dried product, 2.05 g., m.p. 203–204°, was recrystallized from acetone–petroleum ether, giving a pure sample, m.p. 204–205°, $[\alpha]_D$ +114°.

Anal. Calcd. for $C_{26}H_{30}O_5S$: C, 68.70; H, 6.65. Found: C, 68.39; H, 6.71.

3-Methoxy-16α-bromoestra-1,3,5(10)-trien-17α-ol (*VIIa*) *and 3-methoxy-16α-bromoestra-1,3,5(10)-trien-17β-ol* (VIIIa).[30] Twenty grams of 16α-bromo ketone IIIe in 120 ml. of tetrahydrofuran was added in 10 min. to a stirred suspension of 2.0 g. of lithium aluminum hydride in 200 ml. of anhydrous ether at an internal temperature of 5–10°, maintained by an ice-salt bath. Cautious addition of water followed by 50 ml. of 5% hydrochloric acid, the usual extraction with benzene, water, sodium bicarbonate, and drying, followed by distillation *in vacuo*, gave a colorless glass. This was dissolved in 10% benzene–petroleum ether and chromatographed on Florex; elution of the two main fractions was accomplished with 25% benzene and 75% benzene in petroleum ether, respectively.

The first peak, 7.46 g. of crude, crystalline product, was recrystallized from acetone, the pure product appearing as heavy staffs, m.p. 149–150°, $[\alpha]_D$ +75°, ν_{max} 3584 cm.$^{-1}$ This was the *cis*-bromohydrin VIIa.

Anal. Calcd. for $C_{19}H_{25}BrO_2$: C, 62.46; H, 6.90. Found: C, 62.61; H, 6.72.

Proof of the *cis* configuration of VIIa was obtained by refluxing 0.20 g. of the compound in 20 ml. of methanol for 5 hr. with 1.0 g. of potassium hydroxide under nitrogen. The product, 0.15 g., was obtained by dilution, filtration, and washing; it melted at 172–175° and displayed the infrared pattern of estrone methyl ether.

---

(30) We wish to acknowledge with thanks the assistance of Mr. P. Yonan of the Division of Chemical Research in carrying out large scale preparations.

Fractions constituting the second peak, 13.8 g., crystallized slowly. Recrystallization of 3 g. from ether–petroleum ether yielded 1.7 g. of *trans*-bromohydrin VIIIa, m.p. 104–105°, $[\alpha]_D$ +79°, ν_{max} 3650 cm.$^{-1}$

Anal. Found: C, 62.65; H, 6.77.

3,17α-Dihydroxy-16α-bromoestra-1,3,5(10)-triene (VIIb) *and 3,17β-dihydroxy-16α-bromoestra-1,3,5(10)-triene* (VIIIb). Reduction of bromo-ketone IIIb, 3.2 g., in 30 ml. of tetrahydrofuran, with 1.0 g. of lithium aluminum hydride in 100 ml. of ether was carried out during 10 min. at 0°. After an additional 10 min. of stirring, addition of water and then dilute hydrochloric acid and extraction with benzene, 2.70 g. of crystalline product (no infrared carbonyl absorption) was obtained. This was chromatographed on 150 g. of Florisil. The *cis*-bromo-hydrin VIIb was eluted first with benzene; after recrystallization from acetone this amounted to 0.25 g. of pure product, m.p. 253–255°, $[\alpha]_D$ +71.5°.

Anal. Calcd. for $C_{18}H_{23}BrO_2$: C, 61.54; H, 6.60. Found: C, 61.78; H, 6.79.

Continued elution with benzene brought down a mixture of the two bromohydrins followed by the pure *trans* isomer VIIIb. This was recrystallized from acetone–petroleum ether, giving 1.40 g. of good product, m.p 217–219°, $[\alpha]_D$ +81.5°.

Anal. Found: C, 61.65; H, 6.30.

The *cis* configuration of VIIb was confirmed by refluxing 53 mg. of the latter with alcoholic potassium hydroxide under nitrogen for 6 hr. Dilution and acidification yielded 32 mg. of crystals, m.p. 250–262°, identical by infrared absorption with estrone.

3-Methoxy-16α-chloroestra-1,3,5(10)-trien-17α-ol (VIIc) *and 3-methoxy-16α-chlorestra-1,3,5(10)-trien-17β-ol* (VIIIc). Reduction of 15.0 g. of chloro ketone IIIf in 100 ml. of tetrahydrofuran with 2.0 g. of lithium aluminum hydride and 100 ml. of ether was performed exactly as described for IIIe above. Direct recrystallization of the benzene-extracted material from methanol yielded 3.67 g. of the *cis*-chlorohydrin VIIc as rods, m.p. 163–164°, $[\alpha]_D$ +68°, ν_{max} 3597 cm.$^{-1}$

Anal. Calcd. for $C_{19}H_{25}ClO_2$: C, 71.12; H, 7.85. Found: C, 71.39; H, 7.80.

Acetylation of 0.25 g. in 10 ml. of pyridine and 5 ml. of acetic anhydride at 100° for 30 min. and recrystallization of the crude product from aqueous acetone gave 0.25 g. of 3-methoxy-16α-chloroestra-1,3,5(10)-trien-17α-ol acetate, m.p. 141–143°, $[\alpha]_D$ +1.9°.

Anal. Calcd. for $C_{21}H_{27}ClO_2$: C, 69.50; H, 7.50. Found: C, 69.47; H, 7.79.

The structure of VIIc was confirmed by refluxing 1.28 g. in 50 ml. of ethanol and 1.0 g. of potassium hydroxide under nitrogen for 80 hr. Extraction with benzene as usual, and chromatography on silica gel, yielded 0.36 g. of estrone methyl ether.

Mother liquors from crystallization of VIIc yielded a residue which, chromatographed on 200 g. of Florex and eluted with 30% benzene–petroleum ether, produced initially more of the *cis* isomer. Continued elution with this solvent brought down the *trans* isomer which, recrystallized from acetone–petroleum ether, amounted to 5.9 g. of VIIIc, m.p. 113–115°, $[\alpha]_D$ +69.0°, ν_{max} 3650 cm.$^{-1}$

Anal. Found: C, 71.40; H, 7.71.

Acetylation as above resulted in 0.25 g. of 3-methoxy-16α-chloroestra-1,3,5(10)-trien-17β-ol acetate, m.p. 168–169°, $[\alpha]_D$ +50.6°.

Anal. Found: C, 69.39; H, 7.90.

3-Methoxyestra-1,3,5(10),16-tetraene (X). Treatment of 1.0 g. of *cis*-bromohydrin VIIa for 3 hr. at reflux with 2 g. of zinc dust stirred in 40 ml. of acetic acid, followed by cooling, filtration, and dilution with water, precipitated 0.68 g. of product. This was collected, washed, and dried. It melted at 65–67° and was recrystallized from isopropyl alcohol, giving 0.42 g. of long rods, m.p. 71–72°, $[\alpha]_D$ +113°, having the correct analysis and infrared spectrum for the structure X.[13]

Pure *cis*-bromohydrin was not required for this preparation and a simpler method utilized the crude mixture of VIIa and VIIIa obtained directly from lithium aluminum hydride reduction: 42.5 g. of the mixture was stirred at reflux with 20 g. of zinc in 300 ml. of acetic acid. At 10-min. intervals during 1 hr., 10-g. increments of zinc dust were added. Processing as above yielded initially 28.0 g. of crystals, m.p. 55–63°. Chromatography on 200 g. of silica gel and elution with 10% benzene–petroleum ether gave 23.6 g. of crystals, purified from isopropyl alcohol to 19.8 g. of X, m.p. 67–69°.

3-Methoxy-16α,17α-epoxyestra-1,3,5(10)-triene (XI).[13] Epoxidation of 19.75 g. of X in 100 ml. of benzene with 540 ml. of 0.12*M* perbenzoic acid, initially at 10°, at room temperature for 16 hr. followed by three extractions with 2% potassium hydroxide and three extractions with water, drying (anhydrous magnesium sulfate), and concentration *in vacuo* gave a residue which was recrystallized from aqueous methanol to yield 13.5 g. of XI, m.p. 117–119°.

3-Methoxy-16β-chloroestra-1,3,5(10)-trien-17α-ol (XII). Concentrated hydrochloric acid, 40 ml., was cooled to 0°, stirred with 4.3 g. of XI in 100 ml. of chloroform at 0° for 5 min. and the mixture transferred to a separatory funnel, shaken for 5 min., and the layers separated. The chloroform layer was washed three times with water, dried over magnesium sulfate, and evaporated *in vacuo*. Crystallization of the residue from petroleum ether gave 3.85 g. of fluffy crystals, m.p. 62–64°; recrystallization provided an analytical sample XII, m.p. 64–66°, $[\alpha]_D$ +48°, ν_{max} 3643 cm.$^{-1}$

Anal. Calcd. for $C_{19}H_{25}ClO_2$: C, 71.12;H, 7.85 Found: C, 71.12; H, 7.69.

3-Methoxy-16β,17β-epoxyestra-1,3,5(10)-triene (IX). *A. From the transbromohydrin* VIIIa.[30] The crude *trans*-bromohydrin as eluted from the chromatographic column, 27.8 g., was refluxed with stirring for 18 hr. with 1000 ml. of methanol and 5.0 g. of potassium hydroxide. An atmosphere of nitrogen was employed. The solution was cooled, diluted with 2.5 l. of cold water, and the product collected. It was washed with water and dried below 60°; it weighed 22 g. In order to free the oxide from traces of estrone methyl ether this was dissolved in 150 ml. of benzene, adsorbed onto 800 g. of Florex packed under petroleum ether, and eluted with 50% benzene–petroleum ether. The yield of crystalline oxide here was 12 g.; 45 g. of such material was crystallized by adding pentane to a concentrated ether solution and chilling to give 39 g. of epoxide IX, m.p. 110–113°. Analytical material showed m.p. 116–117°, $[\alpha]_D$+115°.

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.04; H, 8.75.

B. From the trans-chlorohydrin VIIIc. A solution of 1.28 g. VIIIc and 1.0g. of potassium hydroxide in 50 ml. of methanol was treated for 3 days under the above conditions. Dilution with water and extraction with benzene yielded 1.22 g. of an oil which was crystallized from aqueous methanol and recrystallized from ether to give 0.13 g. of the pure oxide, m.p. 116.0–116.5°, $[\alpha]_D$ +115°, having the correct analysis and infrared spectrum.

Proof of structure was obtained by treating 0.56 g. of IX in 30 ml. of ether with 0.3 g. of lithium aluminum hydride in 30 ml. of ether with stirring at room temperature for 3 days. The usual work-up yielded a residue which was chromatographed on 30 g. of silica gel. Elution with 2% ethyl acetate in benzene resulted in 0.33 g. of an oil, crystallizing from aqueous ethanol to give 3-methoxy-16β-hydroxyestra-1,3,5-(10)-triene, m.p. 102–105°.[13,31]

3-Methoxy-17α-bromoestra-1,3,5(10)-trien-16-one (XVIa) *A. From the β-oxide* IX. A solution of 5.2 g. of β-oxide IX in 125 ml. of chloroform was chilled in ice and shaken 5 min. with 50 ml. of chilled 48% hydrobromic acid. A rose color developed quickly. Ice water was added, the layers separated, and the chloroform solution washed thoroughly, dried, and

(31) M. N. Huffman and M. H. Lott, *J. Biol. Chem.*, **213**, 343 (1955).

concentrated to dryness *in vacuo* below 50°. The residual glass, a mixture of bromohydrins VIIIa and XVa, would not crystallize. It was dissolved in 60 ml. of pyridine and added at 23° to a suspension of 12.0 g. of chromic anhydride in 120 ml. of pyridine (prepared at 10°). The mixture was stirred 3 hr. and the resulting suspension of black tar then diluted with 500 ml. of cold water and extracted with 900 ml. of ether in four passes. The collected extracts were washed thoroughly with water, 3% hydrochloric acid, water, and brine. Upon drying and concentrating to a small volume this solution deposited crystals which were collected and washed with cold ether, 4.92 g., m.p. 128–160°. This material was dissolved in 100 ml. of ether and the solution decanted from crystals deposited after one hour at room temperature. The decantate, concentrated to 35 ml. and crystallized at room temperature, deposited rosettes of long, hexagonal needles, m.p. 135–137° which were recrystallized twice from ether, once at room temperature and once with chilling, to give pure XVIa, m.p. 135.2–136.9°, $[\alpha]_D$ −5°, ν_{max} 1756 cm.$^{-1}$

Anal. Calcd. for $C_{19}H_{23}BrO_2$: 62.81; H, 6.38; Br, 22.00. Found: C, 62.74; H, 6.40; Br, 21.84.

In another experiment, the rotation of the total crude product, $[\alpha]_D$ +19°, suggested the presence of about 80% of XVIa contaminated with IIIe. Proof of this point was obtained when the collected mother liquors on standing, deposited a "tree" of heavy needles, m.p. 134.6–136.1, $[\alpha]_D$ −4.5°, in the presence of short hexagonal rods, m.p. 176–181°, $[\alpha]_D$ +109°, having all the properties of IIIe.

B. By oxidation of the cis-bromohydrin XVIII. A solution of 0.75 g. of *cis*-bromohydrin, m.p. 125.0–126.5°, in 10 ml. of pyridine was oxidized, as above with 1.8 g. of chromic anhydride. The ethereal extracts yielded 0.64 g. of crystals, purified to 0.45 g. of XVIa, m.p. 135–136°, $[\alpha]_D$ −4.4°, having the correct infrared spectrum.

3-Methoxy-17α-chloroestra-1,3,5(10)-trien-16-one (XVIb). One gram of oxide IX in 25 ml. of chloroform was chilled in ice, shaken for 15 min. with 20 ml. of chilled concd. hydrochloric acid, and worked up with addition of water. Evaporation of the dried chloroform solution left 1.25 g. of a clear oil, the chlorohydrin XVb, which could not be crystallized. The latter in 15 ml. of pyridine was added to a stirred suspension of 2.4 g. of chromic anhydride in 24 ml. of pyridine at room temperature. After 1.5 hr. and mixture was treated as usual with ether and water. The ethereal residue was a clear glass weighing 1.14 g. Chromatography on 30 g. of 100-mesh silicic acid with chloroform yielded 0.91 g. of crystalline material which was further purified through slow crystallization from an evaporating ether solution to give clusters of heavy needles, 0.3 g. Recrystallization once more from ether resulted in pure chloro ketone XVIb, m.p. 111.1–112.5°, $[\alpha]_D$ −49.0°, ν_{max} 1761 cm.$^{-1}$

Anal. Calcd. for $C_{19}H_{23}ClO_2$: C, 71.57; H, 7.27; Cl, 11.12. Found: C, 71.36; H, 7.30; Cl, 11.42.

3-Methoxy-17α-bromoestra-1,3,5(10)-trien-16α-ol (XVIII). A solution of 6.45 g. of XVIa in 60 ml. of tetrahydrofuran was added in 10 ml. to a stirred suspension of 1.0 g. of lithium aluminum hydride in 100 ml. of dry ether at 1–6°. After another 3 min. water was cautiously added, followed by processing as described previously, leaving 6.50 g. of solvent-free residue, a thick, colorless oil. During chromatography on 200 g. of Florex, elution with 40% benzene–petroleum ether provided 4.51 g. of crystalline material. Two recrystallizations from acetone-pentane afforded XVIII, 2.68 g., as transparent plates, m.p. 125.0–126.5°, $[\alpha]_D$ +7.9°, ν_{max} 3558 cm.$^{-1}$

Anal. Calcd. for $C_{19}H_{25}BrO_2$: C, 62.46; H, 6.90; Br, 21.88. Found: C, 62.46; H, 6.64; Br, 21.66.

We were unable to demonstrate the presence of another isomer in any of the chromatographic fractions.

Reoxidation of this bromohydrin to the original ketone, described above, showed retention of halide configuration. Confirmation of the *cis* configuration was obtained by refluxing 0.50 g. of XVIII with 1 g. of potassium hydroxide in 25 ml. of methanol for 20 hr. under nitrogen. Extraction with ether and crystallization of the product twice from ether-pentane yielded 0.15 g. of square plates of 3-methoxyestra-1,3,5(10)-trien-16-one, XIX, m.p. 128.9–130.0°[13,32] depressing the melting point of IX but not that of an authentic specimen of the 16-ketone, with which the infrared spectrum was also identical.

The α-configuration of hydroxyl, and hence of bromide, was demonstrated by hydrogenolysis. A solution of 0.20 g. of XVIII in 60 ml. of ethyl alcohol was stirred 30 hr. with 0.5 g. of 5% palladium on calcium carbonate in a hydrogen atmosphere. After addition of an equal amount of catalyst stirring was continued for 40 hr. Concentration of the filtered solution gave a semicrystalline residue which was triturated with 50 ml. of ether and again filtered. Addition of petroleum ether to the filtrate followed by concentration to a small volume gave 0.12 g. of long rods, m.p. 113–116°. Recrystallization from ether–petroleum ether yielded pure 3-methoxyestra-1,3,5(10)-trien-16α-ol, m.p. 115–116°,[33] $[\alpha]_D$ +79.5°, ν_{max} 3660 cm.$^{-1}$

Anal. Calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.72; H, 9.24.

Since the properties of the latter had apparently not been previously reported, it was prepared otherwise by hydrolysis of 0.54 g. of the acetate[34] in 20 ml. of methanol and 5 ml. of 10% aqueous potassium hydroxide for 2 hr. The solution, cooled, diluted, and filtered, yielded 0.49 g. of compound, m.p. 115–116°, identical in its infrared absorption with the above.

3-Methoxy-17β-bromoestra-1,3,5(10)-trien-16-one (XXa). A solution of 0.20 g. of 17α-bromo ketone XVIa and 0.50 g. of *p*-toluenesulfonic acid in 10 ml. of acetic acid was refluxed for 68 hr. The crude product, 0.17 g., obtained by evaporation *in vacuo* of a washed and dried benzene extract of the diluted reaction mixture, was chromatographed in benzene on 4 g. of silica. The semicrystalline material, 0.16 g., eluted with 1% ethyl acetate was recrystallized from methylene chloride–methanol and finally methanol, giving the pure XXa, m.p. 226–229° (softening at 223°), $[\alpha]_D$ −100°, ν_{max} 1761 cm.$^{-1}$

Anal. Calcd. for $C_{19}H_{23}BrO_2$: C, 62.81; H, 6.38. Found: C, 62.87; H, 6.69.

3-Methoxy-17β-chloroestra-1,3,5(10)-trien-16-one (XXb). The 17α-chloro ketone XVIb was epimerized exactly as described above during 75 hr. Chromatography of 0.15 g. of crude benzene-extracted product on 4 g. of silica yielded first 35 mg. of starting material. Further elution with benzene followed by 1% ethyl acetate, afforded 65 mg. of semicrystalline material. This was recrystallized from aqueous methanol to give 20 mg. of XXb crystallizing as a monohydrate, m.p. 211–213°, $[\alpha]_D$ −92°, ν_{max} 1762 cm.$^{-1}$

Anal. Calcd. for $C_{19}H_{23}ClO_2 \cdot H_2O$: C, 67.74; H, 7.48. Found: C, 67.65; H, 7.28.

3-Methoxy-17β-bromoestra-1,3,5(10)-trien-16β-ol (XXI). The bromo ketone XXa, 0.15 g. in 4 ml. of tetrahydrofuran, was reduced at −5° with 70 mg. of lithium aluminum hydride in 10 ml. of ether during 2 min. After the addition of 0.5 ml. of water and 0.1 ml. of 10% potassium hydroxide, the mixture was filtered through a Supercel-magnesium sulfate bed and the solvent removed. Recrystallization of the product, 145 mg., from acetone–petroleum ether yielded 100 mg. of the *cis*-bromohydrin XXI, m.p. 150–151° (softening at 136°). The analytical sample was obtained after two further recrystallizations from petroleum ether, m.p. 150–151°, $[\alpha]_D$ +70°, ν_{max} 3610 cm.$^{-1}$

---

(32) M. N. Huffman and M. H. Lott, *J. Am. Chem. Soc.*, **75**, 4327 (1953).

(33) This compound has been mentioned but not characterized by M. N. Huffman, U. S. Pat. 2,779,773.

(34) This was prepared from the 16β-hydroxy compound according to the directions given by M. N. Huffman and M. H. Lott, *J. Biol. Chem.*, **215**, 627 (1955).

Anal. Calcd. for $C_{19}H_{25}BrO_2$: C, 62.46; H, 6.90. Found: C, 62.47; H, 6.94.

The bromohydrin, 0.22 g. in 20 ml. of acetic acid, was refluxed with stirring and treated with three 2-g. portions of zinc dust at 30-min. intervals. The mixture was cooled, filtered, and concentrated; it was extracted with 1:1 ether–petroleum ether, the extracts being washed, neutralized, dried, and evaporated. Chromatography of the residue on 4 g. of silica and elution with 1:1 benzene–petroleum ether gave 130 mg. of semicrystalline material, recrystallized to 80 mg. of X, m.p. 67–69°, identical with earlier preparations.

Finally, treatment of XXI with alcoholic alkali by the procedure described earlier yielded 3-methoxyestra-1,3,5(10)-trien-16-one, XIX, identical with other samples.

SKOKIE, ILL.

[CONTRIBUTION FROM THE RESEARCH LABORATORY, SHIONOGI & CO., LTD.]

Angular-Substituted Polycyclic Compounds. I. Cyanation of Δ^4-Cholesten-3-one

WATARU NAGATA, SHOICHI HIRAI, HIROSHI ITAZAKI, AND KEN'ICHI TAKEDA

Received August 12, 1960

Optimum conditions for the cyanation of Δ^4-cholesten-3-one were found to be in dimethylformamide in the presence of ammonium chloride. By this method we have been able to synthesize pure samples of 5α- (IV) and 5β-cyanocholestanone (V). The rate of hydrolysis of these compounds has been examined and the respective configurations determined. Some interesting properties of the corresponding acid amides (II and III) of the 5α- and 5β-cyano compounds are discussed.

The introduction of a C-substituent to the angular position of a condensed alicyclic-ring system has been already achieved by many authors.[1] As far as it is known the C_5-substituted cholestane derivatives are Westphalen's diol,[2] Claisen rearrangement products of 3β-vinyloxy-Δ^4-cholestene,[1c] and the product from the fission of 5(6) β-epoxycholestan-3β-ol by a Grignard reagent.[3]

The action of a Grignard reagent on Δ^4-cholesten-3-one[4] or 7-ketocholesterol[5,6] produced only 1,2-addition products and not the anticipated 1,4-addition products. This clearly shows that in the case of a sterically hindered C_5 position the introduction of a bulky substituent, such as the solvated-Grignard reagent, is difficult. Therefore, we attempted the 1,4-addition of the small yet sufficiently nucleophilic CN^- ion on Δ^4-cholesten-3-one. It is well known that the 1,4-addition reaction of potassium cyanide to α,β-unsaturated ketones is a very useful preparative method in organic chemistry.[7]

When Δ^4-cholesten-3-one (I) was treated with potassium cyanide in boiling methanol, four reaction products together with some starting material were obtained and separated by chromatography on alumina. Following the order of the elution, cholestenone, 5α-cyanocholestanone (IV), the dimer (IX), 3α-amino-3β-hydroxy-5α-carboxycholestane lactam (II), and finally 3β-amino-3α-hydroxy-5β-carboxycholestane lactam (III) were obtained in 17.8%, 21.2%, 3.6%, 2.3%, and 26.2% yield, respectively. 5α-Cyanocholestanone (IV) could also be separated by direct crystallization from the reaction mixture before chromatography. It melts at 181–183° and the analytical values are in good agreement with the formula $C_{28}H_{45}ON$. The infrared spectrum in chloroform solution showed absorption bands at 2237 cm.$^{-1}$ (nitrile) and 1723 cm.$^{-1}$ (six-membered ring ketone) but no band corresponding to the α,β-unsaturated ketone. It did not exhibit selective absorption in the ultraviolet spectrum.

The (5 → 3) α-lactam (II) melted at 249–251° and in chloroform solution in the infrared it exhibited bands at 3697 cm.$^{-1}$ (free-OH), 3477 cm.$^{-1}$ (free —NH), 3327 cm.$^{-1}$ (bonded —N—H), 1705 cm.$^{-1}$ (lactam carbonyl), and 1682 cm.$^{-1}$ (associated lactam carbonyl). The (5 → 3)β-lactam (III) (m.p. 200–202°) displayed similar bands in the infrared, *i.e.* 3605 cm.$^{-1}$ (free —OH), 3445 cm.$^{-1}$ (free —N—H), 3300 cm.$^{-1}$ (bonded —NH), 1702 cm.$^{-1}$ (lactam carbonyl), and 1690 cm.$^{-1}$ (associated lactam carbonyl). Neither lactam showed the band of the noncyclic amide in the 1510–1620 cm.$^{-1}$ region.[8] These findings suggest that II and III are C_5 acid amides epimeric at C_5 and furthermore that they exist in the hemiketal

(1) (a) A. J. Birch and R. Robinson, *J. Chem. Soc.*, 501 (1943); (b) R. B. Woodward, *J. Am. Chem. Soc.*, **62**, 1208 (1940); (c) A. W. Burgstahler and J. C. Nordin, *J. Am. Chem. Soc.*, **81**, 3151 (1959); (d) M. S. Ahmad, G. Baddeley, B. G. Heaton, and J. W. Rasburn, *Proc. Chem. Soc.*, 395 (1959).

(2) B. Ellis and V. Petrow, *J. Chem. Soc.*, 2246 (1952).

(3) Y. Urushibara and M. Chuman, *Bull. Chem. Soc.* (Japan), **22**, 69 (1949).

(4) O. C. Musgrave, *J. Chem. Soc.*, 3121 (1951).

(5) S. Weinhouse and M. S. Kharasch, *J. Org. Chem.*, **1**, 490 (1936).

(6) B. Baun, I. M. Heilbron, and F. S. Spring, *J. Chem. Soc.*, 1274 (1936).

(7) (a) H. H. Inhoffen, S. Chütz, P. Rossberg, O. Berges, K. H. Nordsiek, H. Plenio, and E. Höroldt, *Chem. Ber.*, **91**, 2626 (1958) and previous papers; (b) J. Romo, *Tetrahedron*, **3**, 37 (1958); (c) U. R. Ghatak, *Tetrahedron Letters*, **1**, 19 (1959); (d) E. Adlerová, L. Novák, and M. Protiva, *Coll. Czechoslov. Chem. Commun.*, **23**, 681 (1958).

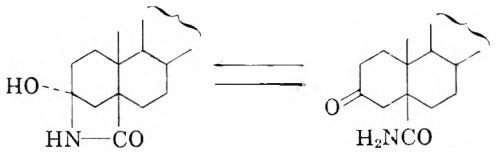


Chart I

form,[9] even in solution. The optical rotatory dispersion curves of II and III showed only plane curves[10]; this is further support for the assigned structures. On the other hand, while the ultraviolet spectrum of II did not show an absorption band corresponding to the carbonyl group that of III showed very weak absorption at 280 mμ (ε 9.6) in ethanol solution. From these findings, the following equilibrium is thought to occur in alcohol solution in the latter case.

The analytical values of the second eluted compound, m.p. 196–198°, agreed with the empirical formula $C_{56}H_{90}O_3N_2$ (Mol.wt. 839.3) and its infrared spectrum showed absorption bands corresponding to a hydroxyl group (3683 cm.$^{-1}$), imide (3443 cm.$^{-1}$), bonded imine (3240 cm.$^{-1}$), nitrile (2255 cm.$^{-1}$), lactam carbonyl (1705 cm.$^{-1}$) and associated lactam carbonyl group (1685 cm.$^{-1}$). Although the molecular weight determination by *Rast* showed only 623.5, the structure of this compound was assumed to be a dimer having either formula IXa, IXb, or IXc.

In this experiment, 5β-cyanocholestanone was not isolated but (5 → 3)β-lactam (III) was obtained in considerable yield. Since the 5α-cyano group is both axial to ring A and B, while its β-epimer is axial to ring A but equatorial to ring B as shown in the Fig. 1, hydrolysis of the 5β-cyano group may

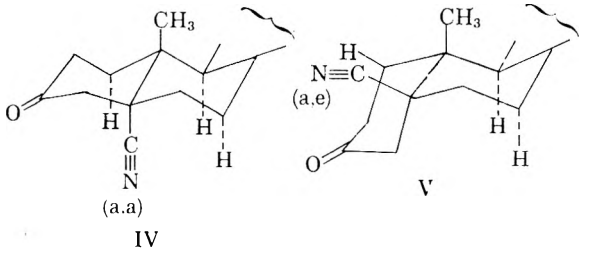


Figure 1

be much more easier than that of the 5α-epimer. For this reason, it is suggested that 5β-cyanocholestanone was more easily hydrolyzed[11] than the 5α-epimer by the action of potassium cyanide as a strong base and yielded (5 → 3)β-lactam (III). In order to avoid this side reaction, cyanation of I was carried out with two mole equivalents of potassium cyanide and 1.5 mole equivalents ammonium chloride in dimethylformamide. As the excess ammonium hydroxide, which was produced by the consumption of cyanide anion, was liberated as ammonia by heating, the reaction mixture was maintained at minimal basicity. Under these conditions, a mixture of 5α- and 5β-cyanocholestanone and a small amount of lactam[12] were obtained in *ca.* 82% (total yield), as expected. Neither starting material nor the dimer (IX) was isolated from the reaction mixture. The separation of each 5α- and 5β-epimer from the reaction mixture by repeated chromatography on alumina and recrystallization was almost always unsatisfactory. The 5β-cyano ketone was eluted together with its 5α-epimer at the same time or after some elution of the 5α-cyano ketone from the alumina column. A similar result was observed in the case of the epimeric pair of (5 → 3)-lactams. Such exceptions have been reported in the literature.[13] However, it was found that the tosyl hydrazones of the 5-cyano epimers were suitable for separation by either chromatography on alumina or by recrystallization. Hydrolysis of each epimer with pyruvic acid then gave the pure 5α- and 5β-cyano compounds. 5β-Cyanocholestanone (V), m.p. 127–128° was thus obtained and showed absorption bands in the infrared in chloroform solution at 2237 cm.$^{-1}$ (CN) and 1723 cm.$^{-1}$ (six-membered ring ketone) and the corresponding monosemicarbazone had m.p. 155–160°. The ratio of the yield of the 5α and 5β derivatives is about 1:1.[14]

From the conformational considerations discussed above, it can be seen that the 5β-cyano compound should be more easily saponified than the 5α-epimer. This was confirmed experimentally by examining the hydrolysis[15,16] rate of both the 5α- and 5β-cyanocholestanone using the absorption band at 2237 cm.$^{-1}$ in the infrared spectrum as a measure of the concentration of the nitrile group. The intensity of the band at 2237 cm.$^{-1}$ of each

(8) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, Methuen & Co., Ltd., London, second edition 1958, p. 203.

(9) It is known that several amides of β-benzoylpropionic acid exist in the hemiketal form in solution. (*cf.* N. H. Cromwell and K. E. Cook, *J. Am. Chem. Soc.*, 80, 4573 (1958) and other references cited there).

(10) We are most grateful to Dr. C. Djerassi for measuring the optical rotatory dispersions.

(11) Ref. D. H. R. Barton and R. C. Cookson, *Quart. Rev.*, 10, 60 (1956).

(12) It was observed that the mixture of 5α- and 5β-cyano ketone gave (5 → 3)β-lactam in *ca.* 25% yield after chromatography on basic alumina. This observation suggested also the sensitivity of the 5β-cyano ketone (V) towards alkali indicating that the actual yield of the formed III was much lower than that actually isolated.

(13) For example, J. A. Cella, E. A. Brown, and R. R. Burtner, *J. Org. Chem.*, 24, 743 (1959).

(14) See Experimental.

(15) The use of the word "saponification or hydrolysis" may not be adequate here. Hence, in this case these words should be interpreted as the decomposition rate of the cyano group, especially in the case of 5α-cyano ketone.[14]

(16) For the measurement of the optical densities, a "Koken DS 301" (double beam) was used. All measurements of infrared spectra were performed by Mr. Y. Matsui in this laboratory, to whom we wish to express our profound thanks.

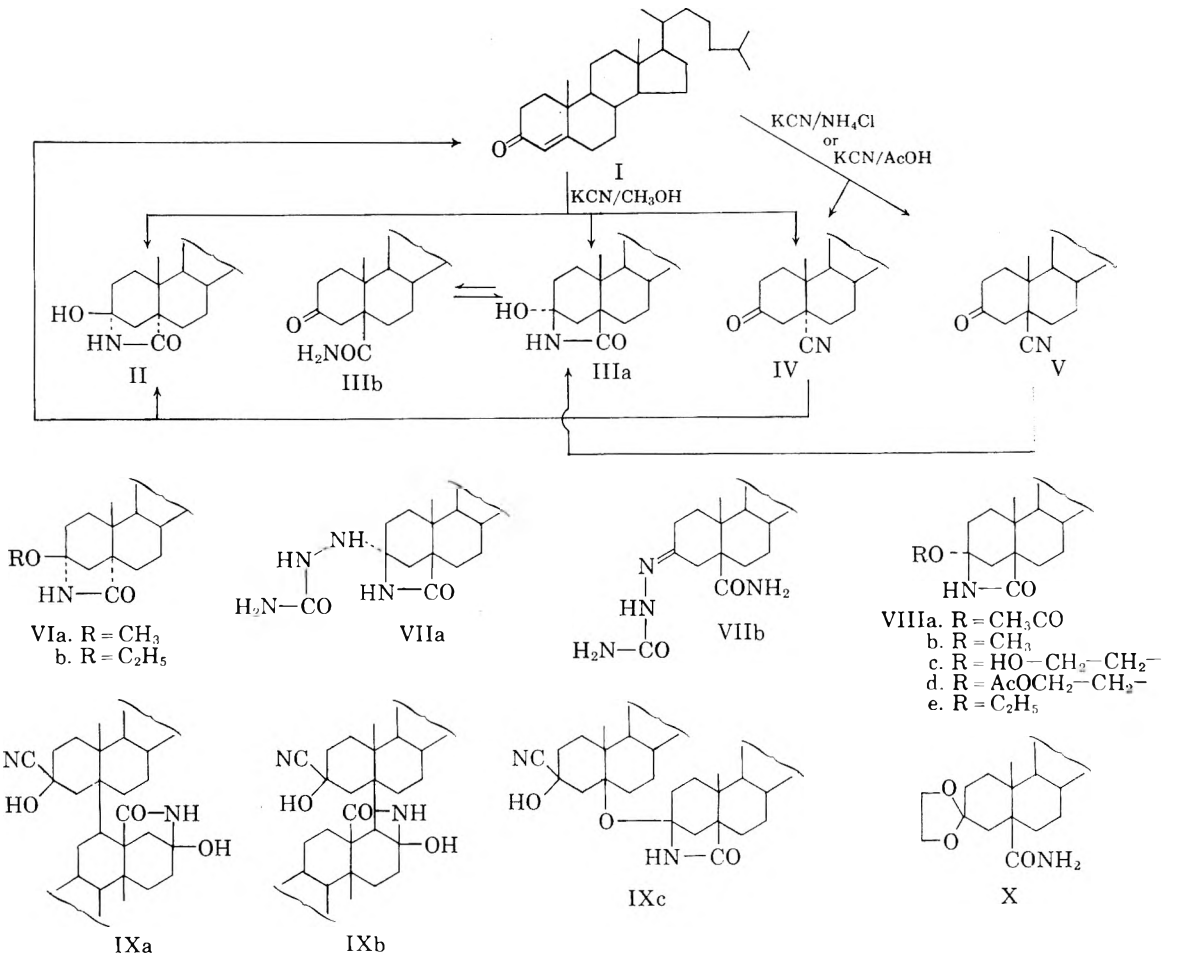


Chart 2

5-cyano derivative obeyed Beer's law below an optical density of 0.2 (Fig. 5). Saponification[15,16] of each 5-cyanocholestanone was carried out with 0.08*N* sodium hydroxide solution in 95% ethanol solution at 55°. There is a marked difference in the saponification rate between the 5α- and 5β-cyano derivatives and 90% of the former was saponified in six and a half hours while the same per cent of the latter saponified in only two hours as shown in Fig. 2. The plotted values of log Co/C against time almost formed a straight line (Fig. 3) so this is applicable to the equation—$1/t$ log Co/C=0.4343 K—when the hydroxide concentration is constant. These results indicate that this reaction proceeds by a base catalyzed pseudo first order reaction. Also the values 0.00609 min.$^{-1}$ and 0.0203 min.$^{-1}$ were given as saponification rate constants $K^{55°}$ of the 5α- and 5β-cyano ketones, respectively. The velocity ratio of the 5α to the 5β compound is 1:3.5. The assignment of configuration to the C_5 epimers from these results is in good agreement with the results of the rotatory dispersion curves[10] (Fig. 4).

In order to confirm the configurations of the two epimeric lactams, 5β-cyanocholestanone was saponified by treatment with sodium hydroxide in boiling methanol for one hour and afforded the (5 → 3)β-lactam in 70% yield, identical with the above-mentioned lactam (III), m.p. 202°. 5α-Cyanocholestanone, on the other hand, gave 50% of the anticipated (5 → 3)α-lactam, identical with the lactam (II), m.p. 251°, and 25% of Δ^4-cholesten-3-one by the action of sodium hydroxide in refluxing methanol for twenty hours. It seems reasonable that cholestenone was obtained by the β-elimination of 5α-cyano ketone and that there exists an equilibrium between the 5α-cyano derivative and cholestenone (Chart 3). These facts were also supported by the

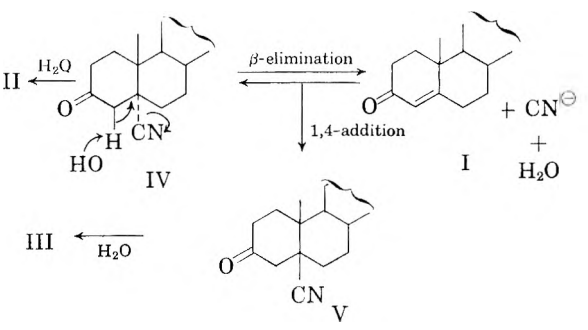


Chart 3

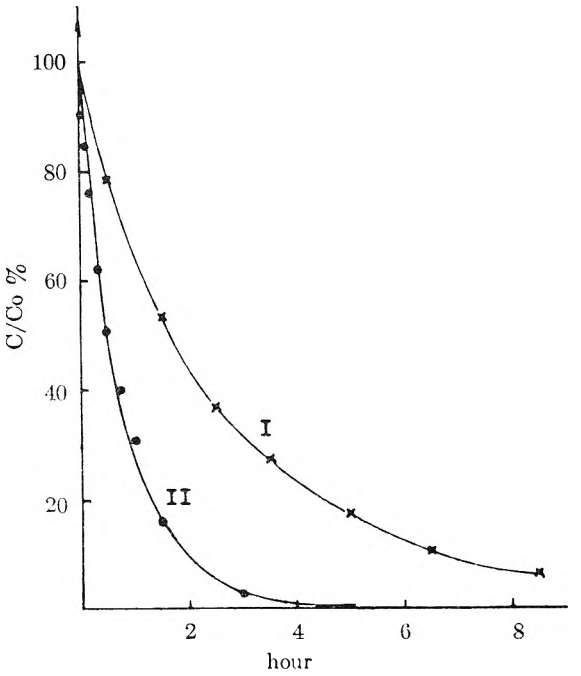


Fig. 2. C/Co values against time in the hydrolysis of 5α- (I) and 5β-cyanocholestan-3-one (II) with 0.08N-sodium hydroxide at 55° ± 1°
Co = initial concn. of cyano ketone in weight %
C = concn. of cyano ketone in weight %

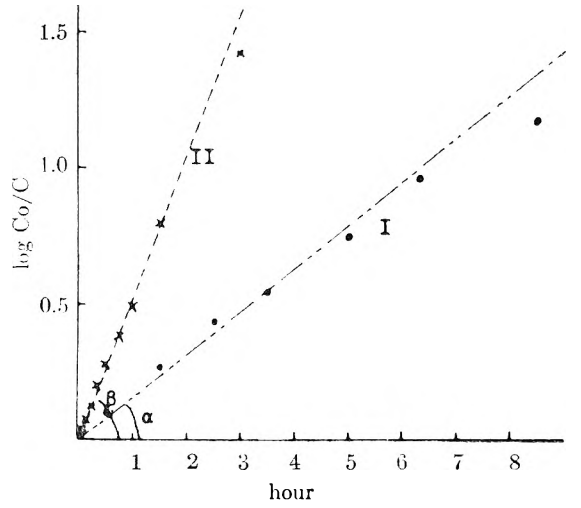


Fig. 3. Pseudo-first-order rate plots for the disappearance of the CN group of each 5-cyanocholestanone
I 5α-cyanocholestan-3-one
II 5β-cyanocholestan-3-one

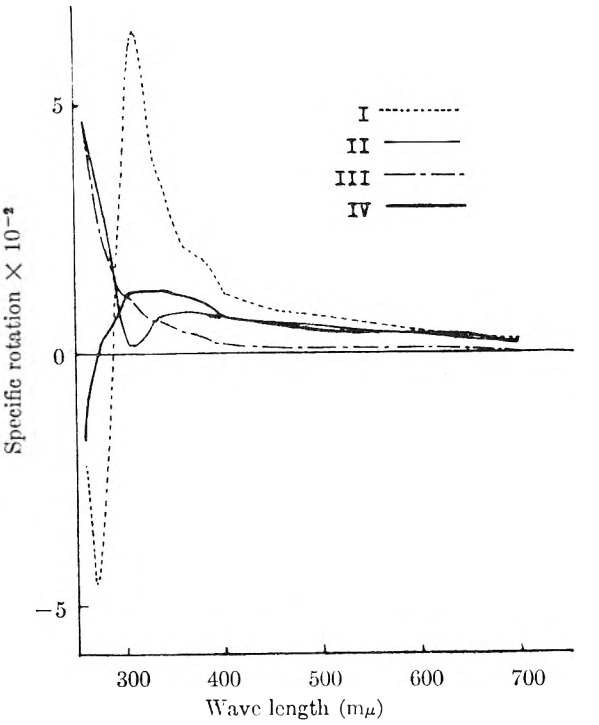


Fig. 4. Optical rotatory dispersion curves of
I 5α-cyanocholestan-3-one (C=0.090, 700–267.5 mμ)
C=0.018, 265–260 mμ)
II 5β-cyanocholestan-3-one (C=0.100, 700–260 mμ)
III 5α-amidocholestan-3-one (C=0.080, 700–262.5 mμ)
IV 5β-amidocholestan-3-one (C=0.085, 700–260 mμ)
in CH_3OH

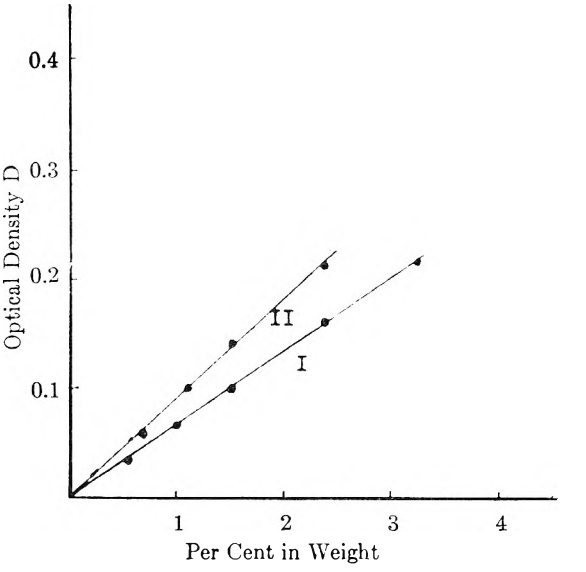


Fig. 5. Calibration curves for determining the concentration of 5α- (I) and 5β-cyanocholestan-3-one (II). The linear relation of the optical density of CN-Absorption at 2237 cm.$^{-1}$ in chloroform to percent in weight

following experiments. When 5α-cyanocholestanone was treated with 10% sodium hydroxide in dimethylformamide under vigorous conditions it gave cholestenone in 14.7% yield, the epimeric (5 → 3)β-lactam (III) in 10% yield and the starting material in 17.9% yield but no (5 → 3)α-lactam (II) was isolated. If the 5α-cyanide were treated with potassium hydroxide in ethanol in the presence of potassium cyanide and heated under reflux for twelve hours, there were obtained 40% of II and 15% of III but no cholestenone. The most probable explanation of the formation of the epimeric (5 → 3)β-lactam (III) from the 5α-cyanide is as follows: Cholestenone and CN^- ion, both liberated from 5α-cyanocholestanone by the β-elimination in the presence of alkali, reacted with each other and afforded the 5β-cyano derivative which then

TABLE I

INFRARED SPECTRA IN CARBON TETRACHLORIDE, CM.$^{-1}$

	Free OH	Free NH	Bonded NH	Acetyl	Lactam CO	Bonded Lactam CO
III	3600	3490	3350, 3130	—	1726	1676
VIIIa	—	3495	—, —	1741	1727	—
VIIIb	—	3490	3230, 3084	—	1722	1702
VIIIc	3610	3482	3250, 3090	—	1722	1695
VIIId	—	3487	3214, 3089	1746	1728	1702

TABLE II

MOLECULAR ROTATION OF 5*X*-CHOLESTANONE AND 5*X*-COPROSTANONE

	X	$[\alpha]_D$ Chf	$[M]_D$ Chf	$\Delta(M)_D^{(CN-H)}$	$\Delta[M]_D^{(5\alpha-5\beta)}$
Cholestanone	H	+41°	+158.5°		>+19.3°
Coprostanone	H	+36°	+139.2°		
5α-Cyanocholestanone	CN	+47.0°	+193.5°	+35.0°	>+80.7°
5β-Cyanocholestanone	CN	+27.4°	+112.8°	−26.4°	

underwent saponification to yield the (5 → 3)β-lactam.

These differences between the epimeric 5-cyano compounds with alkali were also due to the configuration of the 5α- and 5β-cyano groups and in the case of the more hindered 5α-cyano group, the reagents attacked not only the 5α-cyano radical but also the neighboring activated 4β-hydrogen atom.

The (5 → 3)α-lactam afforded its methyl and ethyl ether (VIa and b) when treated with methanol and hydrogen chloride or with ethanol-benzene in the presence of *p*-toluenesulfonic acid, respectively. Similarly, the (5 → 3)β-epimer gave the methyl and ethyl ether (VIIIb and VIIIe) in the same way. It formed an acetate (VIIIa) with acetic anhydride and pyridine or better with acetic anhydride and *p*-toluenesulfonic acid. The (5→3)β-lactam afforded a compound (VIIIc), m.p. 185–187°, when treated with ethylene glycol and a catalytic amount of *p*-toluenesulfonic acid in benzene. The infrared spectrum of this compound shows an absorption band at 3600 cm.$^{-1}$ in chloroform solution corresponding to the hydroxyl group and this was confirmed by the formation of its acetate (VIIId) with acetic anhydride-pyridine at room temperature. From these facts, a reasonable structure of the above-mentioned compound is represented by the formula VIIIc rather than the normal ethylene ketal structure X.

The infrared spectra of these lactam derivatives, VIa, VIb, VIIIa, VIIIb, VIIIc, VIIId, and VIIIe were all lacking the absorption band corresponding to the 2nd band of the non-cyclic amide.[8] All these findings support the hemiketal structures.

The infrared absorption bands due to the intermolecular association were identified from other bands by measurement in carbon-tetrachloride solution and by dilution[17] as in Table I. Thus the assigned absorption band corresponding to the lactam carbonyl group existed between 1722 cm.$^{-1}$ and 1728 cm.$^{-1}$, and this region is located at the shorter wave-length region than that of the primary amide. This gave further support to the assumed hemiketal structure mentioned above.

The contributions of the C_5 substituted cyano group to the molecular rotatory power were summarized in Table II. As shown in the table the effect of the cyano group is opposite to that of the hydroxyl group.[18] As mentioned above the 3-keto group in the 5-acid amide derivatives has a hemiketal type structure, the rotatory powers of these derivatives can not be compared.

EXPERIMENTAL

Melting points were measured on a Kofler-block "Monoscope" (Hans Bock Co., Frankfurt am Main, Germany) and are corrected. Unless otherwise stated, specific rotations were measured in chloroform solution and ultraviolet spectra in 95% ethanol. For rotation and elemental analysis, the samples having the melting points up to 120°, 180°, and over 180° were dried for 3 hr. over phosphorus pentoxide *in vacuo* (1–2 mm.) at room temperature to 60°, 70–90° and 100–120° respectively. Chromatography was usually performed according to the method described by Reichstein and Shoppee.[19]

Reaction of Δ^4-cholesten-3-one with potassium cyanide. A. *With potassium cyanide in methanol.* A solution of potassium cyanide (0.65 g., 0.01 mole) in water (2 ml.) was added to a hot solution of Δ^4-cholesten-3-one (I) (1.93 g., 0.005 mole) in methanol (50 ml.) and refluxed for 6 hr. After cooling, the crystals were separated, washed with ether, and recrystallized from ethanol, to afford 5α-cyanocholestan-3-one (IV), m.p. 181–184°, as fine prisms. The filtrates were combined and evaporated *in vacuo*, water was added, and the product

(17) Infrared spectra were measured by use of a 3-mm. cell with the range of the concentration between 20–95% transmission of carbonyl, which was controlled by dilution.

(18) (a) L. F. Fieser and M. Fieser, *Steroids*, Reinhold, New York, 1959, p. 179; (b) D. H. R. Barton and W. Klyne, *Chem. & Ind.*, 27, 755 (1948).

(19) T. Reichstein and C. W. Shoppee, *Disc. Trans. Farad. Soc.*, No. 7, 305 (1949).

was extracted with chloroform. The chloroform extracts were washed with water, dried, and then evaporated *in vacuo*. The residue (2.08 g.) was chromatographed on alumina (60 g., Brockmann, II). Elution with petroleum ether (b.p. 40–60°)–benzene (4:1) afforded recovered Δ^4-cholesten-3-one (I) (343.2 mg., 17.8%), m.p. 80–82°, undepressed on admixture with an authentic sample. Further elution with petroleum ether–benzene (2:1 and 1:1) afforded IV (223.8 mg.), m.p. 176.5–181°, raised by several crystallizations from ethanol to 182–184° [no depression on admixture with the first separated crystals (IV); the combined yield was 431.7 mg. (21.2%)]. $[\alpha]_D^{27}$ +47.0° (*c*, 0.888), $\lambda_{max}^{C_2H_5OH}$ 288 mμ (ε 40), $\nu_{max}^{CHCl_3}$ 2237 and 1723 cm.$^{-1}$

Anal. Calcd. for $C_{29}H_{45}ON$: C, 81.69; H, 11.02; N, 3.40. Found: C, 81.33; H, 11.07; N, 3.49.

5α-Cyanocholestan-3-one semicarbazone, m.p. 250–253° dec., $[\alpha]_D^{18}$ +72.6° (c 1.018 in chloroform–glacial acetic acid 1:1 v/v), ν_{max}^{Nujol} 3515, 3225, 2232, 1688, 1661, and 1572 cm.$^{-1}$

Anal. Calcd. for $C_{29}H_{48}ON_4$: C, 74.31; H, 10.32; N, 11.95. Found: C, 74.04; H, 10.17; N, 11.97.

Further elution with benzene-chloroform (2:1) gave dimer (IX) (73.2 mg., 3.6%), m.p. 186–192°, raised by crystallization from ethanol to 196–198°, $[\alpha]_D^{20}$ +25.2° (*c*, 0.957), $\nu_{max}^{CHCl_3}$ 3683, 3443, 3240, 2255, 1705, and 1685 cm.$^{-1}$

Anal. Calcd. for $C_{56}H_{90}O_3N_2$: C, 80.00; H, 10.73; N, 3.35. Found: C, 80.19; H, 10.70; N, 3.97.

Molecular weight measurement (*Rast*) gave 623.5.

Further elution with chloroform and chloroform-methanol (199:1) afforded crystals (49.2 mg., 2.3%), m.p. 238–245°. Several crystallizations from ethanol gave 3α-amino-3β-hydroxy-5α-carboxycholestane lactam (II), m.p. 249.5–252°, $[\alpha]_D^{26}$ +10.4° (*c*, 1.022), $\nu_{max}^{CHCl_3}$ 3697, 3477, 3327, 1705, and 1682 cm.$^{-1}$

Anal. Calcd. for $C_{28}H_{47}O_2N \cdot H_2O$: C, 75.12; H, 11.03; N, 3.13. Found: C, 74.96; H, 11.07; N, 2.98.

Further elution with chloroform-methanol (99.5:0.5, 99:1, and 49:1) afforded 3β-amino-3α-hydroxy-5β-carboxycholestane lactam (III) (562.2 mg., 26.2%) as fine prisms from ethanol, m.p. 200–205°, $[\alpha]_D^{26}$ +33.6° (*c*, 1.088), $\lambda_{max}^{C_2H_5OH}$ 280, mμ (ε 9.6), $\nu_{max}^{CHCl_3}$ 3605, 3445, 3300, 1702, and 1690 cm.$^{-1}$

Anal. Calcd. for $C_{28}H_{47}O_2N$: C, 78.27; H, 11.03; N, 3.26. Found: C, 77.34; H, 10.96; N, 3.16.

Tosylhydrazone of IV. 5α-Cyano ketone (50 mg.) and tosylhydrazine[20] (27.3 mg.) was dissolved in ether (4 ml.) and allowed to stand at room temperature overnight. The crystals were filtered and recrystallized from ethanol, 43.5 mg. of rods, m.p. 198–203°. From the filtrate, further 5.6 mg. of crystals were obtained. $[\alpha]_D^{19}$ +70.5° (*c*, 1.519), ν_{max}^{Nujol} 3210, 2205, 1638, 1597, 1490, 1347, 1166, and 809 cm.$^{-1}$.

Anal. Calcd. for $C_{35}H_{53}O_2N_3S$: C, 72.50; H, 9.21; N, 7.25; S, 5.52. Found: C, 72.15; H, 9.14; N, 7.06; S, 5.36.

Tosylhydrazone of V. 5β-Cyanocholestan-3-one [see below] (50 mg.) and tosylhydrazine (27.3 mg.) were dissolved in ether (4 ml.) and allowed to stand at room temperature overnight. The solution was washed with 2*N* hydrochloric acid and water, dried and then evaporated *in vacuo*. The residue (84.5 mg.) was crystallized from ethanol, needles (31 mg.), m.p. 117–123°. From mother liquor, further 19.4 mg. of the hydrazone, m.p. 115–119° was obtained. $[\alpha]_D^{13}$ +13.0° (*c*, 1.483), ν_{max}^{Nujol} 3576, 3243, 3094, 2232, 1630, 1602, 1495, 1322, 1164 and 813 cm.$^{-1}$

Anal. Calcd. for $C_{35}H_{53}O_2N_3S \cdot 1/2H_2O$: C, 71.41; H, 9.24; N, 7.14; S, 5.44 or for $C_{35}H_{53}O_2N_3S$: C, 72.50; H, 9.21; N, 7.25; S, 5.52. Found: C, 71.64; H, 9.23; N, 6.96; S, 5.36.

Regeneration of IV *from its tosylhydrazone.* 5α-Cyanocholestan-3-one tosylhydrazone (50 mg.) was dissolved in chloroform (2 ml.) and ethanol (1 ml.), containing pyruvic acid (0.1 ml.) and allowed to stand overnight. The solution was poured onto ice-water and extracted with ether. The ether extract was washed with 2*N* sodium carbonate and water, dried over anhydrous sodium sulfate and then evaporated *in vacuo*. The crude product (43.5 mg.) was crystallized from ethanol, giving IV (10.8 mg.), fine prisms, m.p. 182–184°. The melting point was undepressed upon admixture with an authentic sample. The second crop (18 mg.) melted at 164–174°.

Regeneration of V *from its tosylhydrazone.* 5β-Cyanocholestan-3-one tosylhydrazone (100 mg.) was treated in the same way as described above. After working up as usual, there was obtained 47.7 mg. of V, needles, m.p. 125–126°, undepressed upon admixture with an authentic sample (see below B).

B. *With potassium cyanide and ammonium chloride in dimethylformamide.* Δ^4-Cholesten-3-one (1.93 g., 0.005 mole), potassium cyanide (0.65 g., 0.01 mole) and ammonium chloride (0.393 g., 0.0075 mole) in dimethylformamide (40 ml.) and water (5 ml.) were heated with occasional shaking for 8 hr. at 100°, during which time ammonia gas was evolved. After cooling the solvent was distilled off *in vacuo*. Water was then added and the product was extracted with chloroform. All extracts were washed with water and dried. Evaporation *in vacuo* afforded 2.18 g. of crude product. 2.15 g. of this product was dissolved in ether (100 ml.), to which tosylhydrazine (1.153 g.) was added and the clear solution was allowed to stand overnight and then further refluxed for 1 hr. The ether was evaporated *in vacuo* and the crude oil (3.38 g.) was crystallized from ethanol. The first crop (264 mg. of rods, m.p. 198–202°) and the second (287.5 mg. of rods, m.p. 196–201°) were mainly 5α-cyanocholestan-3-one tosylhydrazone, the third and the fourth crop (514 mg. of needles, m.p. 108–125° and 380.0 mg. of needles, m.p. 100–125°) were apparently a mixture of both 5α and 5β compounds, but with 5β-compound predominating. The rest (oil) was roughly chromatographed on alumina (15 g., Woelm III, neutral), from which there was obtained 31 mg. of rods, m.p. 196–201° (5α-compounds) and 865.6 mg. of crude crystals, m.p. 100–135°. The total yield of crude crystals was 2.34 g. (82%).

The third, the fourth, and the last crops were combined (1.75 g.) and then chromatographed on alumina. This resulted in the isolation of 1.14 g. of needles, m.p. 115–130° (mixed m.p. with a pure sample of 5β-compound was 112–120°) and further 160 mg. of needles, m.p. 100–135°. As a result, 582.5 mg. of 5α-cyanocholestan-3-one tosylhydrazone (A) and 1.30 g. of a mixture (B) of 5β- and 5α-cyanocholestan 3-one tosylhydrazone were obtained. The latter (B) was proved to be an approximately 4:1 mixture of 5β- and 5α-compounds after hydrolytic cleavage with pyruvic acid (see below).

Hydrolytic cleavage of (A). 5α-Cyanocholestan-3-one tosylhydrazone (582 mg.) was dissolved in chloroform (24 ml.) and ethanol (12 ml.), to which pyruvic acid (1.2 ml.) was added and the solution was refluxed for 1 hr. After working up as above i, there were obtained 435 mg. of residue, which gave after one crystallization from ethanol 313.7 mg. of IV, fine prisms, m.p. 182.5–184°, undepressed on admixture with an authentic sample. Further 28.4 mg. of IV, m.p. 168–173° was obtained from the mother liquor. Total crude yield was 81.5%.

Hydrolytic cleavage of (B). A solution of (B) (1.3 g.), and pyruvic acid (2.6 ml.) in chloroform (52 ml.) and ethanol (26 ml.) was allowed to stand at room temperature overnight. After working up as above i, there was obtained 913 mg. of crude product, which upon direct crystallization from ethanol gave 195 mg. of V, needles, m.p. 117–119°, raised by several crystallizations from ethanol to 127–128°. $[\alpha]_D^{29}$ +27.4° (*c*, 0.660), $\lambda_{max}^{C_2H_5OH}$ 288 mμ (ε 19), $\nu_{max}^{CHCl_3}$ 2223 and 1723 cm.$^{-1}$

Anal. Calcd. for $C_{28}H_{45}ON$: C, 81.69; H, 11.02; N, 3.40. Found: C, 81.63; H, 11.02; N, 3.60.

Semicarbazone. Fine prisms, m.p. 155–160°, $[\alpha]_D^{19}$ −6.5° (*c*, 1.013), ν_{max}^{Nujol} 3536, 3222, 2216, 1693, 1670, and 1573 cm.$^{-1}$

(20) K. Freudenberg and F. Blümmeli, *Ann.*, **440**, 51 (1944).

Anal. Calcd. for $C_{29}H_{48}ON_4$: C, 74.31; H, 10.32; N, 11.95. Found: C, 74.08; H, 10.35; N, 11.74.

The rest (672 mg.) was chromatographed on alumina (15 g., Woelm, neutral II), giving 180 mg. of practically pure V, m.p. 119–120° by elution with petroleum ether–benzene (4:1 and 3:1), 140.6 mg. of the mixture of IV and V, enriched with the latter, m.p. 103–120°, 19.3 mg. of the another mixture, m.p. 107–170° and 37.3 mg. of IV, m.p. 179–183° by elution with petroleum ether–benzene (3:1, 2:1, and 1:1), and 26 mg. of 5α-cyanocholestan-3-one tosylhydrazone, m.p. 197–200° by elution with chloroform-methanol (99:1 and 98:2). These results showed that the original mixture (B) was crude 5β-cyanocholestan-3-one tosylhydrazone containing ca. 20% 5α-isomer.

Saponification of 5α-cyanocholestan-3-one (IV) *with base.*[21] (1) 5α-Cyano ketone (IV) (200 mg.) and sodium hydroxide (300 mg.) were dissolved in methanol (98 ml.) and water (2 ml.), which was refluxed for 20 hr., where the disappearance of cyanide group in IV was checked by infrared spectrum. Methanol was distilled *in vacuo*, water added, and extracted with chloroform. The extract was washed with 2*N* hydrochloric acid and with water, dried over anhydrous sodium sulfate and then evaporated *in vacuo*. The crude product (157 mg.: the yield was lowered because of sampling for infrared measurement) gave II (40.4 mg.) as needles from ethanol, m.p. 247–251°. The rest was chromatographed on alumina (Brockmann) and gave further 35 mg. of cholestenone by elution with petroleum ether-benzene (1:1) and benzene, and further 40.0 mg. of II, m.p. 245–251° by elution with chloroform and chloroform-methanol (99:1).

(2) A solution of the 5α-cyano compound IV (500 mg.), sodium hydroxide (1.5 g.) in dimethylformamide (10 ml.) and water (5 ml.) was heated for 7 hr., after which the reaction mixture was neutralized with acetic acid (2.2 g.) and the solvent was evaporated *in vacuo*. The residue was treated in the usual manner. Chromatography of the chloroform extract (oil 512.7 mg.) on alumina (15 g., Brockmann II) gave 66.3 mg. of Δ^4-cholesten-3-one by elution with petroleum ether–benzene (4:1), 84.4 mg. of starting material (IV) by elution with petroleum ether-benzene (2:1) and benzene, and 54.2 mg. of III, m.p. 195–198°, by elution with chloroform-methanol (99.5:0.5).

(3) A solution of IV (280 mg.), potassium cyanide (280 mg.) and potassium hydroxide (280 mg.) in ethanol (20 ml.) and water (2 ml.) was refluxed for 12 hr. After working up as in (2) gave 308 mg. of crude products, which were chromatographed on alumina (8 g., Brockmann II) and the following products were obtained in the same way as (2); 118.3 mg. of II, m.p. 245–250° and 43.2 mg. of III, m.p. 192–198°.

Hydrolysis of 5β-cyanocholestan-3-one V with base.[21] A solution of the 5β-cyano compound (V) (200 mg.), sodium hydroxide (300 mg.) in methanol (98 ml.) and water (2 ml.) was refluxed for 1 hr., where the disappearance of cyanide group was checked by infrared spectrum. Working up in the same way as above furnished 200 mg. of crude product, which was purified by alumina chromatography (6 g., Brockmann II), giving 138.7 mg. of III, m.p. 186–200°, raised by several crystallizations from ethanol to 200–202° [from the fractions eluted with chloroform and chloroform-methanol (98:2)].

3β-Methoxy-3α-amino-5α-carboxycholestane lactam (VIa). (1) (5→3) α-Lactam II (395 mg.) was dissolved in 40% (w/w) hydrochloric acid–methanol (64 g.) and allowed to stand for 1.5 days. The methanol was evaporated *in vacuo* and worked up as usual. Chromatography of the residue (405 mg.) on alumina (15 g., Brockmann II) gave 302.6 mg. (74.3%) of VIa by elution with benzene-chloroform (9:1, 4:1, 2:1 and 1:1), needles from ether, m.p. 188.5–190°. $[\alpha]_D^{29}$ +25.8° (*c*, 0.887), ν_{max}^{Nujol} 3320, 3140, and 1700 cm.$^{-1}$

Anal. Calcd. for $C_{29}H_{49}O_2N$: C, 78.50; H, 11.13; N, 3.16. Found: C, 78.67; H, 11.05; N, 3.06.

(2) A solution of II (266 mg.) in 5% (w/w) hydrochloric acid–methanol (30 ml.) was heated for 12 hr. under reflux and worked up as above (1). There were obtained in the same way 195 mg. (56%) of VIa, m.p. 186–187°.

3β-Ethoxy-3α-amino-5α-carboxycholestane lactam (VIb). A solution of II (320 mg.) and *p*-toluenesulfonic acid monohydrate (64 mg.) in absolute ethanol (30 ml.) and absolute benzene (50 ml.) was distilled off slowly within 20 hr. through a fractionating column. A total of 45 ml. of absolute ethanol and 75 ml. of absolute benzene were added dropwise during the distillation to keep the initial volume constant. Sodium acetate (anhydrous, 30 mg.) was then added, followed by evaporation *in vacuo*. The product was extracted with chloroform, washed with water, dried over anhydrous sodium sulfate, and then evaporated *in vacuo*. The residue (349 mg.) was chromatographed on alumina (8 g., Brockmann II), to afford 262.4 mg. (77%) of VIb by elution with petroleum ether–benzene (1:1), benzene and benzene-chloroform (9:1 and 4:1) needles from ether, m.p. 159–160°, raised by two crystallizations to 161–162°. $[\alpha]_D^{29}$ +22.2° (*c*, 0.968), ν_{max}^{Nujol} 3245, 3105, and 1704 cm.$^{-1}$

Anal. Calcd. for $C_{30}H_{51}O_2N$: C, 78.72; H, 11.23; N, 3.06. Found: C, 79.12; H, 11.22; N, 2.90.

Further elution with chloroform-methanol (99:1) gave 10.4 mg. of starting material.

3α-Methoxy-3β-amino-5β-carboxycholestane lactam (VIIIb). (5 → 3) β-Lactam III (2 g.) was dissolved in 30% (w/w) hydrochloric acid–methanol (100 g.) and allowed to stand at room temperature overnight. Working up in the same way as above gave 2.332 g. of crude products, which were purified by chromatography on Florisil (60 g.). Elution with benzene-chloroform (2:1 and 1:1) and chloroform gave 1.675 g. (82.1%) of practically pure VIIIb, silky needles from ether-pentane, m.p. 167–168°, raised by one crystallization to 170–171°. $[\alpha]_D^{23.5}$ +22° (*c*, 1.08), infrared: Table I.

Anal. Calcd. for $C_{29}H_{49}O_2N$: C, 78.50; H, 11.13; N, 3.16. Found: C, 78.06; H, 11.05; N, 3.04.

Further elution with chloroform-methanol (98:2) gave 221 mg. of starting material, m.p. 190–192°.

3α-Acetoxy-3β-amino-5β carboxycholestane lactam (VIIIa). (1) (5 → 3) β-Lactam III (1 g.) was dissolved in acetic anhydride (10 ml.), to which *p*-toluenesulfonic acid monohydrate (0.3 g.) was added, and allowed to stand at room temperature for 48 hr. The crystals (VIIIa) were filtered and washed with a little acetic anhydride. The filtrate was evaporated *in vacuo* after addition of excess anhydrous sodium acetate. The residue was extracted with ether and the ether extracts were washed with 2*N* sodium carbonate and with water, dried over anhydrous sodium sulfate, and then evaporated *in vacuo*. The residue gave upon crystallization from acetic anhydride further crude VIIIa, m.p. 89–95°. The combined crude crystals were recrystallized from acetic anhydride, giving 602.7 mg. (63.2%) of VIIIa, m.p. 115–118°, which upon further recrystallization from acetic anhydride gave pure VIIIa (needles) melting at 116–118°. $[\alpha]_D^{23.5}$ +39° (c, 0.992), infrared: Table I.

Anal. Calcd. for $C_{30}H_{49}O_3N$: C, 76.38; H, 10.47; N, 2.97. Found: C, 76.44; H, 10.45; N, 2.93.

(2) III (0.1 g.) was dissolved in pyridine (2.5 ml.) and acetic anhydride (1.5 ml.) and allowed to stand overnight at room temperature. Working up as usual gave 121.4 mg. of crude product, which by chromatography on alumina (4 g., Brockmann II) gave 31.4 mg. (34.5%) of VIIIa, m.p. 115–117°, and 33.8 mg. of starting material, m.p. 187–191°.

3α-(β-Hydroxy)ethoxy-3β-amino-5β-carboxycholestane lactam (VIIIc) (5 → 3β)-Lactam III (600 mg.) was dissolved in absolute benzene (100 ml.), to which ethylene glycol (1 ml.) and *p*-toluenesulfonic acid (50 mg.) were added and the whole was refluxed slowly during 9.5 hr., using a Dean-Stark apparatus to separate the water formed. 2*N* sodium carbonate was added and shaken thoroughly. The water

(21) In this experiment each substance was identified with the corresponding authentic sample by mixed melting point determination.

TABLE III

No.	*t*, Min.	Residue, Mg.	Chloroform, Mg.	Co, in Wt. %	D,	C, in Wt. %	C/Co, × 100	log Co/C
			5α-Cyanocholestan-3-one					
1	30	50.1	2094	2.34	0.125	1.83	78.2	0.106
2	90	51.9	1782	2.83	0.103	1.51	53.4	0.272
3	150	51.2	1486	3.33	0.084	1.23	36.9	0.434
4	210	50.7	1212	4.01	0.076	1.11	27.7	0.558
5	300	52.1	1145	4.35	0.052	0.76	17.5	0.758
6	390	50.7	1106	4.39	0.032	0.47	10.7	0.972
7	510	52.0	949	4.95	0.021	0.30	6.6	1.182
			5β-Cyanocholestan-3-one					
1	2	51.8	2447	2.07	0.174	1.88	91.0	0.042
2	5	52.3	2254	2.27	0.177	1.92	84.6	0.0719
3	10	53.3	1511	3.41	0.235	2.60	76.3	0.114
4	20	52.1	1219	4.09	0.230	2.53	61.9	0.207
5	30	53.4	1353	3.66	0.175	1.90	52.0	0.288
6	45	52.8	1269	3.84	0.143	1.54	40.1	0.398
7	60	50.7	1320	3.70	0.109	1.18	31.9	0.496
8	90	49.5	1219	3.91	0.058	0.62	15.85	0.795
9	180	49.8	1102	4.32	0.012	0.13	3.01	1.522

layer was extracted further with benzene. The extracts were washed with water, dried over anhydrous sodium sulfate and then evaporated *in vacuo* to afford 694 mg. of crude products (from acetone-ether-pentane, m.p. 177–180°). Chromatography over Florisil (20 g.) gave 512.3 mg. of pure VIIIc, recrystallized from benzene-pentane, m.p. 185–187° and an additional 52.3 mg. from the mother liquor, 179–182°, by elution with chloroform-methanol (99.5:0.5, 99:1 and 99:5). Total yield; 565.6 mg. (85.5%). $[\alpha]_D^{20}$ + 26.0° (*c*, 1.037), infrared: Table I.

Anal. Calcd. for $C_{30}H_{51}O_3N$: C, 76.06; H, 10.85; N, 2.96. Found: C, 75.69; H, 10.84; N, 2.84.

3α-(β-Acetoxy)ethoxy-3β-amino-5β-carboxycholestane lactam (VIIId). VIIIc (230 mg.) were acetylated with acetic anhydride (2 ml.) and pyridine (3 ml.) at room temperature overnight. After working up in the usual way, 281.4 mg. of crude acetate was obtained, which was then chromatographed on alumina (8 g., Brockmann II). The fractions eluted with benzene and benzene-chloroform (9:1, 4:1 and 1:1) gave 162 mg. of VIIId, needles from ether and pentane, m.p. 60–63°/84°, raised by two crystallizations from the same solvent to 64–65°/86°. $[\alpha]_D^{19}$ + 22.9° (*c*, 1.151), infrared: Table I.

Anal. Calcd. for $C_{32}H_{53}O_4N$: C, 74.52; H, 10.36; N, 2.72. Found: C, 74.14; H, 10.51; N, 2.59.

3α-Ethoxy-3β-amino-5β-carboxycholestane lactam (VIIIe). A solution of (5→3)β-lactam III (2.49 g.) and *p*-toluenesulfonic acid monohydrate (560 mg.) in absolute ethanol (100 ml.) and absolute benzene (150 ml.) was slowly distilled within 14 hr. through a fractionating column. A total of 50 ml. of absolute ethanol and 80 ml. of absolute benzene were added dropwise in order to maintain the original volume of the reaction mixture. Working up as in the case of VIb (see above) gave 2.6 g. of crude product, which was purified by filtration through an alumina column (60 g. Woelm II). Elution with petroleum ether–benzene (4:1, 2:1 and 1:1) gave a total of 2.28 g. of crude VIIIe (m.p. 149–151°), which upon further crystallization from ethanol gave pure VIIIe as colorless needles m.p. 153–154°. $[\alpha]_D^{20}$ + 24.7° (*c*, 1.156), ν_{max}^{Nujol} 3476 and 1697 cm.$^{-1}$

Anal. Calcd. for $C_{30}H_{51}O_2N$: C, 78.72; H, 11.23; N, 3.06. Found: C, 78.40; H, 11.22; N, 3.02.

Further elution with a chloroform-methanol (95:5 and 90:10) gave 50 mg. (2%) of starting material, m.p. 195–200°.

Determination of the saponification rate[15] *of 5α- and 5β-cyanocholestan-3-one.* (*1*) *The method for determination.* The determination of rates was carried out by measuring the decrease of optical densities with time of the CN-stretching absorption band at 2237 cm.$^{-1}$ in the infrared spectra.

(*2*) *Preparation of calibration curve.* The calibration curve was obtained by plotting the relationship between the optical density (D) of the C≡N band and concentration. As seen in Figure 5, the plots formed straight lines at optical densities below *ca.* 0.2 showing that Beer's relationship was valid.

(*3*) *Procedure.* A mixture of 2*N* sodium hydroxide (4 ml.) and 95% ethanol (96 ml.) in a 200 ml. reaction flask fitted with a reflux condenser was prewarmed at 55° (±1°) (inner temp.). The 5-cyano compound (500 mg.) was then added. Each aliquot (10 ml.) of the reaction mixture was taken out at various times and was carefully neutralized with 0.4 ml. of 2*N* hydrochloric acid, evaporated *in vacuo*, and extracted three times with chloroform. The chloroform layers were worked up as above. The residue (50–53 mg.) was dissolved in sufficient chloroform to give a solution having an optical density less than 0.2. For the optical densities listed in Table III, a mean value from five measurements was obtained. The concentration C (w/w) of the remaining 5-cyano compounds was obtained from the calibration curve prepared above. These values are illustrated in Fig. 2 and summarized in Table III.

(4) *Results.* As shown in Fig. 3, the curve obtained by plotting the relationship between log Co/C and time for both 5α- and 5β-cyanocholestan-3-one formed straight lines, indicating that the rate of the base catalyzed hydrolysis followed the first order kinetic law and the values of the rate constant K were shown by the equation $1/t \log Co/C = 0.4343\ K$, followed by $\tan\alpha = 0.4343\ K_{5\alpha}^{55°}$, $K_{5\alpha}$ = 0.00609 min.$^{-1}$ for 5α-cyano ketone and $\tan\beta = 0.4343\ K_{5\beta}^{55°}$, $K_{5\beta}$ = 0.0203 min.$^{-1}$ for 5β-cyano ketone. It was found that the ratio of their rate constants at 55° was 3.5:1.

Acknowledgment. The authors are indebted to Dr. A. Bowers for valuable discussions and to Dr. T. Kubota and Mr. Y. Matsui for measurement of the spectral data, to Mr. S. Inaba for the optical rotatory data, and to Mrs. K. Miyahara (T. Ieki) for the microanalysis.

HYOHGO PREF., JAPAN

[CONTRIBUTION FROM THE MERCK, SHARP AND DOHME RESEARCH LABORATORIES, DIVISION OF MERCK AND CO., INC.]

17,20;20,21-Bismethylenedioxy Steroids. V. A General Method for Protecting the Dihydroxyacetone Side Chain[1]

R. E. BEYLER,[2] FRANCES HOFFMAN, R. M. MORIARTY, AND L. H. SARETT

Received October 12, 1960

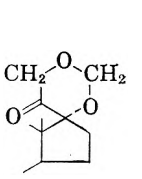
The synthesis of 17,20;20,21-bismethylenedioxy pregnanes (BMD's) from 17α,21-dihydroxy-20-ketopregnanes is reported. This general method for protecting a side chain is discussed, the properties of the bismethylenedioxy grouping are outlined and conditions for formation and reversal are described.

The synthesis of modified adrenocortical steroids has been a subject of major emphasis among steroid chemists during the past several years. These modifications have often involved lengthy syntheses since the activity-enhancing groups had to be inserted at an early stage in a bile acid or sapogenin precursor. Frequently the dihydroxyacetone side chain is not sufficiently stable or inert to the reaction conditions needed to modify the steroid nucleus.

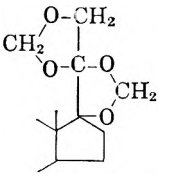
With this fact in mind, several years ago we investigated methods for protecting the sensitive dihydroxyacetone side chain. The initial paper in this series[3] briefly reported the synthesis of five 17,20;20,21-bismethylenedioxy steroids which represented the accomplishment of this objective. The present communication will enlarge upon the details of that work and also present some new information on the bismethylenedioxy (BMD) group.

In the interim period a number of communications from our laboratory[1,4] and from our colleagues at Merck[5] have appeared in which the bismethylenedioxy protecting group was used to synthesize A-, B-, and C-ring modified adrenocortical steroids.

Because of the precedent in the hexose series[6] for preferential formation of 1,3-acetals with formaldehyde, it was hoped that reaction of the dihydroxyacetone side chain with formaldehyde would yield a 17α,21-methylenedioxy compound (I). It was then expected that further protection of the C_{20}-carbonyl group would be required to render the side chain completely inert. Instead, formaldehyde gave a spiroketal system (II) which we have termed the bismethylenedioxy function. This grouping has proven to be remarkably stable to many of the reagents which were later incorporated into the various syntheses that have been reported.[1,4,5]

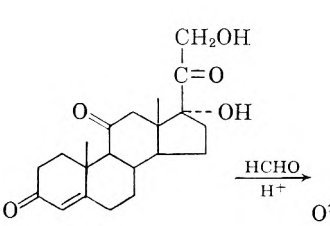


I

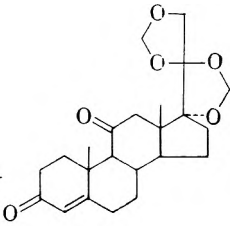


II

The first successful experiment in this investigation was conducted with cortisone (III) and employed a two-phase system of chloroform-formalin and concentrated hydrochloric acid. After the reaction mixture had been stirred at room temperature for fifty-two hours, the layers were separated and the organic phase washed with mild base and concentrated. From the crude residue, which contained considerable formaldehyde polymer, a crystalline compound was obtained directly in good yield. Its infrared spectrum did not preclude the presence of a 20-carbonyl group, such as in I, as a band at 5.85 μ could be assigned to the nonresolved 11- and 20-ketones. The ultraviolet spectrum showed that the 3-keto-Δ^4-chromophore was untouched. At this stage the predicted partial structure (I) was an acceptable one. However, elemental analysis of the product conformed more closely to that for introduction of two formaldehyde units than one. When a quanti-



III



IV

(1) Paper IV in this series, R. E. Beyler, Frances Hoffman, and L. H. Sarett, *J. Am. Chem. Soc.*, 82, 178 (1960).

(2) Present address: Department of Chemistry, Southern Illlinois University, Carbondale, Ill.

(3) R. E. Beyler, R. M. Moriarty, Frances Hoffman, and and L. H. Sarett, *J. Am. Chem. Soc.*, 80, 1517 (1958).

(4) (a) Frances Hoffman, R. E. Beyler, and M. Tishler, *J. Am. Chem. Soc.*, 80, 5322 (1958); (b) R. E. Beyler, A. E. Oberster, Frances Hoffman, and L. H. Sarett, *J. Am. Chem. Soc.*, 82, 170 (1960).

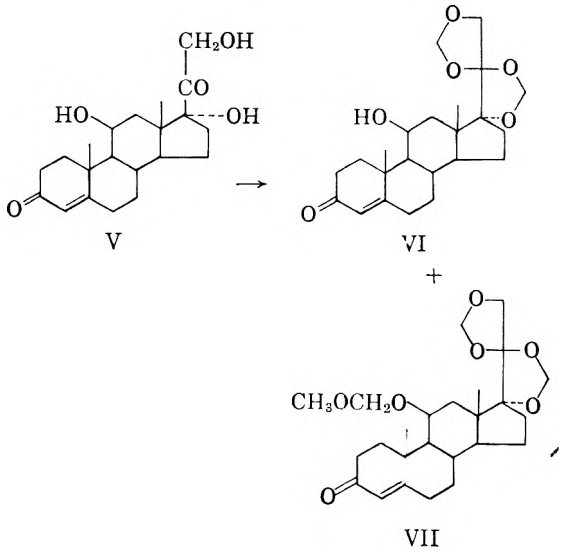
(5) (a) J. H. Fried, G. E. Arth, and L. H. Sarett, *J. Am. Chem. Soc.*, 81, 1235 (1959); (b) N. G. Steinberg, R. Hirschmann, and J. M. Chemerda, *Chem. and Ind.*, 975 (1958); (c) J. H. Fried, G. E. Arth, and L. H. Sarett, *J. Am. Chem. Soc.*, 82, 1684 (1960); (d) R. Hirschmann, G. A. Bailey, R. Walker, and J. M. Chemerda. *J. Am. Chem. Soc.*, 81, 2822 (1959).

(6) S. A. Barker and E. J. Bourne, *Adv. Carbohydrate Chem.*, 7, 177 (1952); S. J. Agyal and G. G. Macdonald, *J. Chem. Soc.*, 686 (1952); J. A. Mills, *Adv. Carbohydrate Chem.*, 10, 1 (1955).

tative methylenedioxy determination was done, using chromotropic acid to measure the formaldehyde generated by acid hydrolysis, the presence of two such groups was confirmed. Thus, the structure IV seemed more probable. Further structure confirmation was obtained by reversal of IV to III (see below). Replacement or cortisone by hydrocortisone in the reaction gave a product without a saturated carbonyl, which proved unequivocally that the 20-ketone was involved in the reaction. Structure IV was then secure. Although stereoisomers at C_{20} in IV are theoretically possible, only one isomer has been isolated in this and all other examples.

The extension of the above findings to other steroids and other aldehydes was next investigated. With respect to the latter it was found that aldehydes other than formaldehyde (butyraldehyde and aryl aldehydes for example) do indeed react to give bisalkylidenedioxy substituents. However, as these products were noncrystalline, formaldehyde remains as the reagent of choice.

When hydrocortisone (V) (or prednisolone) was allowed to react with formalin and acid, an unpredicted side reaction took place. The 11β-hydroxyl function reacted, in part, to form a ketal. The methanol present in commercial formalin and another molecule of formaldehyde gave an 11β-methoxymethyleneoxy substituted bismethylenedioxy compound (VII) as well as the desired bismethylenedioxy hydrocortisone (VI). The structure of VII was assigned on the basis of quantitative methylenedioxy analysis, lack of a hydroxyl band in the infrared spectrum, and acid hydrolysis of VII to hydrocortisone (V).



A mixture of bismethylenedioxy hydrocortisone and the 11-ketal would be useful in syntheses involving A-ring modifications but it would obviously be desirable to form only VI if a multistep synthesis were to be anticipated. Efforts to accomplish this objective were partially successful.

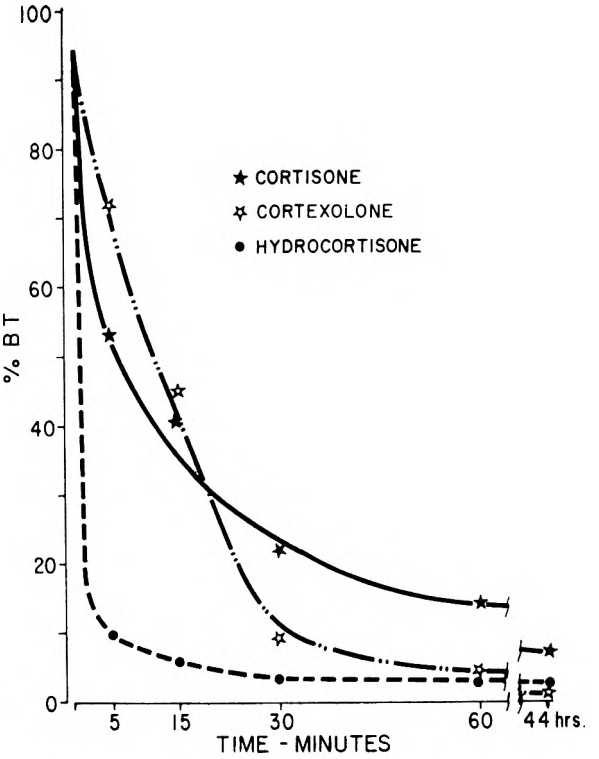


Fig. 1. BMD formation

Because the rate of bismethylenedioxy formation in the 11-hydroxy series is appreciably faster than in the 11-keto series, shorter reaction times were studied. One can avoid formation of most of the 11-ketal (particularly in bismethylenedioxy prednisolone) by shortening the reaction time to an hour or less. However, a more effective method for hydrocortisone involved the use of low-methanol formalin (0.5% methanol) and alcohol-free chloroform or methylene chloride. In this way we were able to prepare bismethylenedioxy hydrocortisone in 50% yield, but the yield was not consistently reproducible. The best way to prepare pure VI is by dioxolanation of bismethylenedioxy cortisone, reduction at C_{11} with lithium aluminum hydride and dioxolane removal.

It is of interest that 11-ketals were not isolated when 9α-fluoro-11β-hydroxy compounds were subjected to bismethylenedioxy-forming conditions. If this reaction does occur, it is only to a minor extent.

Early in our studies it became apparent that the rate of bismethylenedioxy formation was markedly influenced by the substituent at the 11-position. Cortisone was much slower to form a bismethylenedioxy compound, as judged by the disappearance of the blue tetrazoleum (BT) test, than hydrocortisone. As a result of this observation quantitative blue tetrazoleum data on rates of bismethylenedioxy formation were obtained and these are presented in Fig. 1. It can be seen that 50% of the side chain of hydrocortisone is transformed in about one minute whereas cortisone requires about five

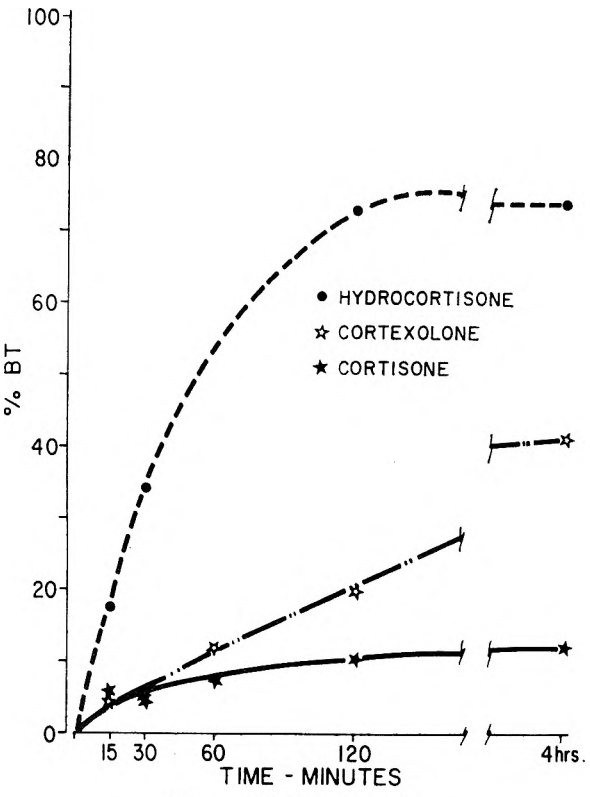


Fig. 2. BMD hydrolysis

minutes and cortexolone (Reichstein's S, no oxygen at C_{11}) about ten minutes. In addition, the final conversion yields differ with the three steroids (*ca.* 1% unchanged cortexolone, *ca.* 2.5% hydrocortisone and *ca.* 6% cortisone after forty-four hours). We do not have a satisfactory explanation for these differences in rate and equilibria. Further, it is noteworthy that in the rate studies, cortexolone was entirely in solution at the beginning of the reaction while hydrocortisone dissolved completely after about five minutes and cortisone did not completely dissolve for about fifteen minutes. The yields of product do not necessarily parallel the blue tetrazoleum data, as one hour is not optimum for preparation of bismethylenedioxy cortisone. Rather is this optimum time more nearly twenty to forty hours.

The hydrolysis of the bismethylenedioxy group to the dihydroxyacetone side chain was first studied with bismethylenedioxy cortisone. Later it was found that the 11-keto compounds were more slowly hydrolyzed than the 11-hydroxy steroids or compounds not substituted at C_{11}. The equilibrium in acid medium also favors the spiroketal in the 11-keto compounds more than in the other two groups of compounds.

The stability to acid hydrolysis is illustrated by the following findings. One part of 10*N* sulfuric acid and nine parts of methanol at reflux for eleven hours gave a product with a weak blue tetrazoleum test. Similarly use of hydriodic acid in methanol or in a two-phase system gave discouraging results (*ca.* 10% "blue tetrazoleum yields") as did also the addition of a "formaldehyde scavenger" (dimedone or chromotropic acid). The use of organic acids (acetic or formic) with or without added mineral acids provided more satisfactory yields. In the case of bismethylenedioxy prednisolone one can obtain 70–75% yield when 60% formic acid is used at 100° for ten minutes.

The rates of bismethylenedioxy-hydrolysis were significantly different for different substituents at C_{11} (Fig. 2). Bismethylenedioxy cortisone was the most sluggish and hydrocortisone the fastest to hydrolyze. Using 50% acetic acid at 100°, the former leveled off at about 10% "blue tetrazoleum yield" after two hours whereas the latter had reached nearly 75% "blue tetrazoleum yield" in this time. Prolonged treatment under these conditions caused the "blue tetrazoleum yield" to diminish, undoubtedly because of side chain destruction under the acid conditions. Again we do not have an entirely satisfactory explanation for the influence of the C_{11}-substituent on the rate of acid hydrolysis. It has been found[7] that variation at even more remote positions of the steroid—as, for example, in the A-ring—can have a marked effect on the rate of bismethylenedioxy-hydrolysis.

This acid stability has been useful in a number of synthetic applications. For instance, a 9,11-oxide was cleaved with hydrochloric acid without damage to the protecting group.[1] Brominations have been carried out on bismethylenedioxy steroids. Dioxolane formations and reversals have been accomplished in the presence of this protecting group.[4,5] Even short-term exposure to catalytic amounts of boron trifluoride etherate has been used.[8] In addition we have prepared 3-enamines of the bismethylenedioxy steroids.

The physical properties of this class of steroids are of interest. In general, they are high melting crystalline solids which can be crystallized from polar or nonpolar solvents. Methanol and ether are generally very satisfactory. In both partition and adsorption chromatography they are markedly less polar than the parent steroid. They always exhibit strong C—O—C absorption at 9.0–9.4 μ in the infrared. The molecular rotation of a large number of bismethylenedioxy compounds shows a levorotatory shift of 400 to 600° from the corresponding 17,21-dihydroxy-20-ketone.

In addition to the bismethylenedioxy compounds reported in our initial communication we have made a number of others, some of which are reported in the experimental section. These include saturated 3-ketones, 4,6-dienones, and various alkylated bismethylenedioxy compounds. It is significant that 16α- and 16β-methyl corticoids

(7) Dr. Ralph Hirschmann, private communication.

(8) R. E. Beyler, Frances Hoffman, L. N. Sarett, and M. Tishler, *J. Org. Chem.*, **26**, 2426 (1961).

also form bismethylenedioxy derivatives satisfactorily. For instance, bismethylenedioxy dexamethasone was prepared in 50% yield in the usual way.

The biological activity of the bismethylenedioxy steroids indicates that the animal is able, in part at least, to remove the bismethylenedioxy group. Diminished but significant activity was found in the biologically active steroid bismethylenedioxy compounds tested.[9] The approximate liver glycogen (glyc.) and granuloma (gran.) activities in terms of hydrocortisone for some of these are as follows: Bismethylenedioxycortisone (glyc. 0.3, gran. 0); bismethylenedioxy hydrocortisone (glyc. 0.25, gran. 0); bismethylenedioxy prednisone (glyc. 1.0, gran. *ca.* 1.9); bismethylenedioxy prednisolone (glyc. 1.0, gran. *ca.* 1.8); bismethylenedioxy-9α-fluorohydrocortisone (glyc. 1.25, gran. 1.8).

EXPERIMENTAL[10]

17α,20;20,21-Bismethylenedioxy-4-pregnene-11β-ol-3-one (hydrocortisone-BMD) (VI). Method A. Two grams of hydrocortisone (V) were dissolved in 100 ml. of chloroform which had been shaken with sulfuric acid, dried over calcium chloride, and distilled. To this mixture was added with cooling 60 ml. of concd. hydrochloric acid and 60 ml. aqueous 37% formaldehyde (containing 0.5% methanol). The reaction mixture was stirred for 7 hr. at room temperature. The chloroform was separated and the aqueous phase extracted with more chloroform. The combined extract was washed with aqueous bicarbonate, dried, and concentrated. From the residue by methanol trituration and washing there was obtained 1.0 g. of bismethylenedioxyhydrocortisone (VI), m.p. 200–220°. Recrystallization from ether and methanol containing a trace of methylene chloride gave the analytical sample, m.p. 220–223°.

Anal. Calcd. for $C_{23}H_{32}O_6$: C, 68.29; H, 7.97. Found: C, 68.01; H, 7.97, $[\alpha]_D^{31}$ + 26°. λ_{max} 241.5 mμ, ϵ 15,600. λ_{max}^{Nujol} 2.88, 5.95, 6.10, 9.0 μ.

Method B. 17α,20;20,21-Bismethylenedioxy-3-ethylenedioxy-5-pregnene-11β-ol. To 2.16 g. of bismethylenedioxycortisone-3-dioxolane[1,4b,5a] in 20 ml. of tetrahydrofuran was added 200 mg. of lithium aluminum hydride. The mixture was stirred overnight at room temperature and then refluxed for 1 hr. A small amount of water was carefully added to decompose the excess lithium aluminum hydride and the material filtered through Supercel. Concentration of the filtrate gave 2.06 g. of crystalline residue. Recrystallization from methanol gave 1.50 g. of bismethylenedioxy hydrocortisone-3-dioxolane, m.p. 162–165°, second crop of 204 mg., m.p. 150–160°. One more recrystallization of the first crop from methanol furnished an analytical sample, m.p. 167–169°.

Anal. Calcd. for $C_{25}H_{36}O_7$: C, 66.94; H, 8.09. Found: C, 67.41, 66.62; H, 8.30, 7.84. λ_{max}^{Nujol} 2.83, 8.9–9.3 μ.

To 200 mg. of the above bismethylenedioxy dioxolane in 4.0 ml. of acetone was added 20 mg. of *p*-toluenesulfonic acid. The mixture was allowed to stand at room temperature for 15 hr. It was poured into saturated aqueous sodium bicarbonate and the acetone distilled off under reduced pressure. It was then extracted with three portions of methylene chloride, dried and concentrated to give 176 mg. of crystalline residue. Recrystallization from methanol yielded 156 mg. in two crops of bismethylenedioxy hydrocortisone, m.p. 222–227°. A mixed m.p. and infrared spectrum proved this compound to be identical with the sample prepared by Method A.

17α,20;20,21-Bismethylenedioxy-4-pregnene-11β-ol-3-one (VI) and 17,20:20,21-bismethylenedioxy-4-pregnene-11β-ol-3-one-11-methoxymethyl ether (VII). Thirty grams of hydrocortisone was combined with 1500 ml. of chloroform and to this solution was added a cooled mixture of 600 ml. of concd. hydrochloric acid and 600 ml. of formalin. The reaction mixture was stirred at room temperature for 1 hr. The two layers were separated, the aqueous layer extracted with chloroform, and the solution combined. The chloroform extract was washed with sodium carbonate, dried, and concentrated *in vacuo*. The entire residue (30.8 g.) was chromatographed on 900 g. of acid washed alumina. Elution of the column with 1:4 petroleum ether (b.p. 40–60°)-ether yielded 7 g. of crude crystalline 17α,20;20,21-bismethylenedioxy - 4 - pregnene - 11β - ol - 3 - one - 11 - methoxymethyl ether (VII). Recrystallization from ether gave 4 g. of analytically pure VII, m.p. 160–165°.

Anal. Calcd. for $C_{25}H_{36}O_7$: C, 66.94; H, 8.09; CH_2O, 20,0; CH_3O, 6.9; mol. wt., 448.54. Found: C, 67.31; H, 8.11; CH_2O, 20.1; CH_3O, 8.8; mol. wt. (East), 475 ± 45. $\lambda_{max}^{CH_3OH}$ 241 mμ, ϵ 15,900. λ_{max}^{Nujol} 6.0, 6.15, 9.0–9.4 μ.

From the ether and ether-chloroform (2:3) effluents there was obtained 10.5 g. of bismethylenedioxy hydrocortisone (VI), m.p. 217–222°.

Acid hydrolysis of a sample of VII, using 50% acetic acid at 100° for 8 hr., acetylation and chromatography yielded *ca.* 25% of hydrocortisone acetate.

17α,20;20,21-Bismethylenedioxy-1,4-pregnadiene-3,11-dione (prednisone-BMD). To a suspension of 500 mg. of prednisone in 25 ml. of chloroform was added a mixture of 10 ml. of formalin and 10 ml. of concd. hydrochloric acid. The two-phase system was stirred at room temperature for 70 hr. The two layers were separated, the aqueous layer extracted with chloroform, and the chloroform extracts combined with the original organic solvent layer. The chloroform was washed with a saturated solution of sodium bicarbonate, dried, and concentrated under reduced pressure to a semicrystalline solid weighing 712 mg. This crude product was triturated with boiling methanol giving 352 mg. of crystalline bismethylenedioxy prednisone m.p. 175–195°. After recrystallization from acetone and methanol, a pure sample of 17α,20;20,21-bismethylenedioxy-1,4-pregnadiene-3,11-dione, m.p. 214–217°, was obtained.

Anal. Calcd. for $C_{23}H_{28}O_6$: C, 68.98; H, 7.05. Found: C, 68.60; H, 7.11. λ_{max} 238 mμ, ϵ 15,300. λ_{max}^{Nujol} 5.87, 6.0, 6.15, 6.2 μ.

17α,20;20,21-Bismethylenedioxy-1,4-pregnadiene-11β-ol-3-one (prednisolone-BMD) and 17α,20;20,21-bismethylenedioxy - 1,4 - pregnadiene - 11β - ol - 3 - one-11-methoxymethyl ether. Twenty-five grams of prednisolone was suspended in 1250 ml. of chloroform. To this was added a precooled (*ca.* 10°) mixture of 500 ml. of formalin and 500 ml. of concd. hydrochloric acid. The two-phase system was stirred vigorously at room temperature for 20 min., the prednisolone dissolving completely after about 1 min. The layers were separated and the aqueous phase extracted with 500 ml. of chloroform. The combined chloroform extract was washed with water and saturated aqueous sodium bicarbonate, dried, and distilled. The residue was dissolved in 250 ml. of methanol and concentrated to dryness twice to remove most of the formaldehyde polymer. The resultant crystalline product was recrystallized from methanol to give 20.8 g. of crude product, m.p. 230–260°. Recrystallization from methanol–methylene chloride yielded 15.0 g. of bismethylprednisolone m.p. 267–271°. An analytical sample was prepared by recrystallization from ethyl acetate, m.p. 270–274°.

(9) We are indebted to Dr. R. H. Silber of the Merck Institute for Therapeutic Research for the biological test results.

(10) All melting points were determined on a Kofler micro-hot stage, ultraviolet absorption spectra were taken in methanol and rotations were taken in chloroform at approximately 1% concentration unless otherwise specified.

Anal. Calcd. for $C_{23}H_{30}O_6$: C, 68.63; H, 7.57. Found: C, 68.37; H, 7.70. λ_{max} 242 mμ, ε 14,600. λ_{max}^{Nujol} 2.90, 6.05, 6.15, 6.2, 9.15 μ $[\alpha]_D$ − 20°.

Concentration of the mother liquors from above gave 4.0 g. of bismethylenedioxy prednisolone-11-methoxymethyl ether, m.p. 210–220°. Recrystallization from acetone gave the analytical sample, m.p. 217–220°.

Anal. Calcd. for $C_{25}H_{34}O_7$: C, 67.24; H, 7.68. Found: C, 66.85; H, 7.46. λ_{max}^{KBr} 6.00, 6.14, 6.2, 9.2 μ.

9α-Fluoro-17α,20;20,21-bismethylenedioxy-4-pregnen-11β-ol-3-one(9α-Fluorohydrocortisone-BMD). This preparation has been described previously.[1]

17α,20;20,21-Bismethylenedioxy-4-pregnene-3-one (cortexolone-BMD). To 500 mg. of cortexolone (4-pregnene-17α,21-diol-3,20-dione) in 25 ml. of chloroform was added a mixture of 10 ml. of formalin and 10 ml. of concd. hydrochloric acid. The two-phase system was stirred at room temperature for 44 hr. (Quantitative blue tetrazoleum measurements subsequently indicated the reaction was essentially complete in 1–2 hr.) The two phases were separated and the aqueous phase extracted with two portions of chloroform. The combined chloroform was washed with aqueous sodium bicarbonate and water, dried, and distilled. The residue, 464 mg., was washed with petroleum ether to give 327 mg. of 17α,20;20,21-bismethylenedioxy-4-pregnene-3-one, m.p. 220–245°. A sample was recrystallized from methanol and methylene chloride–ether, m.p. 250–255°.

Anal. Calcd. for $C_{23}H_{32}O_6$: C, 71.10; H, 8.30. Found: C, 70.76; H, 8.29. λ_{max} 242 mμ, ε 16,500. $\lambda_{max}^{CHCl_3}$ 6.0, 6.15, 9.05–9.15 μ.

16α-Methyl-9α-fluoro-17α,20;20,21-bismethylenedioxy-1,4-pregnadiene-11β-ol-3-one (dexamethasone-BMD). Five hundred milligrams of dexamethasone in 25 ml. of chloroform was stirred with 10 ml. of 37% aqueous formaldehyde and 10 ml. of concd. hydrochloric acid for 1 hr. at room temperature. An additional 25 ml. of chloroform was added and the layers separated. The chloroform layer was washed with a saturated solution of sodium bicarbonate, dried and evaporated to dryness *in vacuo*. Twenty-five milliliters of methanol was added to the solid residue and it was again evaporated to dryness. The total residue was recrystallized from methylene chloride–methanol to yield 255 mg. of analytically pure 16α - methyl - 9α - fluoro - 17α,20;20,21 - bismethylenedioxy-1,4-pregnadiene-11β-ol-3-one, m.p. 310–20°.

Anal. Calcd. for $C_{24}H_{31}O_6F$: C, 66.33; H, 7.19. Found: C, 66.43; H, 7.06. λ_{max}^{Nujol} 2.80, 6.0, 6.2, 9.2 μ, λ_{max} 238 mμ, ε 14,900.

17α,20;20,21-Bismethylenedioxy-3-pyrrolidyl-3,5-pregnadiene-11-one. Five hundred milligrams of bismethylenedioxy cortisone was dissolved in 10 ml. of ethanol containing a little methylene chloride. This was concentrated to *ca.* 5 ml. to remove methylene chloride. To this was added 0.5 ml. of pyrrolidine and the mixture heated for 1 min. on the steam bath. The resultant precipitate was cooled and filtered, washing with ethanol, to give 540 mg. of light yellow prisms, m.p. 205–212° dec. The compound was analyzed without further purification.

Anal. Calcd. for $C_{27}H_{37}O_5N$: C, 71.18; H, 8.19; N, 3.07. Found: C, 70.57; H, 8.21; N, 3.14. λ_{max} 271 mμ, ε 17,000. λ_{max}^{Nujol} 5.90, 6.10, 6.19, 9.0–9.5 μ.

17α,20;20,21-Bisbutyraldioxy-4-pregnene-11β-ol-3-one. To 500 mg. of hydrocortisone, dissolved in 25 ml. of methylene chloride, was added 10 ml. of 40% aqueous butyraldehyde and 10 ml. of concd. hydrochloric acid. The reaction mixture was stirred at room temperature for 6 hr. The solvent layers were separated and the aqueous layer extracted with fresh methylene chloride. The combined methylene chloride extract was washed with water, dried over magnesium sulfate, and concentrated. The residual oil, containing butyraldehyde, was chromatographed on 12 g. of acid washed alumina. From the 4:1 petroleum ether–ether to ether eluates there was obtained 263 mg. of 17α,20;20,21-bisbutyraldioxy-4-pregnene-11β-ol-3-one as a clear glass. λ_{max}^{Nujol} 2.9, 6.0, 6.15, 8.6–9.0 μ. $\lambda_{max}^{CH_3OH}$ 241 mμ, E% 296. Quantitative blue tetrazoleum, 7.3% of hydrocortisone.

The above 263 mg. of product was heated under nitrogen with 50 ml. of 50% acetic acid on the steam bath for 8 hr. The acetic acid was removed by vacuum distillation and the residue purified by extraction into methylene chloride, removal of the organic solvent, and acetylation by heating 10 min. with pyridine–acetic anhydride. The acetylated material (125 mg.) was chromatographed on 5 g. of acid washed alumina. Hydrocortisone acetate was obtained in the 1:4 ether-chloroform eluates, m.p. and mixed m.p. with authentic material 210–217°. The infrared spectrum of this material was essentially identical with that of hydrocortisone acetate.

Bismethylenedioxy group formation time study. Cortisone, hydrocortisone and cortexolone were all treated in exactly the same way as follows: 500 mg. of steroid was dissolved (or suspended) in 25 ml. of chloroform. To this was added a mixture of 10 ml. of formalin and 10 ml. of concd. hydrochloric acid and the mixture immediately stirred at room temperature. This was taken to be "zero time." At time intervals about 1-ml. aliquots of the chloroform layer were withdrawn and washed with saturated aqueous sodium bicarbonate solutions. The chloroform layers were taken to dryness and the residues submitted for ultraviolet and BT analysis.[11] All quantitative blue tetrazoleum results were calculated with reference to the steroid used in the reaction as cortisone, hydrocortisone, and cortexolone give different intensities of absorption at 510 mμ. Because the residues have varying amounts of formaldehyde polymer in them the ultraviolet absorption intensities were used to correct the blue tetrazoleum results with the assumption that the 3-keto-Δ^4-chromophore was not affected by the reaction conditions. These corrected blue tetrazoleum results are plotted in Fig. 1.

Bismethylenedioxy group hydrolyses time study. One hundred twenty milligrams of steroid (cortisone, hydrocortisone, and cortexolone) were heated in 10 ml. of 50% acetic acid at 100°. Aliquots were removed and concentrated to dryness periodically for ultraviolet and blue tetrazoleum assay. There was only about 5% loss of ultraviolet up to 4 hr. but after that the maximum at *ca.* 240 mμ diminished in intensity. Both bismethylenedioxy cortisone and bismethyldioxy hydrocortisone were homogeneous in a minute or less whereas bismethylenedioxy cortexolone required about 4 hr. to dissolve completely. The results of these time studies are presented in Fig. 2.

Acknowledgment. The authors wish to thank Mr. J. J. Wittick and associates for ultraviolet absorption spectra and blue tetrazoleum data and Mr. R. N. Boos and associates for elemental analyses and methylenedioxy determinations.

RAHWAY, N. J.

(11) W. J. Mader and R. R. Buck, *Anal. Chem.*, 24, 666 (1952).

[CONTRIBUTION FROM THE MERCK, SHARP AND DOHME RESEARCH LABORATORIES, DIVISION OF MERCK & CO., INC.]

Bismethylenedioxy Steroids. VI. Synthesis of 9α-Methylhydrocortisone and 9α-Methylprednisolone[1,2]

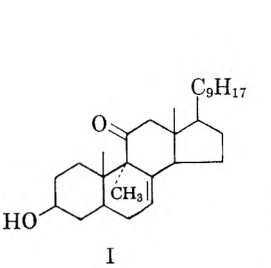
R. E. BEYLER,[3] FRANCES HOFFMAN, L. H. SARETT, AND M. TISHLER

Received October 12, 1960

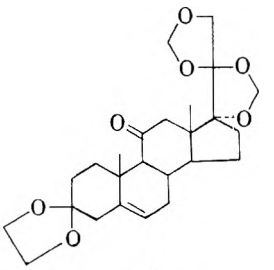
The synthesis of 9α-methylhydrocortisone acetate (XVIb) and 9α-methylprednisolone acetate (XVII) is described. The key step in the synthesis is the reaction of a bismethylenedioxy protected 9α-bromo-11-ketone (XII) with methyl Grignard reagent to give a 9α-methyl-11-ketone (XIII). Alternate methods used to synthesize 9α-methylsteroids are also discussed.

Substituents at the C_9-position of adrenocortical steroids have a profound effect on biological activity. Liver glycogen activities of C_9-substituted hydrocortisones are known to decrease in the following order: F > Cl > H > Br > OH > I > OCH_3 ≃ OC_2H_5. This order correlates (hydrogen and hydroxyl are exceptions) with the inductive effect of the substituents as measured by the acidity constants of the corresponding α-substituted acetic acids.[4] Fried has favored the view that the electronic effect at C_9 has a greater influence on biological activity than the steric effect. As the acidity constant of propionic acid (CH_3) is slightly less than acetic acid (H) and the methyl group approximates a chlorine atom in size[5] we felt that information on the bioactivity of 9α-methyl hydrocortisone would advance the theory of how these effects are mediated. The present study outlines methods for introduction of a methyl group at C_9 and reports on the synthesis of two 9α-methyl corticoids.

Jones, Meakins, and Stephenson[6] have synthesized 9α-methyl-7,22-ergostadiene-3β-ol-11-one (I) by alkylation of the Δ_7-11-ketone with methyl iodide–potassium *t*-butoxide. In a similar fashion we tried to introduce the 9α-methyl group by alkylation of bismethylenedioxy cortisone-3-dioxolane (II). Paper strip data on the alkylation product showed that a trace amount of bismethylenedioxy-9α-methylcortisone (after dioxolane removal) had formed when triphenylmethylsodium–methyl iodide was used. However the major products of the reaction were starting material and polar by-products so that this method did not prove practical for our purpose.[7]

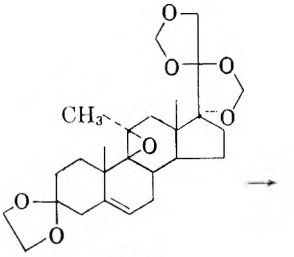


I

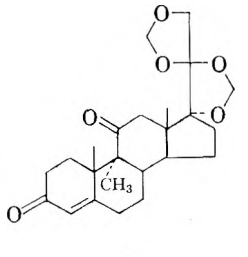


II

Another attractive method for synthesis of a 9α-methylsteroid involved an attempted Wagner-Meerwein rearrangement of 11α-methyl-9,11β-oxido - 17,20;20,21 - bismethylenedioxy - 3 - ethylenedioxy - 5 - pregnene (III)[8] to the 9α-methyl-11-ketone (IV). The Lewis acid catalyzed rearrangement of oxides to ketones is well known.[9] In most of our attempts we used boron trifluoride etherate in solvents of varying polarities (ether, tetrahydrofuran, benzene, methylene chloride, chloroform). In general the desired electrophilic attack on the



III



IV

(1) Paper V in this series: R. E. Beyler, Frances Hoffman, R. M. Moriarty, and L. H. Sarett, *J. Org. Chem.*, **26**, 2421 (1961).

(2) A preliminary communication of part of this work has been published. Frances Hoffman, R. E. Beyler, and M. Tishler, *J. Am. Chem. Soc.*, **80**, 5322 (1958).

(3) Present address: Department of Chemistry, Southern Illinois University, Carbondale, Ill.

(4) J. Fried and A. Borman in *Vitamins and Hormones*, Academic Press, New York, Vol. 16, p 322.

(5) A. Burger and R. D. Foggio, *J. Am. Chem. Soc.*, **78**, 4419 (1956).

(6) E. R. H. Jones, G. D. Meakins, and J. S. Stephenson, *J. Chem. Soc.*, 2156 (1958).

(7) More recently in another study, Dr. John Fried has treated bismethylenedioxycortisone-3-dioxolane (II) with sodium hydride–methyl iodide. From a chromatographic fraction which was less polar than starting material, we again obtained paper strip evidence for the presence of a trace of bismethylenedioxy-9α-methylcortisone after dioxolane removal.

(8) Paper IV in this series: R. E. Beyler, Frances Hoffman, and L. H. Sarett, *J. Am. Chem. Soc.*, **82**, 178 (1960).

(9) A recent example is the conversion of methyl acetyl-12,13α-oxido-18-isooleanolate to methyl acetyl-12 keto-dihydro-11-isooleanolate with boron trifluoride etherate in methylene chloride: E. J. Corey and J. J. Ursprung, *J. Am Chem. Soc.*, **78**, 183 (1956). Also see C. W. Shoppee, M. E. H. Howden, R. W. Killick, and G. H. R. Sumners, *J. Chem. Soc.*, 630 (1959) for conversion of 4,5α-oxidocholestane to 5α-cholestan-4-one.

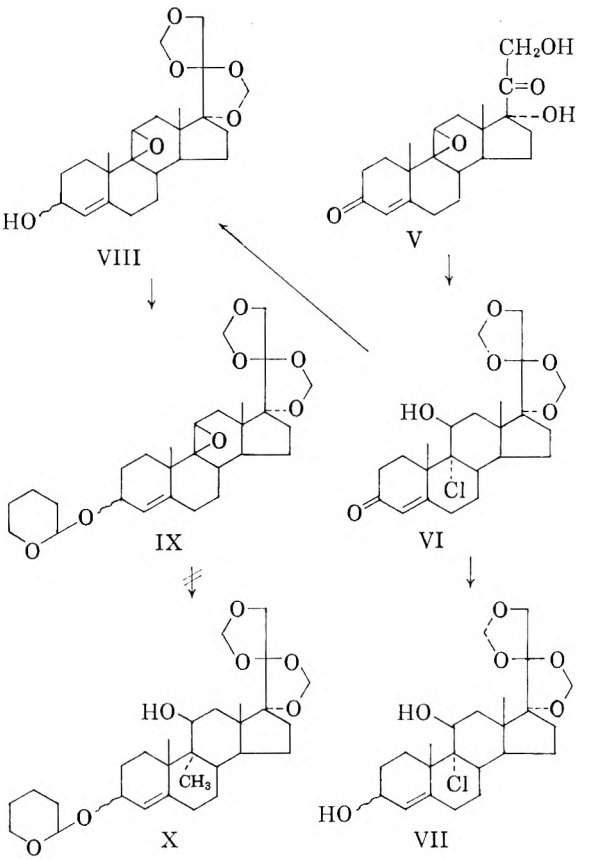
9,11-oxide was superseded by reaction at the dioxolane and to a lesser extent the bismethylenedioxy group; vigorous conditions (excess boron trifluoride in polar solvents) gave polar non-crystalline products and mild conditions (limited amounts of boron trifluoride in ether or tetrahydrofuran) gave starting material or the corresponding 3-keto-Δ^4 analog. Some of the crude material showed saturated ketone by infrared but no pure 9α-methyl-11-ketone was obtained in these experiments. Other catalysts tried on III or its 3-keto-Δ^4 analog include ferric chloride, perchloric acid, *p*-toluenesulfonic acid and hydrogen fluoride.

The cleavage of oxides with methyl Grignard reagent or methyllithium, which has been used to make 6- and 12-methylsteroids,[10,11] seemed to be a possible approach to the 9α-methyl-11β-ol. We are aware of one reported cleavage of a steroid oxide with Grignard reagents to give a bridgehead methyl substituent. That is the cleavage of 5,6β-oxidocholestan-3β-ol with methylmagnesium iodide to give 5α-methylcholestane-3β,6β-diol.[12] It was felt that this method for making a 9α-methylsteroid was deserving of our attention.

Therefore, the desired oxide (IX) for Grignard cleavage attempts was synthesized as follows: bismethylenedioxy - 9α - chlorohydrocortisone (VI) was prepared from either 9,11β-oxidocortexolone[13] (V) or from 9α-chlorohydrocortisone using hydrochloric acid–formalin in the standard way. Treatment of VI with sodium methoxide or potassium *t*-butoxide yielded bismethylenedioxy-9,11β-oxidocortexolone. The latter would have been useful for oxide cleavage if it could have been protected further with a 3-dioxolane. However attempts to make bismethylenedioxy-9,11β-oxidocortexolone-3-dioxolane met with failure due to acid catalyzed rearrangement in the C-ring.[14]

As an alternative, the chlorohydrin (VI) was reduced with sodium borohydride to the chlorohydrin -3 ξ-ol (VII). The latter could be transformed to the 9,11-oxide-3 ξ-ol (VIII) by means of potassium *t*-butoxide or refluxing sodium borohydride. With this information it was then found possible to go directly from bismethylenedioxy-9α-chlorohydrocortisone (VI) to 9,11β-oxido - 17α,20;20,21-bismethylenedioxy - 4 - pregnene-3 ξ-ol (VIII) in one step by means of sodium borohydride in refluxing ethanol. The required tetrahydropyranyl ether group was then added to give the fully protected oxide (IX) as an oil.

All attempts to cleave IX with methyllithium, methylmagnesium iodide and methylmagnesium chloride were unsuccessful. Only starting material and polar oils resulted from these reactions. Similar reactions with the unprotected 3-hydroxy Δ^4-compound (VIII) also met with failure.



A usable yield of 9α-methylsteroid was finally obtained by reaction of a 9α-bromo-11-ketone with methyl Grignard reagent. It is well known[15] that α-halo ketones can react with Grignard reagents in at least four different ways: (1) normal addition to the C=O to give a tertiary alcohol, (2) replacement of the α-halogen by the organic radical of the Grignard reagent, (3) reductive enolization

(10) G. B. Spero, J. L. Thompson, B. J. Magerlein, A. R. Hange, H. C. Murray, O. K. Sebek, and J. A. Hogg, *J. Am. Chem. Soc.*, 78, 6213 (1956); J. H. Fried, G. E. Arth, and L. H. Sarett, *J. Am. Chem. Soc.*, 81, 1235 (1959).

(11) B. G. Christensen, R. G. Strachan, N. R. Trenner, B. H. Arison, R. Hirschmann, and J. M. Chemerda, *J. Am. Chem. Soc.*, 82, 3995 (1960).

(12) M. Chuman, *J. Chem. Soc., Japan*, 70, 253 (1949).

(13) J. Fried and E. F. Sabo, *J. Am. Chem. Soc.*, 79, 1130 (1957); Cortexolone has been proposed as a trivial name for Reichstein's Substance S: L. F. Fieser and M. Fieser, *Steroids*, Reinhold, New York, p. 602.

(14) The crude product from the dioxolanation always exhibited a sizeable ultraviolet absorption at *ca.* 240 mμ and a saturated carbonyl in the infrared spectrum. In another connection we have observed the conversion of 9,11β-oxidocortexolone acetate to cortisone acetate using *p*-toluenesulfonic acid in refluxing benzene in at least 40% yield.

Dioxolanation of 9α-halo-11β-hydroxysteroids is also not feasible, so we could not reverse the order of steps to get a bismethylenedioxy-9,11-oxide dioxolane. For example dioxolanation attempts on bismethylenedioxy-9α-fluorohydrocortisone gave a bad mixture of products which we have not characterized other than infrared spectra on selected chromatographic fractions.

(15) M. S. Kharasch and O. Reinmuth, *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, New York, 1954, p. 181.

with loss of halogen and (4) enolization of the α-halo ketone. The reaction we desired (number 2 above) is exemplified in the simplest case by conversion of 2-chlorocyclohexanone to 2-methylcyclohexanone.[16] A more recent example is that of the conversion of 2-chlorotetralone to 2-phenyltetralone.[17]

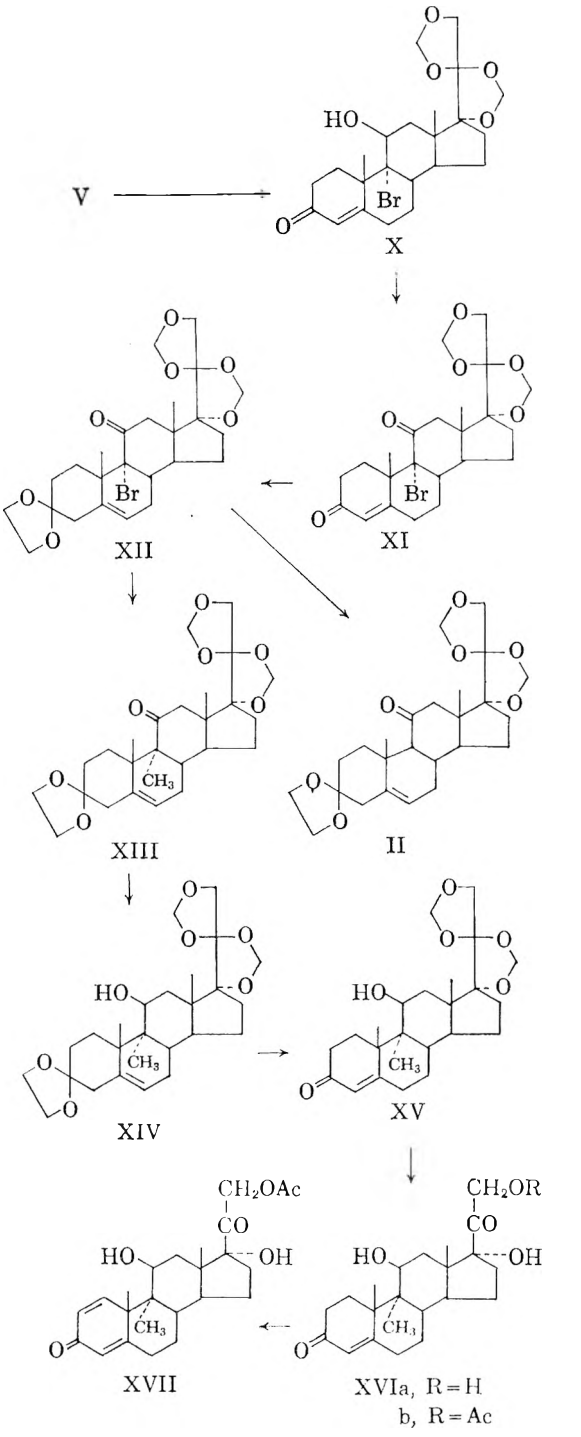
Synthesis of the requisite 9α-bromo-11-ketone (XII) was done as follows: 9,11β-Oxidocortexolone (V) reacted with formaldehyde–hydrobromic acid to give bismethylenedioxy-9α-bromohydrocortisone (X). Chromic acid oxidation of X gave bismethylenedioxy-9α-bromocortisone (XI). Conventional dioxolanation then yielded the fully protected 9α-bromo-11-ketone (XII).

When this α-halo ketone was allowed to react with methylmagnesium iodide and excess methyl iodide in refluxing ether-tetrahydrofuran two products resulted. These were separated by careful alumina chromatography and proved to be bismethylenedioxy 9α-methylcortisone-3-dioxolane (XIII) and bismethylenedioxy cortisone-3-dioxolane (II). The former was obtained in a maximum 30% yield and the yield of II varied widely depending upon the solvents and temperatures used. The 9α-methyl substituent was proven to be present by means of nuclear magnetic resonance, which showed three tertiary C—CH_3 bands.

The rotatory dispersion curves of II and XIII[18] were also very similar, as would be predicted for two compounds differing by only a CH_3 and H adjacent to the carbonyl. This data confirmed the fact that no serious rearrangement had occurred during the reaction.

With regard to the mechanism of this reaction, it seems probable that the first step is the formation of an enolate anion[19] with loss of the bromine atom at C_9. The resultant C_9-carbanion can then be alkylated with excess methyl iodide to give methyl ketone XIII. Alternatively, a proton supplied during the work-up would give the unmethylated ketone (II).

The completion of the synthesis was done as follows: the 11-keto compound (XIII) was reduced with lithium aluminum hydride to the bismethylenedioxy-9α-methylhydrocortisone-3-dioxolane (XIV). The dioxolane was removed with acetone–*p*-toluenesulfonic acid and the bismethylenedioxy-group was reversed with 50% acetic acid to give 9α-methylhydrocortisone (XVIa). Acetylation afforded the 21-acetate (XVIb).



Dehydrogenation of XVIb with selenium dioxide in *t*-butyl alcohol acetic acid produced 9α-methylprednisolone-21-acetate (XVII). The infrared spectra of all intermediates and the final products were consistent with the assigned structures.

It is of interest to examine the influence of 9α-substituents on the ultraviolet absorbing 3-keto-Δ^4-chromophore (Table I). Since an electronegative substituent such as fluorine at C_9 has a hypsochromic effect (−3 mμ) and the methyl group, which is electron releasing, has a bathochromic effect (+1 to 2.5 mμ) it seems probable that the

(16) M. Tiffeneau and B. Tchoubar, *Compt. rend.*, 198, 941 (1934).

(17) A. S. Hussey and R. R. Herr, Abstracts of Papers Presented at the 135th Meeting of the American Chemical Society, Boston, Mass., April, 1959, p. 18-c.

(18) We are indebted to Dr. D. E. Williams for these measurements.

(19) E. P. Kohler and M. Tishler, *J. Am. Chem. Soc.*, 54, 594 (1932); E. P. Kohler and M. Tishler, *J. Am. Chem. Soc.*, 57, 217 (1935).

TABLE I

11-Ketone Series	λ_{max}	
Cortisone-BMD	238 mμ	Δλ for F = −3 mμ Δλ for CH_3 = +1 mμ
9α-Fluorocortisone-BMD	235	
9α-Methylcortisone-BMD	239	
11-Hydroxy Series		
Hydrocortisone-BMD	241.5 mμ	Δλ for F = −3 mμ Δλ for CH_3 = +2.5 mμ
9α-Fluorohydrocortisone-BMD	238.5	
9α-Methylhydrocortisone-BMD	244	

C_9-C_5 transannular inductive effect has an appreciable influence on the ultraviolet absorption maximum.

The biological test results[20] expressed in terms of hydrocortisone, were as follows: 9α-Methylhydrocortisone (XVIa) was *ca.* 0.1 (p.o.) and 9α-methylprednisolone acetate (XVII) was *ca.* 1.75 (p.o.) in the liver glycogen assay. XVIa was *ca.* 0.25 (s.c.) and XVII was *ca.* 1.6–1.8 (p.o.) in the cotton pellet granuloma assay. Both XVIa and XVII caused slight sodium retention in adrenalectomized rats.

EXPERIMENTAL[21]

Methylation of bismethylenedioxycortisone-3-dioxolane. To 2.59 g. of dry bismethylenedioxycortisone-3-dioxolane suspended in 50 ml. of sodium dried ether was added 4.7 ml. (1 equivalent) of 0.128*M* triphenylmethyl sodium in ether. The mixture was stirred at room temperature for 20 min. Since a loss of red color indicated the base was being consumed, 15.3 ml. more triphenylmethyl sodium was added. Stirring was continued for another hour during which time a fine yellow solid formed. Then 5.0 ml. of methyl iodide was added and stirring was continued at room temperature for 96 hr. About 20 ml. of water was cautiously added and the ether layer separated. The aqueous layer was extracted with two portions of methylene chloride, the combined ether–methylene chloride extract dried and concentrated to give 3.36 g. of yellow gum. This was chromatographed on 100 g. of alumina. From the early petroleum ether–ether (3:7) fractions 506 mg. of crystalline product was selected for removal of the 3-dioxolane group. It was dissolved in 10 ml. of acetone and 100 mg. of *p*-toluenesulfonic acid added. After 24 hr. at room temperature it was concentrated to dryness under reduced pressure. The residue was dissolved in methylene chloride and washed with saturated aqueous sodium bicarbonate. After concentration of the extract the residual 447 mg. of gum was chromatographed on 20 g. of alumina. A crystalline product was obtained in the ether to ether–chloroform (1:4) effluents. Paper strips on the first three fractions, totalling 49 mg., showed a spot more mobile than bismethylenedioxycortisone. The relative Rf with respect to bismethylenedioxy cortisone was about 1.4 in a cyclohexane-formamide system and about 1.3 in a cyclohexane–propylene glycol system. The major spot from these fractions, however, was bismethylenedioxy cortisone; it was estimated to approximate 75% of the ultraviolet absorbing material.

(20) We are indebted to Dr. R. H. Silber and Dr. H. C. Stoerk of the Merck Institute for Therapeutic Research for these data. The designation p.o. and s.c. designates oral and subcutaneous administration, respectively.

(21) All melting points were determined on a Kofler micro hot stage. Ultraviolet spectra were determined in methanol.

Similar results were obtained with methyl iodide and bismethylenedioxycortisone-3-dioxolane using metallic potassium in refluxing benzene or toluene with vigorous stirring. With potassium *t*-butoxide no evidence for methylation was obtained in two experiments.

9α-Chloro-17α,20;20,21-Bismethylenedioxy-4-pregnene-11β-ol-3-one (VI) *A. From 9α-Chlorohydrocortisone acetate.* One gram of 9α-chloro-4-pregnene-11β,17α,21-triol-3,20-dione-21-acetate was dissolved in 100 ml. of methylene chloride and stirred at room temperature for 18 hr. with 25 ml. of 37% formaldehyde and 25 ml. of concd. hydrochloric acid. The methylene chloride layer was separated, washed with aqueous sodium bicarbonate and dried. Evaporation *in vacuo* yielded crystals which, upon recrystallization from methylene chloride–methanol gave 550 mg. of analytically pure 9α-chloro-17α,20;20,21-bismethylenedioxy-4-pregnene-11β-ol-3-one, m.p. 220–230° dec.

Anal. Calcd. for $C_{23}H_{31}O_6Cl$: C, 62.93; H, 6.95; Cl, 8.07; CH_3O, 13.6. Found: C, 62.46; H, 6.97; Cl, 8.59; CH_2O, 13.8. λ_{max}^{Nujol} 5.99, 6.10, 9.0 μ.

B. *From 9,11β-oxidocortexolone* (V). One gram of 9,11β-oxido-4-pregnene-17α,21-diol-3,20-dione[13] was dissolved in 100 ml. of methylene chloride and stirred for 18 hr. at room temperature with 25 ml. of formalin and 25 ml. of concd. hydrochloric acid. After the usual work-up, the resultant crystals were recrystallized from methylene chloride–methanol to yield 350 mg. of 9α-chloro-17,20;20,21-bismethylenedioxy-4-pregnene-11β-ol-3-one, m.p. 220–230° dec. The infrared spectrum of this compound was identical with that of the sample prepared above.

9,11β-Oxido-17,20;21,21-bismethylenedioxy-4-pregnene-3-one. A. *Potassium t-butoxide method.* To a stirred solution of 1.0 g. of 9α-chloro-17α,20;20,21-bismethylenedioxy-4-pregnene-11β-ol-3-one in 50 ml. of *t*-butyl alcohol was added, in an atmosphere of nitrogen, 4.0 ml. of 0.84*M* potassium *t*-butoxide. After 48 hr., a few drops of acetic acid were added and the *t*-butyl alcohol was concentrated *in vacuo*. The residue was extracted with methylene chloride, washed with a saturated solution of sodium bicarbonate, dried and concentrated to yield 1.02 g. of amber gum. Trituration with methylene chloride–ether afforded 155 mg. of the desired product. The residue was chromatographed on acid-washed alumina and elution of the column with ether and ether-chloroform (4:1) gave, after recrystallization from methylene chloride–methanol, 540 mg. of analytically pure 9,11β-oxido-17α,20;20,21-bismethylenedioxy-4-pregnene-3-one, m.p. 210–215°.

Anal. Calcd. for $C_{23}H_{30}O_6$: C, 68.63; H, 7.51. Found: C, 68.52; H, 7.54. λ_{max}^{Nujol} 6.0, 6.15, 9.0–9.1 μ.

B. *Sodium methoxide method.* Two hundred milligrams of 9α - chloro - 17α,20;20,21 - bismethylenedioxy - 4 - pregnene-11β-ol-3-one was combined under nitrogen with 20 ml. of methanol and 1.0 ml. of 2*N* sodium methoxide and heated under reflux for 18 hr. The reaction mixture was cooled, enough 2.5*N* hydrochloric acid added to effect neutrality, the methanol concentrated to a small volume *in vacuo* and the residue extracted with ethyl acetate. After washing the organic phase with water, drying over magnesium sulfate, and concentrating under reduced pressure, crystals were obtained. Recrystallization from methanol afforded 50 mg. of analytically pure 9,11β-oxido-17,20;20,21-bismethylenedioxy-4-pregnene-3-one, m.p. 205–215°, identical with the sample prepared above.

9α-Chloro-17α,20;20,21-bismethylenedioxy-4-pregnene-3ξ,11β-diol (VII). Two hundred milligrams of bismethylenedioxy-9α-chlorohydrocortisone (VI) was dissolved in 10 ml. of 95% ethanol and 10 ml. of methylene chloride. To this was added 200 mg. of sodium borohydride and the mixture stirred at room temperature for 16 hr. Water was added and the solution concentrated to an aqueous suspension of oil. This was extracted thrice with methylene chloride, dried and concentrated to give 208 mg. of crystalline residue, m.p. 180–195°. Recrystallization from ether–methylene chloride gave 102 mg., m.p. 193–202°. The analytical sample of VII

was prepared by recrystallization from acetone-ether and methylene chloride–ether, m.p. 205–208° dec.

Anal. Calcd. for $C_{23}H_{33}O_6Cl$: C, 62.64; H, 7.53; Cl, 8.04. Found: C, 62.91; H, 7.27; Cl, 8.78. λ_{max}^{Nujol} 2.75–3.0, 6.0 (weak), 9.0–9.2 μ.

9,11β-Oxido-17α,20;20,21-bismethylenedioxy-4-pregnen-3β-ol (VIII) **A.** *Potassium t-butoxide on* VII. To 30 mg. of the above chlorohydrin (VII) in 1.5 ml. of *t*-butyl alcohol was added 0.1 ml. of 1*M* potassium *t*-butoxide. This mixture, under nitrogen, was kept at room temperature for 2 hr. Then two drops of glacial acetic acid was added and it was concentrated to near-dryness. Saturated aqueous sodium bicarbonate was added and the resultant suspension extracted with methylene chloride. Drying and concentration of solvent gave 13 mg. of crystalline residue. It was recrystallized from ether to give 8 mg. of analytically pure oxide (VIII), m.p. 176–178°.

Anal. Calcd. for $C_{23}H_{32}O_6$: C, 68.29, H, 7.97. Found: C, 68.00; H, 8.32. λ_{max}^{Nujol} 3.0–3.3, 6.0 (weak), 8.9–9.4 μ.

B. *Sodium borohydride on* VII. To 25 mg. of chlorohydrin (VII) in 1.0 ml. of 95% ethanol was added 25 mg. of sodium borohydride. The mixture was heated under reflux for 1.5 hr. Work-up was the same as above except for the use of ethyl acetate in the extraction. The residual 29 mg. was recrystallized from ether and methanol to give VIII, m.p. 176–178°, undepressed when mixed with the sample above.

C. *Sodium borohydride on* VI. To 200 mg. of bismethylenedioxy-9α-chlorohydrocortisone (VI) in 10 ml. of 95% ethanol and 10 ml. of methylene chloride was added 200 mg. of sodium borohydride. The methylene chloride was distilled and the ethanol solution stirred under reflux for 20 hr. Using a work-up as in A above, 162 mg. of crude product was obtained. This was recrystallized to give 86 mg. of VIII, m.p. 165–175°. Further recrystallization from methanol and ether–methylene chloride gave a pure sample, m.p. and mixed m.p. with the analytical sample above, 175–178°.

9α-Bromo-17α,20;20,21-Bismethylenedioxy-4-pregnene-11β-ol-3-one (X). Seventy-six grams of 9,11β-oxido-4-pregnene-17α,21-diol-3,20-dione (V)[13] was suspended in 3 l. of chloroform. A mixture of 600 ml. of 36% formaldehyde and and 600 ml. of 42% hydrobromic acid was then added. The reaction mixture was stirred at room temperature for 76 hr. After 4.5 hr. 300 ml. of methylene chloride was added to effect complete solution of the suspension. The layers were separated and the chloroform layer was washed with water and saturated sodium bicarbonate solution, dried over magnesium sulfate and evaporated *in vacuo*. Trituration of the resulting oil with methanol, filtration and methanol washing gave 22 g. of 9α-bromo-17α,20;20,21-bismethylenedioxy-4-pregnene-11β-ol-3-one, m.p. 170–190°C.

Anal. Calcd. for $C_{23}H_{31}O_6Br$: C, 57.14; H, 6.46. Found: C, 57.35; H, 6.34. λ_{max} 243 mμ, ε 15,500.

9α-Bromo-17α,20;20,21-bismethylenedioxy-4-pregnene-3,11-dione (XI). Sixteen grams of 9α-bromo-17α,20;20,21-bismethylenedioxy-4-pregnene-11β-ol-3-one (X) was dissolved in 160 ml. of glacial acetic acid. To this was added a solution of 16 g. of chromium trioxide in 5 ml. of water and 160 ml. of glacial acetic acid. The reaction mixture was stirred at room temperature for 1.25 hr. After the addition of 3 ml. of methanol, the reaction mixture was cooled and 700 ml. of cold 40% aqueous potassium hydroxide was added slowly with stirring. It was extracted with ethyl acetate three times, washed with a saturated solution of sodium bicarbonate, dried, and evaporated *in vacuo*. The resulting 9.5 g. of crystalline 9α-bromo-17α,20;20,21-bismethylenedioxy-4-pregnene-3,11-dione (XI) was collected, m.p. 175–205° dec.

Anal. Calcd. for $C_{23}H_{29}O_6Br$: C, 57.38; H, 6.07. Found: C, 57.48; H, 5.97. λ_{max}^{Nujol} 5.65, 5.90, 6.1, 9.0 μ.

9α-Bromo-3-ethylenedioxy-17α,20;20,21-bismethylenedioxy-5-pregnene-11-one (XII). One gram of 9α-bromo-17α,20;20,21-bismethylenedioxy-4-pregnene-3,11-dione (XI) was suspended in 150 ml. of benzene to which 10 ml. of ethylene glycol and 100 mg. of *p*-toluenesulfonic acid was added. The reaction mixture was refluxed with a water separator for 5 hr. It was cooled and a saturated solution of sodium bicarbonate was added. It was then separated and extracted further with ether, dried, and evaporated *in vacuo*. Chromatography of the resulting 950 mg. of oil on 20 g. of acid-washed alumina yielded 320 mg. of 9α-bromo-3-ethylenedioxy-17α,20;20,21-bismethylenedioxy-5-pregnene-11-one (XII) upon elution with petroleum ether–ether (2:3), m.p. 190, 215–220° dec.

Anal. Calcd. for $C_{25}H_{33}O_7Br$: C, 57.14; H, 6.33. Found: C, 57.48; H, 6.04. λ_{max}^{Nujol} 5.85, 9.0 μ.

9α-Methyl-3-ethylenedioxy-17α,20;20,21-bismethylenedioxy-pregenene-11-one (XIII). One hundred milligrams of magnesium was suspended in 20 ml. of sodium dried ether. Methyl iodide was added to the stirred suspension until all the magnesium was consumed in the formation of the Grignard complex. An excess of 5 ml. of methyl iodide was then added. To this Grignard reagent was added 15 ml. of tetrahydrofuran (freshly distilled from lithium–aluminum hydride) containing 100 mg. of 9α-bromo-3-ethylenedioxy-17α,20;20,21-bismethylenedioxy-5-pregnene-11-one. The reaction was stirred for 15 min. at room temperature and was then heated under reflux for 1 hr. It was cooled, decomposed carefully with water, extracted well with ethyl acetate, dried over magnesium sulfate and evaporated *in vacuo*. The resulting 100 mg. of oil gave a negative Beilstein test. It was chromatographed on 4 g. of acid-washed alumina and elution with petroleum ether–ether (1:1) gave crystals which were combined and recrystallized from methylene chloride–ether to yield 30 mg. of analytically pure 9α-methyl-3-ethylenedioxy - 17α,20;20,21 - bismethylenedioxy - 5-pregnene-11-one, m.p. 222–228°.

Anal. Calcd. for $C_{26}H_{36}O_7$: C, 67.80; H, 7.88. Found: C, 67.85; H, 7.51, $[\alpha]_D^{23} = -85.9 \pm 2°$ (c = 1,$CHCl_3$). NMR analysis indicates three C-methyl groups. λ_{max}^{Nujol} 5.87, 9.0–9.2 μ.

Further elution of the column with petroleum ether–ether (1:4) gave crystals which melted at 195–200° and whose infrared spectrum was identical with 3-ethylenedioxy-17,20:20,21-bismethylenedioxy-5-pregnene-11-one (cortisone BMD-3-dioxolane).

9α-Methyl-3-ethylenedioxy-17α,20;20,21-bismethylenedioxy-5-pregnene-11β-ol (XIV). Sixty milligrams of 9α-methyl-3-ethylenedioxy - 17α,20;20,21 - bismethylenedioxy - 5-pregnene-11-one (XIII) was dissolved in 20 ml. of tetrahydrofuran. To this solution was added 25 mg. of lithium aluminum hydride. The reaction mixture was stirred for 1 hr. at room temperature and then heated under reflux for 2 hr. It was decomposed by adding ethyl acetate, then water to the reaction mixture and then concentrated to a small volume *in vacuo*. The remaining aqueous solution was extracted with ethyl acetate and the ethyl acetate dried and evaporated *in vacuo*. Chromatography of the residual, 50 mg. of oil, on 4.2 g. of acid-washed alumina gave 24 mg. of 9α-methyl-3-ethylenedioxy-17α,20;20,21-bismethylenedioxy-5-pregnene-11β-ol (XIV) m.p. 230–233°.

Anal. Calcd. for $C_{26}H_{38}O_7$: C, 67.51; H, 8.28. Found: C, 67.61; H, 7.94. λ_{max}^{Nujol} 2.65, 9.0–9.1 μ.

9α-Methyl-17α,20;20,21-bismethylenedioxy-4-pregnene-3-one-11β-ol (XV). Forty-four milligrams of 9α-methyl-3-ethylenedioxy - 17α,20;20,21 - bismethylenedioxy - 5 - pregnene-11β-ol (XIV) was dissolved in 2 ml. of acetone and 10 mg. of *p*-toluenesulfonic acid added to the solution. It was allowed to stand at room temperature for 2 days. The acetone was then distilled and 3 ml. of a saturated solution of sodium bicarbonate was added. It was extracted with ethyl acetate, dried and evaporated *in vacuo*. Upon trituration of the resulting oil with methanol–methylene chloride, 38 mg. of 9α-methyl-17α,20;20,21-bismethylenedioxy-4-pregnene-3-one-11β-ol (XV) was obtained, m.p. 295–305°.

Anal. Calcd. for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found: C, 68.40; H, 8.15. $\lambda_{max}^{CH_3OH}$ 244 mμ, ε 14,800. λ_{max}^{Nujol} 2.7, 5.99, 6.15, 9.0 μ.

9α-Methylhydrocortisone (XVIa). Thirty-four milligrams of 9α-methyl-17,20;20,21-bismethylenedioxy-4-pregnene-11β-ol-3-one was suspended in 2 ml. of 50% acetic acid and treated at 100° for 2.5 hr. It was then evaporated *in vacuo* and extracted with ethyl acetate and with methylene chloride, washed with a saturated sodium bicarbonate solution, dried and evaporated. Trituration of the resulting oil with methanol–methylene chloride gave 26 mg. of 9α-methylhydrocortisone (XVIa), m.p. 220–230°.

Anal. Calcd. for $C_{22}H_{32}O_5$: C, 70.18; H, 8.57. Found: C, 70.42; H, 8.73. λ_{max} 244 mμ ε 14,300. λ_{max}^{Nujol} 2.8, 5.80, 6.0, 6.15, 7.2 μ.

9α-Methyl-4-pregnene-3,20-dione-11β,17α,21-triol-21-acetate (XVIb). Two hundred twenty-four milligrams of 9α-methyl-4-pregnene-3,20-dione-11β,17α,21-triol was combined with 1 ml. of pyridine and 1 ml. of acetic anhydride and allowed to stand at room temperature for 18 hr. It was then diluted with water, extracted with methylene chloride and the organic phase washed with 2.5*N* hydrochloric acid, a saturated solution of sodium bicarbonate, dried and evaporated to dryness *in vacuo*. Trituration with acetone afforded crystals which upon recrystallization from acetone-ether yielded 136 mg. of analytically pure 9α-methyl-4-pregnene-3,20-dione-11β,17α,21-triol-21-acetate, m.p. 235–238.

Anal. Calcd. for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found: C, 69.16; H, 8.15. λ_{max} 243 mμ, ε 16,500. $\lambda_{max}^{CHCl_3}$ 2.9, 5.75, shoulder 5.80, 6.04, 6.26, 8.2 μ.

9α-Methylprednisolone acetate (XVII). Fifty milligrams of 9α-methylhydrocortisone acetate (XVIb) was dissolved in 2.2 ml. of *t*-butyl alcohol. To this solution was added 0.04 ml. of glacial acetic acid, 30 mg. of selenium dioxide, 50 mg. of mercury and 50 mg. of mercuric oxide. This reaction mixture was refluxed with stirring for 3.5 hr. After cooling, the mixture was filtered through Supercel and washed with additional *t*-butyl alcohol. The *t*-butyl alcohol was then concentrated to dryness and the residue dissolved in ethyl acetate. The organic phase was washed with a saturated solution of sodium thiosulfate until no more color was removed and with a 10% sodium bicarbonate solution. After drying over magnesium sulfate and concentrating *in vacuo*, the resulting 40 mg. of oil was chromatographed on acid-washed alumina. Elution of the column with ether-chloroform (1:4) and chloroform yielded 9α-methylprednisolone acetate (XVII), m.p. 228–230°.

Anal. Calcd. for $C_{24}H_{32}O_6$: C, 69.21; H, 7.74. Found: C, 69.02; H, 7.91. λ_{max}^{Nujol} 2.8, 5.70, 5.79, 6.01, 6.18, 6.25, 8.05 μ. λ_{max} 244 mμ, ε 14,000.

Acknowledgment. The authors are indebted to Dr. N. R. Trenner and Mr. B. H. Arison for the nuclear magnetic resonance data reported, to Mr. James Wittick and associates for ultraviolet spectra and Mr. R. N. Boos and associates for microanalytical data.

RAHWAY, N. J.

[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

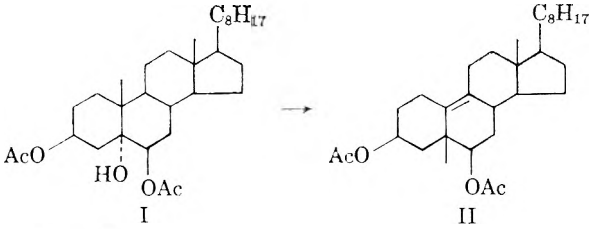
Rearranged Steroid Systems. I. Studies in the Pregnane Series[1,2]

O. R. RODIG, P. BROWN,[3] AND P. ZAFFARONI[4]

Received November 21, 1960

Pregnenolone and prenenolone methyl ether have been converted to 19-nor-5-methyl steroids by the Westphalen rearrangement. An attempt to carry pregnenolone ethylene ketal through a similar series of reactions was unsuccessful. An isomeric substance, obtained in the preparation of pregnenolone methyl ether, was identified as the 17α-epimer.

In 1915, Westphalen[5] obtained a dehydration product from cholestane-3β,5α,6β-triol diacetate (I) by treating this compound with acetic anhydride and sulfuric acid. The product was shown by later workers[6] to have structure II, the C-10 methyl group having migrated to the C-5 position. Spectrographic[7] and chemical[8] evidence are in accord with assigning the 9,10 position to the double bond, while the probable *beta* orientation of the C-5 methyl group is supported by optical rotatory dispersion measurements.[9]



This C-10 to C-5 methyl shift, commonly referred to as the Westphalen rearrangement, has been investigated mainly in the cholestane series[10] and to a lesser extent with androgen derivatives.[11] The current interest in 19-nor steroids as progestational, antiestrogen and cancer agents led us to extend this rearrangement to some

(1) Presented in part at the Southeastern Regional Meeting of the American Chemical Society in Birmingham, Ala., November 1960.

(2) Supported by Grant CY-3377 of the National Cancer Institute, U. S. Public Health Service.

(3) Postdoctoral Research Associate, 1957–58.

(4) Postdoctoral Research Associate, 1959–60.

(5) T. Westphalen, *Ber.*, **48**, 1064 (1915).

(6) H. Lettré and M. Müller, *Ber.*, **70**, 1947 (1937); V. A. Petrow, O. Rosenheim, and W. W. Starling, *J. Chem. Soc.*, 677 (1938); V. Petrow, *J. Chem. Soc.*, 998 (1939).

(7) P. Bladen, H. B. Henbest, and G. W. Wood, *J. Chem. Soc.*, 2737 (1952).

(8) B. Ellis and V. Petrow, *J. Chem. Soc.*, 2246 (1952).

(9) H. Aebli, C. A. Grob, and E. Schumacher, *Helv. Chim. Acta*, **41**, 774 (1958).

(10) For additional references, see M. Davis and V. Petrow, *J. Chem. Soc.*, 2211 (1951); Y. F. Shealy and R. M. Dodson, *J. Org. Chem.*, **16**, 1427 (1951); C. A. Grob and E. Schumacher, *Helv. Chim. Acta*, **41**, 924 (1958).

(11) (a) M. Davis and V. Petrow, *J. Chem. Soc.*, 2973 (1949); (b) 1185 (1950).

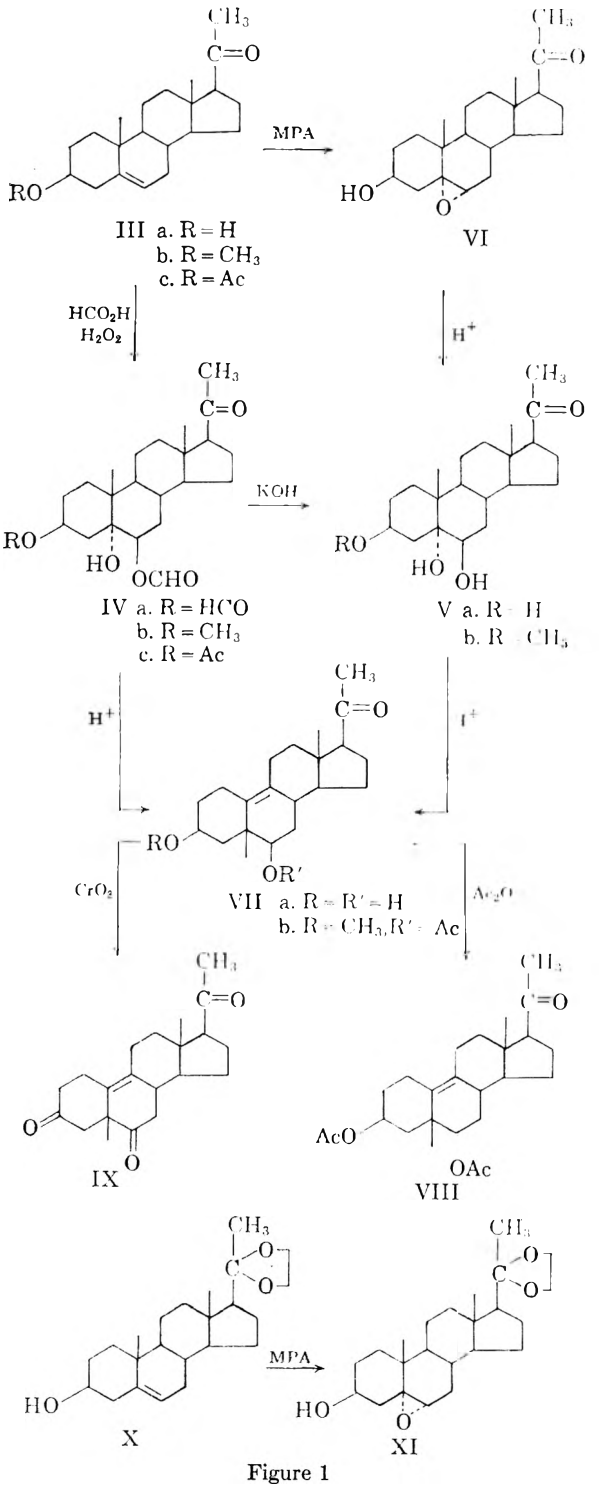


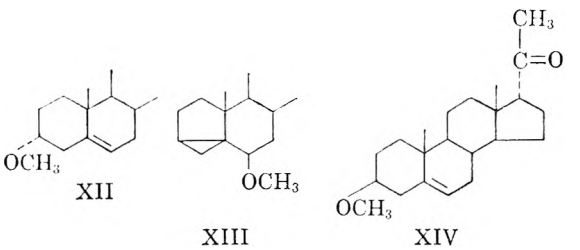
Figure 1

20-ketopregnanes, and the transformations reported in the present paper are shown in Fig. 1.

When pregnenolone (IIIa) was treated with hydrogen peroxide and formic acid, the 5α-hydroxy-3β,6β-diformate IVa was obtained. This diester was readily hydrolyzed in base to yield the known 3β,5α,6β-triol Va. A similar series of reactions on pregnenolone acetate (IIIc) gave the same triol (Va) *via* the 3β-acetoxy-5α-hydroxy-6β-formate IVc. The triol was prepared by still another method, albeit in poorer yield, by the acid hydrolysis of pregnenolone α-epoxide (VI).

When the triol Va was treated with acetic anhydride containing a trace of sulfuric acid a product was obtained which yielded a small amount of diol VIIa on hydrolysis. The latter compound gave a positive Tortelli-Jaffé Test, a negative color reaction with trichloroacetic acid and exhibited a strongly dextrorotatory optical rotation, properties characteristic of 19-nor-5-methyl steroids.[6,8,10] A much higher yield of the diol VIIa (43%) could be obtained by carrying out the rearrangement directly on the diformate IVa. In general, the rearrangements were accompanied by the formation of minor amounts of other products, as well as tarry material. Decomposition could be kept to a minimum by carrying out the reaction at 0°. However, even at this temperature by-products were formed. Usually these were not further identified because they were obtained in low yield and have been investigated to some extent in another series.[9] The diol VIIa was readily acetylated to yield the diacetate VIII and underwent oxidation with chromic acid, giving the triketone IX.

The rearrangement was also found to occur quite readily with 3-methoxy derivatives. When pregnenolone methyl ether (IIIb) was prepared from the tosylate by a modification of the method described by Butenandt and Grosse,[12] a second product was isolated which showed a high negative optical rotation and which was isomeric with IIIb. The infrared spectra of the two compounds were very similar, suggesting only a minor structural difference. A high negative optical rotation was inconsistent with the 3α-methoxy structure XII[13] and a direct comparison with an authentic sample of 6β-methoxy-i-pregnan-20-one[12] (XIII) showed the two substances to be different. The compound was identified as the 17α-epimer XIV from its optical



rotatory dispersion curve which exhibits a negative Cotton effect[14] (Fig. 2).

The pregnenolone methyl ether (IIIb) was converted to the diol Vb through the 5α-hydroxy-6β-formoxy derivative IVb. Rearrangement of the diol was effected with acetic anhydride–sulfuric

(12) A. Butenandt and W. Grosse, *Ber.*, 70, 1446 (1937).
(13) W. Klyne, *The Chemistry of the Steroids*, John Wiley & Sons, Inc., New York, 1957, pp. 53 ff.
(14) C. Djerassi, *Optical Rotatory Dispersion*, McGraw-Hill Book Co., Inc., New York, 1960, p. 51.

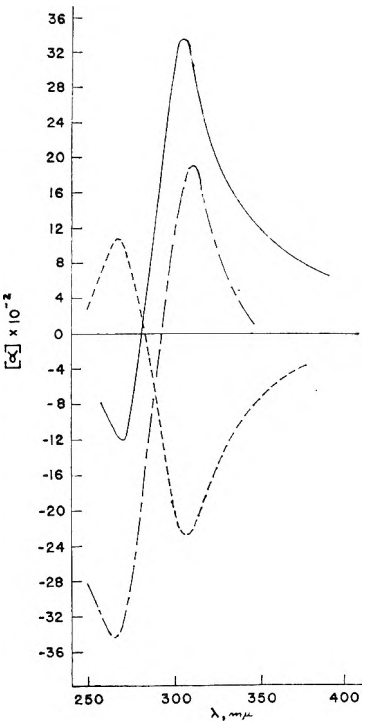


Fig. 2. Rotatory dispersion curves: (———) 3β,6β-dihydroxy-5β-methyl-19-nor-9-pregnen-20-one (VIIa); (— - —) 17β-pregnenolone methyl ether (IIIb); (- - - -) 17α-pregnenolone methyl ether (XIV)

acid, yielding the rearranged product as the 6β-acetate VIIb.

In an attempt to diminish interference from the 20-keto group, the ketal X[15] was converted to the 5,6-epoxide XI[16] with monoperphthalic acid. However, attempts to open the epoxide ring under basic conditions were unsuccessful. The epoxide VI was likewise recovered unchanged under basic hydrolysis conditions. *Beta* hydroxyl attack is undoubtedly hindered by steric interference of the C-10 methyl group.

EXPERIMENTAL[17]

3β,6β-Diformoxy-5α-hydroxypregnan-20-one (IVa). A solution of 10.0 g. of pregnenolone (IIIa) in 100 ml. of 98% formic acid was cooled in ice and 10 ml. of 30% hydrogen peroxide was added dropwise with stirring. Forty-five minutes after the beginning of the addition a crystalline product separated. The mixture was stirred for an additional 3 hr. 15 min. with occasional chilling in ice. Sixty milliliters of water was then added and the solid collected by filtration. The yield of *3β,6β-diformoxy-5α-hydroxypregnan-20-one* was 8.16 g. (64%), m.p. 227–230°. For analysis, the compound was recrystallized from acetone, m.p. 229–230°, $[\alpha]_D$ −9.0° (c = 1.04).

Anal. Calcd. for $C_{23}H_{34}O_6$: C, 67.95; H, 8.43. Found: C, 67.98; H, 8.38.

When 90% formic acid[18] was used, the yield was 59%.

3β-Acetoxy-5α-hydroxy-6β-formoxypregnan-20-one (IVc). Ten milliliters of 30% hydrogen peroxide was added to a stirred solution of 10.5 g. of pregnenolone acetate[19] in 60 ml. of carbon tetrachloride and 80 ml. of 98% formic acid. The mixture was heated at 40–45° for 1 hr. and then at 50–55° for 6.5 hr. It was then poured into a saturated solution of aqueous sodium chloride and extracted with ether. The extracts were washed with a saturated solution of sodium bicarbonate, dried (sodium sulfate), and the solvent removed. The remaining white solid was recrystallized from aqueous ethanol, yielding 7.2 g. (59%) of 3β-acetoxy-5α-hydroxy-6β-formoxypregnan-20-one (IVc), m.p. 218–220°, $[\alpha]_D$ −9.6° (c = 0.99) [lit.,[20] m.p. 215–217°, $[\alpha]_D$ ± 0° (chloroform)].

Anal. Calcd. for $C_{24}H_{36}O_6$: C, 68.54; H, 8.63. Found: C, 68.58; H, 8.45.

Pregnenolone α-epoxide (VI). A solution of 4.50 g. of monoperphthalic acid in 50 ml. of ether was added to a solution of 10.0 g. of pregnenolone (IIIa) in 50 ml. of chloroform and 25 ml. of ether, and the mixture let stand for 22 hr. in a refrigerator (0°). The solid (phthalic acid) which had separated was filtered off, and the filtrate washed thoroughly with 5% aqueous sodium carbonate, water, ferrous sulfate solution, and again with water. The organic phase was dried over sodium sulfate and the solvent removed. The remaining crude product was triturated with 10 ml. of acetone and filtered, yielding 8.70 g. of crystalline solid, m.p. 170–178°. Recrystallization from methanol gave 6.73 g. (64%) of pregnenolone α-epoxide, m.p. 180–182°. Recrystallization from ethyl acetate and then acetone raised the melting point to 185–187°. $[\alpha]_D^{30}$ + 6.8° (c = 1.05) [lit., m.p. 185–187°[21]; 188–190°, $[\alpha]_D$ + 17° (chloroform)[22]].

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.76; H, 9.48.

The infrared spectrum showed a doublet in the carbonyl region at 1712 and 1699 cm.$^{-1}$

3β,5α,6β-Trihydroxypregnan-20-one (Va.) (a) *From hydrolysis of 3β-acetoxy-5α-hydroxy-6β-formoxypregnan-20-one* (IVc). A solution of 0.5 g. of the diester, 0.5 g. of potassium hydroxide, and 10 ml. of methanol was refluxed for 6 hr. The reaction mixture was poured into water, extracted with chloroform, and the organic phase dried over sodium sulfate. Removal of the solvent left a solid residue which was recrystallized from acetone, yielding 0.18 g. (43%) of 3β,5α,-6β-trihydroxypregnan-20-one (Va), m.p. 256–258° (lit., m.p. 256–258°,[18] 252–255°[18]).

Anal. Calcd. for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 71.70; H, 9.46.

(b) *From hydrolysis of 3β,6β-diformoxy-5α-hydroxypregnan-20-one* (IVa). Employing the same conditions described above for the 3β-formoxy-6β-acetoxy compound, the hydrolysis of 0.16 g. of the 3β,6β-diformate IVa yielded 0.045 g. (33%) of the triol Va, m.p. 252–253°, unchanged on admixture with a sample of the triol prepared above.

(15) P. Ziegler and K. R. Bharucha, *Chem. and Ind. (London)*, 1955, 1351.

(16) The epoxide ring is assigned the *alpha* configuration from analogy with similar epoxidations and from its optical rotation which lacks the dextrorotatory shift characteristic of *beta* epoxidation. *Cf.* Fieser and Fieser, *Steroids*, Reinhold Publishing Corporation, New York, 1959, pp. 193 ff.

(17) All melting points are uncorrected. All rotations were determined in chloroform at room temperature unless otherwise stated. Infrared spectra were determined on a Perkin-Elmer model 21 spectrophotometer and ultraviolet spectra on a Perkin-Elmer model 4000A Spectracord. A Rudolph Photoelectric Spectropolarimeter was used for the optical rotatory dispersion measurements. Microanalyses were carried out by Mrs. M. Logan and Mrs. D. Ellis.

(18) O. Mancera, G. Rosenkranz, and C. Djerassi, *J. Org. Chem.*, 16, 192 (1951).

(19) M. Ehrenstein, *J. Org. Chem.*, 4, 506 (1939).

(20) A. Bowers, E. Denot, R. Urquiza, and L. M. Sanchez-Hidalgo, *Tetrahedron*, 8, 116 (1960).

(21) Y. Urusibara, M. Chuman, and S. Wada, *Bull. Chem. Soc. Japan*, 24, 83 (1951).

(22) A. Bowers, E. Donet, M. B. Sanchez-Hidalgo, and H. R. Ringold, *J. Am. Chem. Soc.*, 81, 5233 (1959).

(c) *From acid hydrolysis of pregnenolone α-epoxide* (VI). A solution of 5.00 g. of the epoxide in 70 ml. of methanol and 50 ml. of 2*N* sulfuric acid was refluxed for 3 hr. The methanol was partly removed by distillation, chloroform was added, and the layers were separated. The organic phase was washed with 5% aqueous sodium carbonate and water, and dried over sodium sulfate. Removal of the solvent left an oil which crystallized when treated with ether, yielding 1.25 g. (24%) of 3β,5α,6β-trihydroxypregnan-20-one (Va), m.p. 200–212°. Recrystallization from ethanol raised the melting point to 245–252°. The infrared spectrum was identical with those of the products obtained in (a) and (b) above. Evaporation of the ether filtrate left a yellow oil which yielded small amounts of two additional solids after chromatography, m.p.'s 150–160 and 142–146°. These were not further characterized.

Basic hydrolysis of pregnenolone α-epoxide proved unsuccessful. Thus, when 0.50 g. of the epoxide in 6 ml. of 5% methanolic potassium hydroxide was refluxed for 2 hr. on a steam bath, 0.45 g. of starting material was the only identifiable substance recovered.

3β,6β-Dihydroxy-5β-methyl-19-nor-9-pregnen-20-one (VIIa). (a) *From 3β,6β-diformoxy-5α-hydroxypregnan-20-one* (IVa). A stirred suspension of 8.00 g. of the diformate IVa in 80 ml. of acetic anhydride was cooled in an ice bath and a solution of 6 drops of concd. sulfuric acid in 5 ml. of acetic anhydride added. After 45 min., the mixture had turned brown and the solid had partly dissolved. Two drops of sulfuric acid was added and the temperature was allowed to rise to 16°. After 30 min., the solid had completely dissolved. The dark brown solution was taken up in benzene–ethyl acetate, washed with dilute aqueous sodium bicarbonate, and then water. Removal of the solvent from the dried (sodium sulfate) organic phase left an oil, which was refluxed with 60 ml. of 5% methanolic potassium hydroxide for 1 hr. on a steam bath. After removal of the methanol, the residue was dissolved in ethyl acetate and washed thoroughly with water. The organic layer was dried over sodium sulfate and the solvent removed, leaving an oil which was treated twice with a hot mixture of toluene–petroleum ether (1:1). The remaining semicrystalline solid was crystallized from ethyl acetate, yielding 2.78 g. (43%) of *3β,6β-dihydroxy-5β-methyl-19-nor-9-pregnen-20-one* (VIIa), m.p. 152–155°. For analysis, a sample was recrystallized from ethyl acetate, m.p. 158–159°, $[\alpha]_D$ + 218° (*c* = 1.0), Tortelli-Jaffé test (+), Trichloroacetic acid test (−), not precipitated with digitonin. RD in methanol (*c* = 0.011), 24°; $[\alpha]_{589}$ +253°, $[\alpha]_{305}$ +3371°, $[\alpha]_{270}$ −1213°, $[\alpha]_{260}$ −812° (l = 1 dm.) (Fig. 2).

Anal. Calcd. for $C_{21}H_{32}O_4$: C, 75.86; H, 9.70. Found: C, 75.67; H, 9.67.

Chromatography of the mother liquors on alumina yielded additional product (VIIa), 0.76 g., m.p. 160–161° eluted with ethyl acetate and 0.31 g., m.p. 140–145° eluted with ethyl acetate–methanol. Further elution with ethyl acetate–methanol yielded a different solid, 0.05 g., m.p. 179–180°, $[\alpha]_D$ + 62.7°, Tortelli-Jaffé test delayed and faint (+), which was not further characterized.

Anal. Calcd. for $C_{21}H_{32}O_4$: C, 75.86; H, 9.70. Found: C, 75.30; H, 9.61.

(b) *From 3β,5α,6β-trihydroxypregnan-20-one* (Va). To a hot suspension (steam bath) of 1.0 g. of triol (Va) in 10 ml. of acetic anhydride was added 0.2 g. of potassium hydrogen sulfate. The organic material dissolved readily, accompanied by the development of a slight brown color. After 10 min. the solution was chilled in ice and a solution of 2 drops of sulfuric acid in several milliliters of acetic anhydride slowly added. Several seconds of heating on a steam bath turned the solution dark brown. It was quickly cooled in ice and the acetic anhydride was removed by vacuum distillation. The oily residue was dissolved in ethyl acetate, washed successively with 5% sodium carbonate solution and water, and dried over sodium sulfate. Removal of the solvent left an oil which was refluxed for 1 hr. with 20 ml. of a 5% solution of potassium hydroxide in aqueous methanol and let stand at room temperature overnight. After removal of the methanol, the product was taken up in an ether–ethyl acetate mixture and washed thoroughly with water. Removal of the solvent left a glass which crystallized when treated with ethyl acetate to give 0.12 g. (13%) of *3β,6β-dihydroxy-5β-methyl-19-nor-9-pregnen-20-one* (VIIa), m.p. 156–157.5°. The infrared spectrum was identical with that of the product (VIIa) obtained in part (a).

No attempt was made to develop conditions for optimum yields in this reaction because it was found that rearrangement of the diformate IVa provided a better route to VIIa [see (a) above].

3β,6β-Diacetoxy-5β-methyl-19-nor-9-pregnen-20-one (VIII). A solution of 0.5 g. of the diol VIIa in 8 ml. of pyridine and 4 ml. of acetic anhydride was allowed to stand at room temperature for 3 days. The addition of 50 ml. of water produced an oil which was separated from the supernatant liquid by decantation. After drying over potassium hydroxide in a vacuum desiccator, the oil crystallized from methanol. Recrystallization from this solvent yielded 0.13 g. (21%) of 3β,6β-diacetoxy-5β-methyl-19-nor-9-pregnen-20-one (VIII) as colorless plates, m.p. 129.5–130.5° (micro hot stage), $[\alpha]_D$ + 152.7° (*c* = 1.02), Tortelli-Jaffé test (+), Trichloroacetic acid test (−). Davis and Petrow[11a] reported m.p. 120° and Tortelli-Jaffé test (−).

Anal. Calcd. for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71. Found: C, 72.11; H, 8.50.

An additional 0.24 g. (39%), m.p. 123–125°, was obtained as a second crop. The semicarbazone was recrystallized from methanol, m.p. 212.5–215° dec. (lit.,[11a] m.p. 213–219°).

Anal. Calcd. for $C_{26}H_{39}O_5N_3$: C, 65.93; H, 8.30; N, 8.87. Found: C, 65.93; H, 7.99; N, 9.20.

Pregnenolone tosylate. Sixty grams of *p*-toluenesulfonyl chloride was added to a solution of 30.0 g. of pregnenolone (IIIa) in 180 ml. of warm pyridine. The mixture was warmed *gently* until the solid dissolved, and allowed to stand overnight at room temperature. The mixture, containing some crystalline material, was poured into water, and the oil which separated soon solidified. After cooling in an ice bath the mixture was filtered, and the colorless solid obtained was recrystallized from acetone, yielding 39.0 g. (88%) of pregnenolone tosylate, m.p. 137.5–138° (lit.,[12] m.p. 139–140°).

Pregnenolone methyl ether (IIIb) and 17α-pregnenolone methyl ether (XIV).[23] A solution of 10.0 g. of pregnenolone *p*-toluenesulfonate in 80 ml. of absolute methanol was refluxed for 4 hr. The pregnenolone methyl ether, which crystallized on cooling, was filtered off. When water was added to the mother liquor, a crude solid was obtained which yielded additional methyl ether IIIb when recrystallized from petroleum ether (b.p. 30–60°). Recrystallization of the combined crops from aqueous methanol gave 6.07 g. (87%) of pregnenolone methyl ether, m.p. 124–125° (lit.,[12] m.p. 123–124°). RD in methanol (*c* = 0.05), 24°, $[\alpha]_{345}$ +160°, $[\alpha]_{311}$ +1920° $[\alpha]_{265}$ −3440°, $[\alpha]_{250}$ −2920° (l = 0.1 dm.) (Fig. 2).

The solvent was removed from the petroleum ether mother liquor, and the solid residue was recrystallized from absolute methanol, yielding 0.80 g. (11%) of *17α-pregnenolone methyl ether* (XIV), m.p. 131–132°, $[\alpha]_D^{26}$ −154° (*c* = 1.4). RD in methanol (*c* = 0.06), 24°, $[\alpha]_{350}$ −900°, $[\alpha]_{305}$ −2250°, $[\alpha]_{269}$ + 1083°, $[\alpha]_{250}$ + 267° (l = 0.1 dm.) (Fig. 2).

Anal. Calcd. for $C_{22}H_{34}O_2$: C, 79.89; H, 10.37. Found: C, 79.62; H, 10.11.

Because of the large difference in the optical rotations of IIIb and XIV, equilibration of these two isomers was easily followed by observing the rotation change with a polarimeter. Thus, when a solution of 1.0 g. of XIV and 0.5 g. of *p*-toluenesulfonic acid in 9.7 ml. of methanol was kept at 50°, equilibrium was attained in 2.25 hr. The equilibrated mixture contained approximately 15% of XIV and 85% of IIIb, as de-

(23) This experiment was performed by D. Savage.

termined from the optical rotation values of the mixture and of the pure isomers.

3β-Methoxy-5α-hydroxy-6β-formoxypregnan-20-one (IVb). Three milliliters of 30% hydrogen peroxide was slowly added at room temperature to a stirred mixture of 2.50 g. of pregnenolone methyl ether (IIIb) in 15 ml. of carbon tetrachloride and 20 ml. of 98% formic acid. After maintaining the temperature at 40–45° for 1 hr. and then at 50–55° for 6 hr., the mixture was cooled and poured into saturated sodium chloride solution. The water solution was extracted with ether, and the organic phase washed with dilute aqueous sodium bicarbonate until the washings were basic. The solvent was removed from the dried (sodium sulfate) organic layer and the remaining oil crystallized from acetone petroleum ether (b.p. 30–60°), giving 2.40 g. (80%) of *3β-methoxy-5α-hydroxy-6β-formoxypregnan-20-one* (IVb), m.p. 180–182°, $[\alpha]_D$ + 5° (*c* = 7.0).

Anal. Calcd. for $C_{23}H_{36}O_5$: C, 70.37; H, 9.24. Found: C, 70.37; H, 9.19.

3β-Methoxy-5α,6β-dihydroxypregnan-20-one (Vb). To a stirred solution of 7.90 g. of pregnenolone methyl ether (IIIb) in 48 ml. of carbon tetrachloride and 64 ml. of 98% formic acid were added 9.6 ml. of 30% hydrogen peroxide. The reaction was run and worked up in the manner described above, except that the oil which was obtained was refluxed for 4 hr. with a solution of 9.0 g. of potassium hydroxide in 200 ml. of methanol. The reaction mixture was poured into water and extracted with chloroform. The organic phase was dried over sodium sulfate, the solvent removed, and the residue recrystallized from aqueous acetone. The *3β-methoxy-5α,6β-dihydroxypregnan-20-one* (Vb) was obtained as colorless crystals, 5.50 g. (63%), m.p. 191–193°, $[\alpha]_D$ +39.3° (*c* = 0.98).

An analytical sample, prepared from another run, had m.p. 192–194°.

Anal. Calcd. for $C_{22}H_{36}O_4$: C, 72.49; H, 9.96. Found: C, 72.52; H, 10.10.

3β-Methoxy-5β-methyl-6β-acetoxy-19-nor-9-pregnen-20-one (VIIb). A stirred solution of 500 mg. of the diol Vb in 9 ml. of acetic anhydride (warmed to dissolve) was cooled in an ice bath and 0.9 ml. of a solution of 1 drop of concd. sulfuric acid in 1.0 ml. of acetic anhydride was added. After 1.25 hr., the dark mixture was diluted with benzene and washed with 10% aqueous sodium carbonate and with water. The organic phase was dried (Drierite-magnesium sulfate) and the solvent removed, leaving 450 mg. of a brown oil, which was chromatographed on 12 g. of alumina. Elution with benzene–petroleum ether yielded 70 mg. of an oil which solidified on standing. Recrystallization from methanol gave 50 mg. of colorless solid, m.p. 127.5–128°, Tortelli-Jaffé test (−), trichloroacetic acid test (yellow-pink). This substance was not further identified.

The desired product was obtained on elution with benzene as 110 mg. (21%) of pale yellow needles, m.p. 128–132°, Tortelli-Jaffé test (+). Recrystallization from acetone-water and finally pure acetone gave 74 mg. of *3β-methoxy-5β-methyl-6β-acetoxy-19-nor-9-pregnen-20-one* (VIIb), m.p. 138–139°, $[\alpha]_D$ +155° (*c* = 0.99), Trichloroacetic acid test (−).

Anal. Calcd. for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 73.76; H, 9.26.

5β-Methyl-19-nor-9-pregnene-3,6,20-trione (IX). A solution of 61 ml. of 2% chromic acid in glacial acetic acid was added dropwise over a 1-hr. period to a stirred solution of 1.90 g. of diol VIIa in 50 ml. of glacial acetic acid. The mixture was allowed to stir for 22 hr. at room temperature, and the acetic acid then removed by distillation. The remaining oil was taken up in ethyl acetate, washed with water, and dried (sodium sulfate). Removal of the solvent left an oil which crystallized from methanol, giving 0.68 g. (36%) of *5β-methyl 19-nor-9-pregnene-3,6,20-trione* (IX), m.p. 163–167°. Recrystallization from ethanol-water and finally pure ethanol provided an analytical sample, m.p. 167–169° $[\alpha]_D^{28}$ +7.8 (*c*, = 1.09), Tortelli-Jaffé test (+), $\lambda_{max}^{CH_3OH}$ 292 mμ (ε = 167).

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.49; H, 8.52.

Pregnenolone ethylene ketal (X). A vigorously stirred mixture (two layers) of 3.00 g. of pregnenolone (IIIa), 25 ml. of ethylene glycol, 50 ml. of toluene, and 0.03 g. of *p*-toluenesulfonic acid was refluxed for 5 hr. the water formed being collected in a Dean-Stark water separator. Five milliliters of 5% methanolic potassium hydroxide were added to the warm solution and the mixture then poured into an equal amount of water. Extraction with ether caused some solid to separate, which was removed by filtration and recrystallized from methanol, yielding 1.30 g. (35%) of pregnenolone ethylene ketal (X), m.p. 162–164°.

Two drops of pyridine were added to the filtrate, the solution was dried, and the solvent removed under vacuum. The semicrystalline residue was combined with some additional solid which separated from the aqueous layer on letting stand at room temperature overnight and the mixture was recrystallized from methanol. This yielded an additional 1.20 g. (32%) of ketal, X, m.p. 161–163° (lit., 164–167°;[15] 163–166°, $[\alpha]_D^{26}$ − 39 ± 2°[24]).

Pregnenolone ethylene ketal oxide (XI), *and attempted hydrolysis of the epoxide ring under alkaline conditions.* A solution of 1.2 g. of pregnenolone ethylene ketal (X) in 25 ml. of chloroform was chilled in ice and 1.4 g. of monoperphthalic acid in 30 ml. of ether added. The clear solution was let stand in a refrigerator for 18 hr., then washed thoroughly with 5% sodium carbonate solution, water, ferrous sulfate solution, and again with water. The organic layer was dried over sodium sulfate, the solvent removed, and the solid product recrystallized from ethanol, yielding 0.70 g. (56%) of *pregnenolone ethylene ketal α-epoxide* (XI), m.p. 183–185°, $[\alpha]_D$ −51.2 (*c* = 0.94).

Anal. Calcd. for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64. Found: C, 73.17; H, 9.67.

When the ketal epoxide was refluxed for 2 hr. with methanolic potassium hydroxide or heated on a steam bath for 2.5 hr. with aqueous methanolic sodium bicarbonate, mainly starting material was recovered.

Acknowledgment. The authors wish to thank Mrs. Katherine S. Warren, National Institutes of Health, Bethesda, Md., for determining the rotatory dispersion curves, Mr. David Savage for aiding in some of the experimental work, and the Fulbright Commission for a travel grant for one of us (P. Z.).

CHARLOTTESVILLE, Va.

(24) M. Gut, *J. Org. Chem.*, **21**, 1327 (1956).

[CONTRIBUTION FROM THE ORGANIC CHEMISTRY DEPARTMENT, RESEARCH DIVISION, ABBOTT LABORATORIES]

gem-Difluorosteroids

JACK TADANIER AND WAYNE COLE

Received November 16, 1960

Several new types of fluorosteroids have been prepared by adaptation of a known method using sulfur tetrafluoride to replace ketonic oxygen by fluorine. 3,3-Difluoro and 17,17-difluoro compounds in the androstane series are described as well as 3,3-difluoro and 20,20-difluoro derivatives of C_{21} steroids. Ease of fluorination, reflected in yields of products, was greatly dependent on the site and nature of the carbonyl function undergoing reaction.

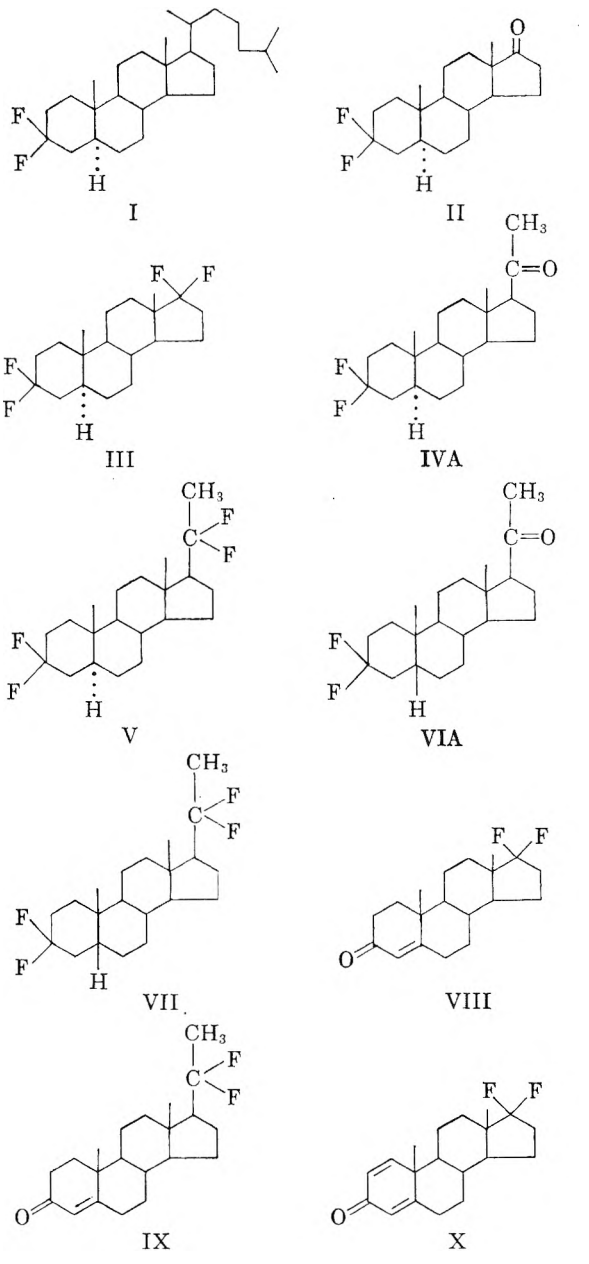
The introduction of fluorine into the steroid molecule has, in a number of cases, resulted in remarkable and useful modification of physiological activities.[1] Since certain desoxy analogues of steroidal hormones have been shown to possess some physiological activity,[2] it was hoped that certain *gem*-difluorosteroids, with fluorine substitution at sites occupied by carbonyl groups in the naturally occurring hormones, might be of therapeutic value. The recent report of sulfur tetrafluoride as a reagent for the preparation of *gem*-difluorides by replacement of carbonyl oxygen by fluorine[3] suggested a convenient route to such steroids.

Fluorination experiments were carried out with several types of diketosteroids to determine the extent to which reactivity differences of carbonyl groups at different positions in the steroid nucleus could be exploited to effect selective fluorination.

5α-Androstane-3,17-dione, 5α-pregnane-3,20-dione, and 5β-pregnane-3,20-dione (Table I) all gave mixtures of di- and tetrafluorinated products. In these cases the difluoroketones which were fluorinated at C_3 predominated in molar ratios of 3:1, 7:1, and 4:1 respectively.

In contrast to the relative ease of fluorination at C_3 with the saturated ketones, no characterizable products of fluorination at C_3 were isolated from 3-ketones having α,β-unsaturation. Treatment of androst-4-ene-3,17-dione, progesterone, and androsta-1,4-diene-3,17-dione with sulfur tetrafluoride resulted in the isolation, in low yields, of 17,17-difluoroandrost-4-en-3-one (VIII), 20,20-difluoropregn-4-en-3-one (IX), and 17,17-difluoroandrosta-1,4-dien-3-one (X), respectively.

With the exception of the difluorinated products obtained from 5α-pregnane-3,20-dione and 5β-pregnane-3,20-dione, structural assignments are based on infrared absorption patterns. The frequency of the carbonyl absorption characterized the nature of the ketone function in the difluoroketones[4] and thus determined the site of fluorination.



The lack of resolution of steroidal 3- and 20-keto absorptions precluded structural assignments by means of infrared to the difluorinated products

(1) *Cf.*, L. F. Fieser and M. Fieser, *Steroids*, Reinhold Publishing Co., New York, 1959, pp. 593, 682–6.

(2) *Cf.*, M. S. de Winter, C. M. Siegmann, and S. A. Szpilfogel, *Chem. & Ind. (London)*, 905 (1959).

(3) W. R. Hasek, W. C. Smith, and V. A. Englehardt, *J. Am. Chem. Soc.*, 82, 543 (1960).

(4) R. N. Jones and F. Herling, *J. Org. Chem.*, 19, 1252 (1954).

TABLE I

Starting Material	Catalyst	Products	Yield, %	$[\alpha]^{23}_{D}$	M.P.	ν_{max} (cm.$^{-1}$)	Formula	Calcd. C	Calcd. H	Calcd. F	Found C	Found H	Found F
Cholestan-3-one	HF	I	32	+24°	109–111	—	$C_{27}H_{46}F_2$	79.37	11.35	9.28	79.28	11.42	8.97
5α-Androstane-3,17-dione	HF	II	37	+92	123–124	1730	$C_{19}H_{28}F_2O$	73.56	9.02	12.25	73.67	9.07	12.18
		III	11	+7	84–85	—	$C_{19}H_{23}F_4$	68.65	8.49	22.86	69.12	8.63	21.93
5α-Pregnane-3,20-dione	HF	IVA	33	+88	145–147	1703	$C_{21}H_{32}F_2O$	74.51	9.53	11.23	74.76	9.82	11.04
		V	5	+12	120–121	—	$C_{21}H_{28}F_4$	69.96	8.95	—	69.80	8.67	—
5β-Pregnane-3,20-dione	HF	VIA	29	+87	100–102	1706	$C_{21}H_{32}F_2O$	74.51	9.53	11.23	74.58	9.47	11.26
		VII	7	+20	101–106	—	$C_{21}H_{32}F_4$	69.96	8.95	21.08	70.13	9.20	21.27
Androst-4-ene-3,17-dione	A HF	VIII	3	+82	179–182	1668 1622							
	B BF_3	VIII	10	+82	181–183	1668 1622	$C_{19}H_{26}F_2O$	74.00	8.50	—	73.84	8.41	—
Progesterone	BF_3	IX	2	+94	108–110	1672 1620	$C_{21}H_{30}F_2O$	74.95	8.99	11.29	75.15	8.95	11.55
Androstra-1,4-diene-3,17-dione	BF_3	X	3	+33	116–117	1673 1630 1613	$C_{19}H_{24}F_2O$	74.48	7.90	12.40	74.27	8.10	12.77

resulting from the pregnanediones. Two products were possible in each case: the 3,3-difluoro 20-ketones IVA and VIA from 5α- and 5β-pregnane-3,20-dione, respectively, or the 20,20-difluoro 3-ketones, IVB and VIB.

IVB

VIB

Assignment of structures IVA and VIA, respectively, to the difluoro ketones resulting from fluorination of 5α-pregnane-3,20-dione and 5β-pregnane-3,20-dione was made on the basis of their NMR spectra (Table II). As methyl ketones, both IVA and VIA must exhibit a singlet in their NMR spectra due to C_{21}-methyl protons. On the other hand, the C_{21}-methyl proton absorptions of IVB and VIB would be multiplets due to spin-spin coupling with the two fluorine atoms at C_{20}. Both difluoro ketones isolated show three distinct singlet absorptions attributable to C_{18}-, C_{19}-, and C_{21}-methyl protons. In both cases, the position of the C_{21}-methyl proton absorption is in good agreement with the value reported by Shoolery and Rogers for C_{21}-methyl 20-ketosteroids.[5]

The positions of the C_{18}- and C_{19}-methyl proton absorptions of IVA and VIA are compared in Table II with those reported by Shoolery for 5α-pregnane-3,20-dione and 5β-pregnane-3,20-dione.[5] It is of interest that while the chemical shift of the C_{19}-methyl protons of the diketones is independent of the nature of the A/B ring junction, the absorption of the C_{19}-methyl protons of the A/B-*trans* difluoro ketone (IVA) lies at higher field (11 c.p.s.) than does the corresponding A/B-*cis* compound (VIA). A similar dependence of the chemical shift of the angular methyl absorption on the nature of the ring junction has been reported for androstane (XI) and its 5-epimer (XII).[6] The absorption of the C_{19}-methyl protons of the A/B-*trans* compound (XI) lies at higher field (7 c.p.s. at 60 mc.) than does that of the *cis* compound

XI

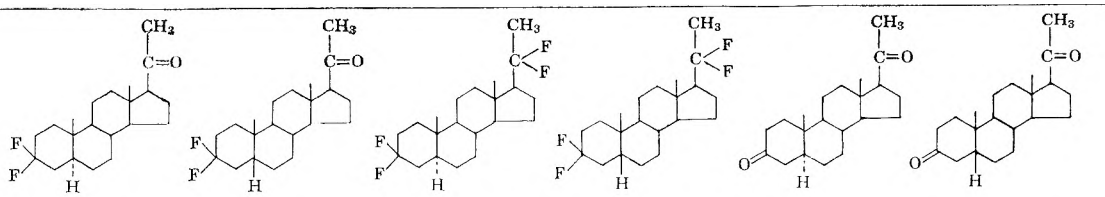
XII

(5) J. N. Shoolery and M. T. Rogers, *J. Am. Chem. Soc.*, 80, 5121 (1958).

(6) J. A. Pople, W. G. Schneider, and H. J. Bernstein, *High Resolution Nuclear Magnetic Resonance Spectra*, McGraw-Hill, New York, N. Y., 1959, pp. 291–2.

TABLE II

NUCLEAR MAGNETIC RESONANCE SPECTRA[a]



Methyl Protons	IVA[b]	VIA[b]	V[b]	VII[b]	c	c
C_{21}	125	126	—	—	128	128
C_{19}	49	60	52	60	62	62
C_{18}	36	37	52	49	38	40

[a] C.p.s. relative to tetramethylsilane at 60 mc., measured in the direction of decreasing field. [b] Determined in ethanol-free chloroform solution using tetramethylsilane as an internal standard. [c] Calculated from the data of Shoolery and Rogers[5] using the value of 385 ± 1 c.p.s. reported by L. L. Smith *et al.* for the position of the tetramethylsilane peak measured relative to benzene as an external reference.[7]

(XII), while the chemical shift of the C_{18}-methyl protons is the same for both compounds.

The NMR spectra of 3,3,20,20-tetrafluoro-5α pregnane (V) and 3,3,20,20-tetrafluoro-5β-pregnane (VII) were also measured. Neither compound showed an absorption maximum at or near 125 c.p.s. (relative to tetramethylsilane), and no singlet absorption other than those attributable to the angular methyls was evident. The 5α-pregnane derivative showed only a single peak at 52 c.p.s. due to the overlapping absorptions of the C_{18} and C_{19} methyl protons. That this was the case was indicated by a comparison of the absorptions of the C_{18} angular methyl of 3,3,20,20-tetrafluoro-5β-pregnane (VII) and the C_{19} angular methyl of 3,3-difluoro-5α-pregnan-20-one (IVA) which should lie in essentially the same environments, respectively, as the C_{18} and C_{19} methyls of V. Both absorptions lie at the same frequency, which is in reasonable agreement with that found for the angular methyl absorption of V.

In addition, it was found that, for V, the ratio of the area of absorption, other than that of the angular methyl groups, to the area of the peak attributed to the overlapping angular methyls was 3.44. The corresponding ratio for VII, using the sum of the areas of the angular methyl peaks was 3.6. The calculated value for this quantity is 4.3. The ratio of the areas of the two angular methyl peaks of VII was found to be 1.0.

The C_{19} angular methyl of the A/B-*trans* tetrafluoride (V), thus, lies at approximately 8 c.p.s. higher field than does that of the A/B-*cis* compound (VII), an effect similar to that observed with the 3,3-difluoro ketones (IVA and VIA).

The effect of acid catalysis on sulfur tetrafluoride fluorination has been reported.[3] It was also reported that Lewis acids such as boron trifluoride have a much greater specific catalytic effect than do Bronsted acids such as hydrogen fluoride. In the present work, acid catalysis was found necessary in all cases. The hydrogen fluoride catalyst was generated *in situ* by the reaction of ethanol, added to the solvent, with the sulfur tetrafluoride reagent.

Attempted fluorination of cholestan-3-one in ethanol-free chloroform or in ether led to almost quantitative recovery of starting material. When the fluorination was carried out in chloroform containing 0.75% ethanol, the infrared spectrum of the crude product showed complete absence of carbonyl absorption and 3,3-difluorocholestane (I) was isolated in 32% yield.

Under the conditions used to effect complete fluorination of cholestanone, fluorination of 5α-androstan-3,17-dione at C_3 was incomplete. The infrared spectrum of the crude product showed strong carbonyl absorptions characteristic of both 3- and 17-ketone groups. When the reaction was carried out in chloroform containing 3% ethanol, under otherwise identical conditions, the infrared spectrum showed no trace of absorption characteristic of the 3-keto function, and 3,3-difluoro-5α-androstan-17-one (II) was isolated in 37% yield together with 11% of 3,3,17,17-tetrafluoro-5α-androstane (III).

Fluorinations of 5α- and 5β-pregnane-3,20-dione were also carried out in chloroform containing 3% ethanol. Yields of difluorinated and tetrafluorinated products are recorded in Table I.

Fluorination of androst-4-ene-3,17-dione in chloroform containing 3% ethanol yielded 3% of 17,17-difluoroandrost-4-en-3-one (VIII) with recovery of a large amount of starting material. Using boron trifluoride as catalyst and employing a somewhat shorter reaction time, 10% of VIII was isolated, but there was considerable resinification and low recovery of starting material.

In view of the higher isolated yield of VIII using boron trifluoride, this catalyst was employed in the fluorinations of progesterone and androsta-1,4-

(7) L. L. Smith, M. Marx, J. J. Garbarini, T. Foell, and J. J. Goodman, *J. Am. Chem. Soc.*, **82**, 4616 (1960).

diene-3,17-dione. In both cases there was considerable resinification and the yields of the difluorides (IX) and (X) were low.

This study is being continued with other ketosteroids. It is apparent that by adjustment of reaction conditions, ketones of different reactivities may be converted into the *gem*-difluoro derivatives. Although bioassay of the substances described in this report is incomplete, several of the difluoroketosteroids tested have mild androgenic activity. Substances VIA and VIII have some additional effects on endocrine balance.

EXPERIMENTAL

The fluorinations were carried out in a stainless steel hydrogenation cylinder. The gaseous reagents were introduced by means of a gas buret using bromobenzene as the displaced liquid.

Ethanol-free chloroform, used in runs employing boron trifluoride as the acid catalyst, was prepared by washing reagent chloroform with concentrated sulfuric acid.[8]

Melting points were taken by the capillary tube method and are uncorrected. Infrared spectra were taken on chloroform solutions using a Perkin-Elmer Model 21 spectrophotometer. The NMR spectra were taken on a Varian nuclear magnetic resonance spectrometer at 60 mc. using tetramethylsilane as an internal reference. Optical rotations were measured in a 1 dm. tube at 23° using freshly-distilled chloroform solvent.

Neutral alumina of activity III (Woelm) and Davison silica gel, 100–200 mesh, were used for the chromatographic separations.

The procedures in which hydrogen fluoride was used as the acid catalyst are illustrated for the fluorinations of 5α-pregnane-3,20-dione and androst-4-ene-3,17-dione. The use of boron trifluoride is illustrated for the fluorination of androst-4-ene-3,17-dione.

3,3-Difluoro-5α-pregnan-20-one (IVA) *and 3,3,20,20-tetrafluoro-5α-pregnane* (V). 5α-Pregnane-3,20-dione (2.0 g.) and 20 ml. of chloroform containing 3% ethanol were heated at 40° for 15 hr. with 10.6 g. of sulfur tetrafluoride.[3] The gaseous reactants and products were stripped and the residue was washed into a 500-ml. separatory funnel with five 50-ml. portions of chloroform. The resulting chloroform solution was washed with two 100-ml. portions of water, 100 ml. of 5% sodium bicarbonate solution, two 100-ml. portions of water, and dried over anhydrous magnesium sulfate. The chloroform was stripped under aspirator pressure on the steam bath leaving 2.47 g. of a partially crystalline, dark brown solid.

The product was heated with 50 ml. of boiling ethanol and the mixture was treated with carbon and filtered through Celite. The carbon-Celite mat was washed with 80 ml. of boiling ethanol and the washings were added to the original ethanol filtrate. The ethanol was stripped under aspirator pressure on the steam bath leaving 1.48 g. of a dark orange, crystalline solid.

This material was chromatographed on 50 g. of alumina. Elution with 1:10 benzene–petroleum ether (b.p. 68–70°) yielded 1.3 g. of an orange, crystalline solid, m.p. 130–136°, which was rechromatographed on 80 g. of silica gel. Elution with 1:5 chloroform–petroleum ether yielded 120 mg. of a white, crystalline solid. The infrared spectrum of this material showed no significant absorption between 1500 and 2700 cm.$^{-1}$ A portion of this material (83.4 mg.) was recrystallized from ethanol–water solution to yield 72.2 mg. of 3,3,20,20-tetrafluoro-5α-pregnane, m.p. 120–121°.

Anal. Calcd. for $C_{21}H_{32}F_4$: C, 69.96; H, 8.95. Found: C, 69.80; H, 8.67.

Elution with chloroform yielded 1.1 g. of a light orange, crystalline solid. This material was recrystallized from ethanol to yield 710 mg. of 3,3-difluoro-5α-pregnan-20-one, white crystals, m.p. 143–147°, ν_{max}1703 cm.$^{-1}$ The analytical sample, prepared by further recrystallization from ethanol, melted at 145–147°.

Anal. Calcd. for $C_{21}H_{32}F_2O$: C, 74.51; H, 9.53; F, 11.23. Found: C, 74.76; H, 9.82; F, 11.04.

17,17-Difluoroandrost-4-en-3-one (VIII). *Run* A. Two grams of androst-4-ene-3,17-dione and 20 ml. of chloroform containing 3% ethanol were heated at 40° for 15 hr. with 10.6 g. of sulfur tetrafluoride. The reaction mixture was allowed to cool to room temperature and the gaseous reactants and products were stripped. The chloroform extraction was carried out in the usual manner to yield 2.41 g. of a black tar.

The product was dissolved in 80 ml. of boiling ethanol, treated with carbon and filtered through Celite. The carbon–Celite mat was washed with 80 ml. of boiling ethanol and the washings were combined with the original ethanol filtrate. The ethanol was stripped on the steam bath under aspirator pressure leaving 1.45 g. of a black tar which crystallized on standing. The infrared spectrum of this material showed strong absorption peaks at 1730, 1668, and 1622, cm.$^{-1}$

This material was chromatographed on 100 g. of alumina. Elution with 1:1 benzene–petroleum ether yielded 89.8 mg. of a white, crystalline solid, m.p. 166.5–174°, ν_{max} 1668, 1622 cm.$^{-1}$ This material was recrystallized from ethanol-water solution to yield 69.6 mg. of 17,17-difluoroandrost-4 en-3-one, m.p. 178.5–182°.

Elution with benzene yielded 1.02 g. of a crystalline solid, ν_{max} 1730, 1668, and 1622 cm.$^{-1}$ This was recrystallized from acetone–petroleum ether to yield 660 mg. of androst-4-ene-3,17-dione, m.p. 171–172°, lit.,[9] m.p. 172. 5–173.5°.

Run B. Androst-4-ene-3,17-dione (2.1 g.) was heated at 40° for 10 hr. with 20 ml. of ethanol-free chloroform, 8 g. of sulfur tetrafluoride, and 0.4 g. of boron trifluoride. The reaction mixture was allowed to cool to room temperature and the gaseous reactants and products were stripped. The chloroform extraction was carried out in the usual manner to yield 1.15 g. of a black, crystalline solid. A large amount of a chloroform-insoluble black resin adhered to the walls of the reaction vessel and was discarded.

The product was heated with 80 ml. of boiling ethanol and the ethanol solution was treated with carbon and filtered through Celite. The carbon–Celite mat was washed with three 25-ml. portions of boiling ethanol and the washings were added to the original ethanol filtrate. The ethanol was stripped under aspirator pressure on the steam bath leaving 0.611 g. of a brown oil which readily crystallized on cooling.

This material was chromatographed on 70 g. of alumina. Elution with 1:1 benzene–petroleum ether yielded 277 mg. of a pale yellow, crystalline solid. This was recrystallized from ethanol–water solution to yield 227.3 mg. of 17,17-difluoroandrost-4-en-3-one, m.p. 178–180.5°, ν_{max} 1668, 1622 cm.$^{-1}$ For analysis this material was recrystallized twice from ethanol-water solution to yield 160 mg., m.p. 181–182.8°.

Anal. Calcd. for $C_{19}H_{26}F_2O$: C, 74.00; H, 8.50. Found: C, 73.84; H, 8.41.

Elution with 1:10 chloroform–benzene yielded 192 mg. of a white crystalline solid, m.p. 160–168.5°, ν_{max} 1730, 1668 1622 cm.$^{-1}$

(8) A. I. Vogel, *A Textbook of Practical Organic Chemistry*, Longmans, Green and Co. Ltd., London, 2nd Ed., 1951, p. 174.

(9) Elsevier, *Encyclopedia of Organic Chemistry*, Springer-Verlag, Berlin, 1959, 14s, p. 2880.

Acknowledgment. The authors are indebted to Messrs. M. Freifelder and G. Stone for assistance with the pressure reactions, to Mr. William Washburn for infrared determinations, and to. Mr. E. F. Shelberg for microanalyses.

NORTH CHICAGO, ILL.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, NATIONAL DRUG CO.]

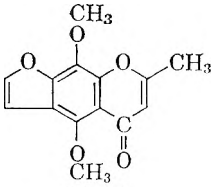
Synthesis in the Chromone Series. 5,8-Dimethoxy-2-substituted Chromones and Nitrogen Analogs

JOHN KOO[1]

Received November 1, 1960

A series of 5,8-dimethoxy-2-substituted chromones was synthesized and a nitrogen analog, 5,8-dimethoxy-4-keto-1,2,3,4-tetrahydroquinaldine, was prepared more conveniently by direct cyclization of the corresponding acid with polyphosphoric acid than by previously reported methods.

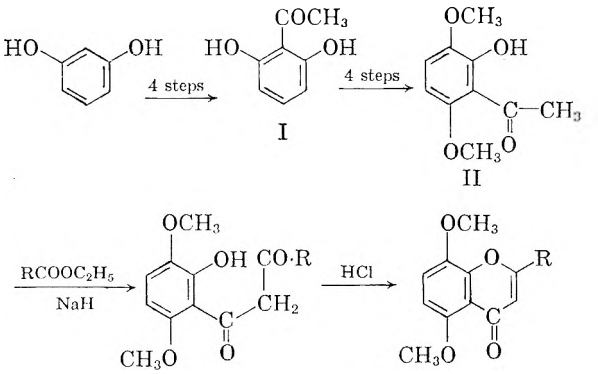
Khellin is the principal active component isolated[2] from the fruit of the Mediterranean plant, *Ammi visnaga.* Its structure has been elucidated as 5,8-dimethoxy-2-methyl-4′,5′-furo-6,7-chromone and its synthesis achieved.[2,3] For centuries the fruit of the plant has been employed as an antispasmodic by Egyptian natives in treating renal colic. In recent years, Khellin has been shown in various pharmacological studies[4] to be a potent relaxant to smooth muscle, and the coronary arteries are affected tremendously by this relaxant action.



Khellin

Accordingly, the structure of Khellin contains a chromone nucleus, and some synthetic chromones have shown characteristic Khellinlike action. Especially the 5,8-dimethoxy-2-methyl chromone, which differs from Khellin by the absence of the condensed furan ring, has been found[5] to be even more active than Khellin itself. As part of a search for new and more effective compounds with Khellinlike activity, a series of 5,8-dimethoxy-2-substituted chromones were synthesized for pharmacological study.

2,5-Dimethoxy-6-hydroxyacetophenone, the common starting material in these syntheses, was obtained according to the method of Baker[6] in four steps from 2,6-dihydroxyacetophenone, which, in turn, was prepared in another four steps from resorcinol by following the general procedure of Frye,[7] except for the first step product, 4-methyl-7-hydroxycoumarin, which was obtained more conveniently by using polyphosphoric acid instead of sulfuric acid as the condensing agent.[8]



R represents a group listed in table I — III

R represents a group listed in table II — IV

Condensation of 2,5-dimethoxy-6-hydroxyacetophenone (II) with an appropriate ester in the presence of sodium hydride provided the diketones (III) listed in Table I. Most of these diketones are yellow solids, and the yields were generally good to excellent. However, a few appeared as yellow oils, which were directly used for ring closure without further purification.

Treatment of the diketones III with concentrated hydrochloric acid for a short period produced the desired chromones (IV) in fair to good yields. All these chromones, listed in Table II, were colorless solids except 2-(2′,3′-dimethoxystyryl)-5,8-dimethoxychromone, which appeared as yellow needles,

(1) Present address: Geigy Research Laboratories, Ardsley, N. Y.

(2) E. Späth and W. Gruber, *Ber.*, **71**, 106 (1938).

(3) R. A. Baxter, *et al.*, *J. Chem. Soc.*, S 30 (1949); T. S. Gardner *et al.*, *J. Org. Chem.*, **15**, 841 (1950); A. Schonberg and A. Sina, *J. Am. Chem. Soc.*, **72**, 1611, 3396 (1950).

(4) G. V. Anrep *et al.*, *J. Pharm. & Pharmacol.*, **1**, 164 (1949); *Am. Heart J.*, **37**, 531 (1949); K. Samaan *et al.*, *J. Pharm. & Pharmacol.*, **1**, 538 (1949).

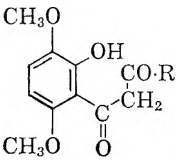
(5) G. Jongebreur, *Arch. Int. Pharm.*, **90**, 384 (1952).

(6) W. Baker, *J. Chem. Soc.*, 1922 (1939).

(7) J. R. Frye, *Org. Syntheses*, Coll. Vol. III, 282 (1955).

(8) J. Koo, *Chemistry and Industry*, 455 (1955).

TABLE I



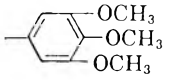
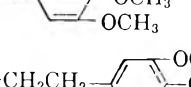
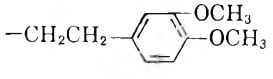
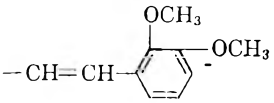
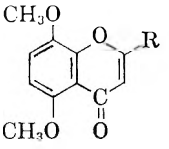
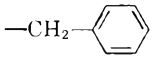
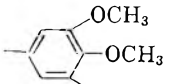
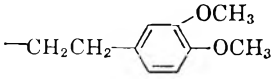
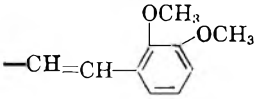
R	M.P.	Yield, %	Recryst. from	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
$-CH_2CH_3$	94–96	84	Ligroin	$C_{13}H_{16}O_5$	61.89	61.93	6.39	6.34
$-CH_2CH_2CH_3$	73–74	91	Ligroin	$C_{14}H_{18}O_5$	63.14	63.10	6.81	6.65
	142–144	87	Benzene–Petroleum ether	$C_{20}H_{22}O_8$	61.53	61.67	5.68	5.97
	117–118	89	Benzene-Ligroin	$C_{21}H_{24}O_7$	64.94	65.05	6.23	6.36
	156–157	78	Benzene–Petroleum ether	$C_{21}H_{22}O_7$	65.27	65.37	5.74	5.80
								

TABLE II



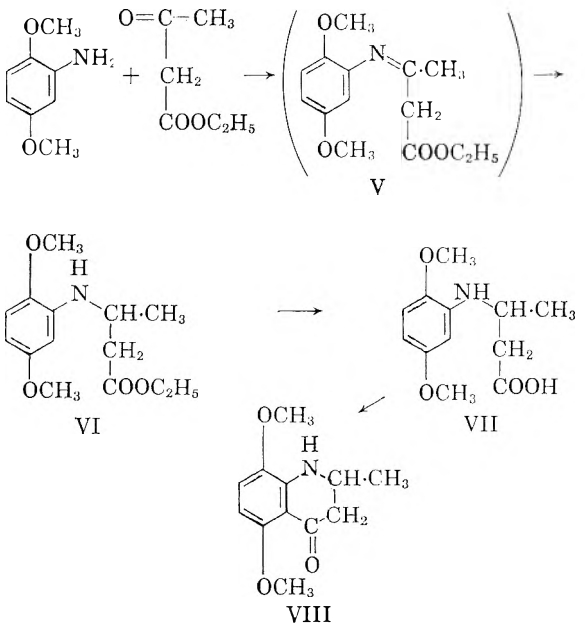
R	M.P.	Yield, %	Recryst. from	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
$-CH_2CH_3$	136–137	99	Benzene–Petroleum ether	$C_{13}H_{14}O_4$	66.65	66.69	6.02	6.06
$-CH_2CH_2CH_3$	102–103	81	Benzene–Petroleum ether	$C_{14}H_{16}O_4$	67.73	67.82	6.50	6.57
$-CH(CH_3)_2$	98–99	59	Petroleum ether	$C_{14}H_{16}O_4$	67.73	67.80	6.50	6.54
$-CH_2CH_2CH_2CH_3$	87–88	67	Petroleum ether	$C_{15}H_{17}O_4$	68.68	68.82	6.92	7.01
	133–135	34	Petroleum ether	$C_{18}H_{16}O_4$	72.96	73.24	5.44	5.38
	202–204	86	Benzene–Petroleum ether	$C_{20}H_{20}O_7$	64.50	64.86	5.41	5.79
	180–182	87	Benzene	$C_{21}H_{22}O_6$	68.09	68.07	5.99	6.00
	180–181	68	Benzene	$C_{21}H_{20}O_6$	68.47	68.65	5.47	5.33

probably because of the presence of a conjugating double bond in the side chain.

In exploring variations in the general structure of IV, it was thought that 5,8-dimethoxy-4-keto-1,2,3,4-tetrahydroquinaldine (VIII), which is a nitrogen analog of IV, might be of interest. Earlier, Johnson and his collaborators[9] and also Elderfield *et al*[10] reported the preparation of other 4-keto-1,2,3,4-tetrahydroquinolins. The present route appears to be more convenient:

(9) W. S. Johnson, E. L. Woroch, and B. G. Buell, *J. Am. Chem. Soc.*, 71, 1901 (1949); W. S. Johnson and B. G. Buell, *J. Am. Chem. Soc.*, 74, 4513 (1952).

(10) R. C. Elderfield and A. Maggiolo, *J. Am. Chem. Soc.*, 71, 1906 (1949); R. C. Elderfield *et al.*, *J. Am. Chem. Soc.*, 68, 1259 (1946).



Condensation of 2,5-dimethoxyaniline and ethyl acetoacetate catalyzed by acetic acid yielded V, which was hydrogenated to give anilinobutyric ester (VI). The anilino acid (VII) was obtained by saponification of the ester (VI). It was then found that this type of anilinoacid could be cyclized directly with polyphosphoric acid, according to the general method for cyclizations,[11] to yield the desired 5,8-dimethoxy-4-keto-1,2,3,4-tetrahydroquinaldine (VIII). It seems of interest to note that previously reported[9,10] cyclization procedures for compounds similar to VIII required protection of the secondary amino- group by tosylation and subsequent removal of the tosyl group. Therefore, by eliminating two steps, this seems to offer a simpler and general procedure in the synthesis of quinoline derivatives.

EXPERIMENTAL[12,13]

Preparation of diketones (III, R represents a group listed in Table I). The condensation of 2,5-dimethoxy-6-hydroxyacetophenone with an appropriate ester is illustrated by the preparation of *1-(2,5-dimethoxy-6-hydroxybenzoyl)-2-butanone* (III. R = C_2H_5). To a solution of 2.4 g. of 2,5-dimethoxy-6-hydroxyacetophenone (II) in 25 ml. of ethyl propionate, was added 2.5 g. of sodium hydride in several portions with shaking during a 30-min. period. The mixture was then gently heated on the steam bath for 10 min. (for higher molecular weight esters the heating must be longer) and kept at room temperature overnight. The dark reaction mixture was poured into ice water with stirring and the solution was extracted once with ether. The aqueous phase part was acidified with dilute acetic acid, and the yellow oil that separated was extracted with ether. The ether solution was washed with cold water, dried over magnesium sulfate, filtered, and evaporated. The yellow oily residue soon solidified and weighed 2.6 g., m.p. 90–93°. It was recrystallized from ligroin to give bright yellow prisms, m.p. 94–96°.

Preparation of chromones (IV, R represents a group listed in Table II). The ring closure reaction is illustrated by the preparation of *5,8-dimethoxy-2-ethyl chromone* (IV. R = C_2H_5). To a 2.2 g. of the above diketone was added 15 ml. of concd. hydrochloric acid, and the mixture was stirred by hand for about 3 min. The dark, clear solution was poured into ice water and nearly neutralized with sodium hydroxide solution. The separated material was extracted with chloroform, which was dried over anhydrous magnesium sulfate, filtered and evaporated to yield 2.05 g. of pale yellow solid, m.p. 130–133°. Recrystallization from benzene-petroleum ether (30–60°) gave colorless needles, m.p. 136–137°.

Ethyl β-(2,5-dimethoxyanilino)butyrate (VI). To a solution of 38.3 g. of 2,5-dimethoxyaniline and 32.5 g. of ethyl acetoacetate in 100 ml. of benzene was added 1 ml. of glacial acetic acid. The solution was placed in a 300 ml. flask, fitted with a Dean-Stark trap, and refluxed for 10 hr., during which time 3.9 ml. of water was collected. The benzene and some unchanged ethyl acetate were distilled under reduced pressure. The dark residual condensation product V was not purified but dissolved in 150 ml. of ethanol, and 6 g. of palladium-on-carbon catalyst was added. The mixture was then hydrogenated at room temperature at 40 lb. pressure for 5 hr. The catalyst was filtered off and the ethanol was evaporated. The oily residue was distilled at 146°/0.4 mm. to yield 36 g. (54% for two steps) of a colorless oil. n_D^{25} 1.5284.

Anal. Calcd. for $C_{14}H_{21}NO_4$: C, 62.90; H, 7.92; N, 5.26. Found: C, 62.94; H, 7.79; N, 5.09.

β-(2,5-Dimethoxyanilino)butyric acid (VII). A mixture of 36 g. of the above ester and 200 ml. of 15% sodium hydroxide solution containing 30 ml. of ethanol was gently refluxed for 3 hr. After cooling, the alkaline solution was extracted with ether and then acidified with acetic acid. The oil that separated was extracted with benzene, washed with water, dried, and evaporated. The residue formed a dark, thick paste weighing 20 g. (62%). A small portion of this material was dissolved in ether and treated with hydrogen chloride gas. The hydrochloride that separated was recrystallized from absolute ethanol and ether to give colorless crystals, m.p. 172–173°.

Anal. Calcd. for $C_{12}H_{17}NO_4$·HCL: Cl; 12.86, N; 5.08. Found: Cl; 13.16; N; 4.93.

5,8-Dimethoxy-4-keto-1,2,3,4-tetrahydroquinaldine (VIII). A mixture of 16 g. of the crude acid VII and 150 g. of polyphosphoric acid was stirred and heated on a steam bath for 30 min. After cooling, the mixture was poured into 400 ml. of ice water and the solution was extracted with ether, which was dried and evaporated to give 1.5 g. of yellow product, m.p. 114–116°. The acidic aqueous solution was then neutralized with potassium carbonate until it became weakly basic and the solution was repeatedly extracted with ether. The combined ether extracts were dried and evaporated to give 4 g. of the product, m.p. 112–115°. The combined yield was 5.5 g. (36%).[14] A sample recrystallized from benzene-petroleum ether, formed bright yellow prisms, m.p. 117–118°.

Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.30; H, 6.83; N, 6.12.

PHILADELPHIA 44, PA.

(11) J. Koo, *J. Am. Chem. Soc.*, **75**, 1891 (1953).

(12) All melting points are uncorrected.

(13) The experiments described here were carried out in 1953; later work in this field will appear in future publication.

(14) The percentage yield was obtained in the first and only experiment, and there is reason to believe that the yield can be considerably improved with some development.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, KALAMAZOO COLLEGE]

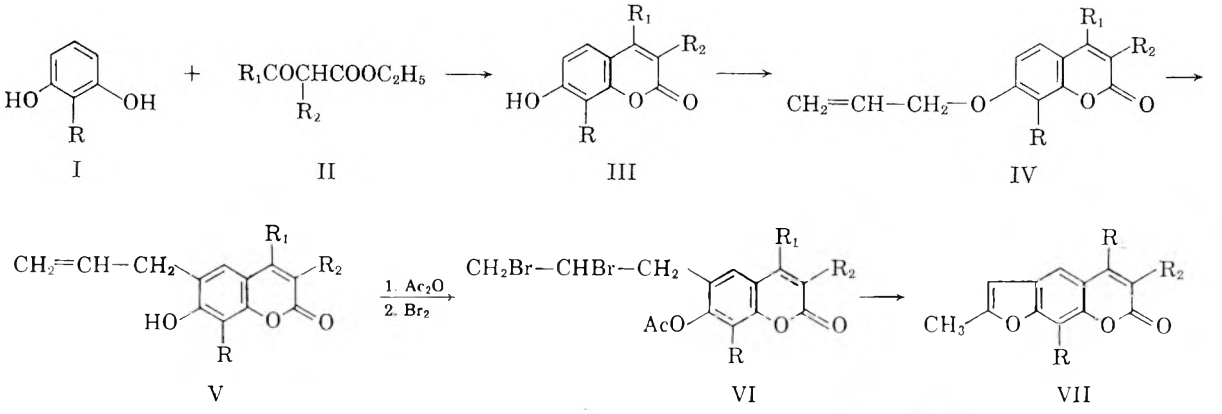
Synthetic Furocoumarins. II.[1] Synthesis of Several Alkylated Psoralenes and of a Dihydroisopsoralene

KURT D. KAUFMAN, FRED J. GAISER, THOMAS D. LETH, AND LEONARD R. WORDEN

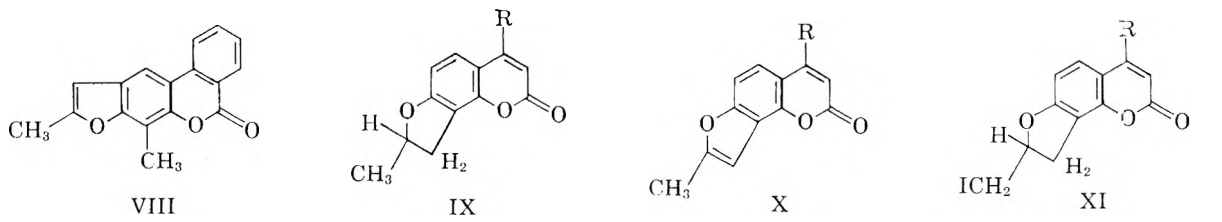
Received November 18, 1960

Five new alkylated psoralenes have been synthesized *via* 6-allyl-7-hydroxycoumarins to enable comparing their photosensitizing activity with psoralene. A dihydroisopsoralene has been prepared and it is suggested that two compounds, previously assigned the structures of dihydroisopsoralenes, are actually isopsoralenes.

The synthetic method described in Part I[1] of this series has been utilized for the synthesis of several psoralenes bearing alkyl substituents in the 3-, 4-, 8-, or 5′- positions.[2] Wide applicability of the process has thereby been illustrated and, at the same time, a variety of methyl and higher alkyl psoralenes have been made available for biological studies directed toward a better understanding of their photosensitizing action. The results of the biological studies are reported elsewhere.[3]



I–VIIa. R = R_1 = R_2 = CH_3
b. R = R_1 = CH_3; R_2 = n-C_4H_9
c. R = CH_3; R_1—R_2 = $-(CH_2)_4-$
d. R = n-C_3H_7; R_1 = CH_3; R_2 = H



The general synthetic method is summarized by structures I through VII and all of the new compounds actually isolated and characterized are listed in Table I at the end of this section. Five new substituted psoralenes have been obtained and are listed in the last part of the table. One of them, 3,4-benzo-5′,8-dimethylpsoralene (VIII), was obtained by dehydrogenation of 5′,8-dimethyl-3,4-cyclohexenopsoralene (VIIc) over palladium on charcoal in refluxing diphenyl ether.

4,5′-Dimethyl-8-*n*-propylpsoralene (VIId) was obtained from 7-hydroxy-4-methyl-8-*n*-propylcoumarin (IIId), which was prepared by catalytic hydrogenation of 8-allyl-7-hydroxy-4-methylcoumarin (III. R = allyl; R_1 = CH_3; R_2 = H).[1] When the synthesis of the latter compound was repeated (by Claisen rearrangement of 7-allyloxy-4-methylcoumarin), a small amount of an alkali insoluble side product, m.p. 117.6–117.8°, was obtained. The structure of 4′,5′-dihydro-4,5′-dimethylisopsoralene (IX. R = CH_3) has been assigned to this compound on the basis of micro-combustion analysis and the fact that it was dehydrogenated to give 4,5′-dimethylisopsoralene (X. R = CH_3).[1]

Krishnaswamy and Seshadri[4] have previously obtained a substance, m.p. 182–183°, which they alleged to be 4′,5′-dihydro-4,5′-dimethylisopsoralene

(1) Part I. K. D. Kaufman, *J. Org. Chem.*, 26, 117 (1961).
(2) For numbering of the psoralene system, see Part I of this series.
(3) M. A. Pathak, J. B. Fellman, and K. D. Kaufman, *J. Invest. Dermatol.*, 35, 165–183 (1960).
(4) B. Krishnaswamy and T. R. Seshadri, *Proc. Indian Acad. Sci.*, 13A, 43–48 (1941).

TABLE I

Compound	Yield, %	Recrystn. Solvent[a]	M.P.[b]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
7-Hydroxycoumarins (III)								
IIIa[c]	65	C	279–280	$C_{12}H_{12}O_3$	70.57	70.58	5.92	5.85
IIIb[c]	22	B	156–157	$C_{15}H_{18}O_3$	73.15	73.19	7.32	7.34
IIIc[d]	47	C	279–281	$C_{14}H_{14}O_3$	73.02	73.26	6.13	5.99
IIId[e]	96[f]	A	186–186.5	$C_{13}H_{14}O_3$	71.60	71.49	6.47	6.06
7-Allyloxycoumarins (IV)								
IVa	97[f]	A	126–126.5	$C_{15}H_{16}O_3$	73.75	73.41	6.60	6.57
IVb	98[f]	B	94.5–95	$C_{18}H_{22}O_3$	75.52	75.59	7.69	7.67
IVc	84	A	143.5–144	$C_{17}H_{18}O_3$	75.53	75.85	6.71	6.69
IVd	90	D	89	$C_{16}H_{18}O_3$	74.40	74.69	7.02	7.42
6-Allyl-7-hydroxycoumarins (V)								
Va	78[f]	E	179–181	$C_{15}H_{16}O_3$	73.75	73.81	6.60	6.71
Vb	86[f]	B	133.5–134	$C_{18}H_{22}O_3$	75.52	75.39	7.69	7.85
Vc	35[f]	E	162.5–165	$C_{17}H_{18}O_3$	75.53	75.32	6.71	6.66
Vd	50[g]	A, E	145–145.5	$C_{16}H_{18}O_3$	74.40	74.88	7.02	7.37
7-Acetoxy-6-allylcoumarins								
Va Acetate[h]	66	C	127–127.5	$C_{17}H_{18}O_4$	71.06	70.98	6.31	6.30
Vb Acetate[i]	56	F	97–98	$C_{20}H_{24}O_4$	73.14	73.35	7.37	7.43
Vc Acetate[h]	96	A	125.5	$C_{19}H_{20}O_4$	73.06	73.15	6.45	6.55
Vd Acetate[i]	97	D	112–113	$C_{18}H_{20}O_4$	71.99	71.84	6.71	6.46
7-Acetoxy-6-(2′,3′-dibromopropyl)coumarins (VI)								
VIa	98[f]	A	148–149	$C_{17}H_{18}O_4Br_2$	45.76	45.92	4.07	4.34[j]
VIb	74	G	100.5–101	$C_{20}H_{24}O_4Br_2$	49.20	49.58	4.96	5.22[j]
VIc	83	A	154.5–155.5	$C_{19}H_{20}O_4Br_2$	48.32	48.26	4.27	4.14
VId	100[f]	A	119–120	$C_{18}H_{20}O_4Br_2$	46.98	46.67	4.38	4.31[j]
Furocoumarins (VII, VIII, and IX)								
VIIa	74	A, E	203.5–204.5	$C_{15}H_{14}O_3$	74.36	74.63	5.82	5.47
VIIb	69	A	119–120	$C_{18}H_{20}O_3$	76.02	75.68	7.10	6.96
VIIc	59	A	176.5–178	$C_{17}H_{16}O_3$	76.10	76.01	6.01	5.73
VIId	61	A	171.3–171.8	$C_{16}H_{16}O_3$	74.98	74.99	6.29	6.86
VIII	25[k]	E	232–233	$C_{17}H_{12}O_3$	77.25	76.91	4.58	4.21
IX (R = CH_3)	8[l]	A	117.6–117.8	$C_{13}H_{12}O_3$	72.20	72.20	5.60	5.81

[a] A, 95% ethanol; B, ligroin (*d* 0.69–0.72); C, acetic acid; D, *n*-hexane; E, benzene; F, methanol-water; G, methanol. [b] All melting points were determined in soft glass capillaries and are corrected. [c] Condensing medium: polyphosphoric acid. [d] Condensing medium: concd. sulfuric acid. [e] Obtained by hydrogenation of 8-allyl-7-hydroxy-4-methylcoumarin[2] as described in the experimental section. [f] Yield of crude material, suitable for use in the next step. [g] Based on recovery of unchanged starting material after refluxing for only one hour. [h] From acetic anhydride-pyridine. [i] From acetic anhydride-sodium acetate. [j] Bromine analyses: (a) Calcd. 35.82; found 35.69. (b) Calcd. 32.73; found 32.13. (d) Calcd. 34.72; found 34.81. [k] From the dehydrogenation of VIIc. [l] A side product in the preparation of 8-allyl-7-hydroxy-4-methylcoumarin.

(IX. R = CH_3). Their compound was obtained by the treatment of 4′,5′-dihydro-5′-iodomethyl-4-methyl-isopsoralene (XI. R = CH_3) with sodium in ethyl alcohol, which they assumed reduced the iodomethyl group. We suggest that sodium ethoxide, produced by the reaction of sodium with ethyl alcohol, caused the elimination of hydrogen iodide followed by prototropic rearrangement to give 4,5′-dimethylisopsoralene (X. R = CH_3), which has been reported[1] to have m.p. 182–183°. Furthermore, the same authors[4] report m.p. 148–149° for the compound obtained by treatment of XI (R = H) with sodium in ethyl alcohol and they propose structure IX (R = H) for it. Very probably, they obtained instead 5′-methylisopsoralene (X. R = H), reported[1] to have m.p. 153–154°. Whether or not their products were isopsoralenes, as seems likely, there can be no doubt that their compound, m.p. 182–183°, is not 4′,5′-dihydro-4,5′-dimethylisopsoralene, as our sample of that compound melts over 60° lower.

Three of the new psoralenes were obtained from 2-methylresorcinol (I. R = CH_3) using different β-keto esters (II) in the first step, which is a v. Pechmann condensation. With methylacetoacetic ester (IIa) and *n*-butylacetoacetic ester (IIb) condensation was effected by heating the reactants in polyphosphoric acid on a steam bath as suggested by Koo.[5] With ethyl cyclohexanone-2-carboxylate (IIc) condensation occurred readily in concentrated sulfuric acid at 0–10°. In all cases, the 7-hydroxycoumarins (III) were converted smoothly to 7-

(5) J. Koo, *Chem. & Ind.*, 445 (1955). The polyphosphoric acid was donated by the Victor Chemical Co., Chicago, Ill.

allyloxycoumarins (IV) by reaction with allyl bromide and anhydrous potassium carbonate in refluxing acetone.

Claisen rearrangement of the 7-allyloxycoumarins was effected in two different ways. 7-Allyloxy-3-*n*-butyl-4,8-dimethylcoumarin (IVb) was heated alone for three hours at 215° to give the 6-allyl product (Vb), which was very discolored and difficult to purify. The other 7-allyloxycoumarins were refluxed from sixty to ninety minutes in diethylaniline (b.p. 213–216°), which produced 6-allyl compounds that were less discolored and easier to purify. In one case, a sixty-minute reflux period left a large quantity of unchanged starting material, indicating that a longer reflux period is, in general, a safer procedure. Acetylation of the 6-allyl-7-hydroxy coumarins (V) was accomplished either with acetic anhydride and sodium acetate or with acetic anhydride and pyridine.

Chloroform solutions of the acetylated compounds readily absorbed one mole of bromine per mole of reactant to give 7-acetoxy-6-(2′,3′-dibromopropyl)coumarins (VI). In one experiment, designed to test whether acetylation is necessary before the bromine addition step, 6-allyl-7-hydroxy-4-methyl-8-*n*-propylcoumarin (Vd) in chloroform was treated with bromine. Hydrogen bromide was evolved and the product was a mixture of bromo derivatives which was not purified. These observations indicate that deactivation of the hydroxyl group, through acetylation, is necessary even when both of the positions *ortho* to the hydroxyl group are occupied. Cyclization of the dibromopropyl acetates (VI) to psoralenes (VII) was accomplished in each case by treatment with sodium ethoxide in absolute ethanol.

EXPERIMENTAL

Data for the new compounds described in this paper are summarized in Table I. Typical procedures are given in this section. Although the data are not given, infrared and ultraviolet spectra were determined for all of the psoralenes and most of the intermediate coumarins and were consistent with the structures proposed.

7-Hydroxy-3,4,8-trimethylcoumarin (IIIa). Polyphosphoric acid (250 g.) was added to a solution of 2-methylresorcinol (82.30 g., 0.66 mole) in ethyl α-methylacetoacetate (94.80 g., 0.66 mole). The mixture was stirred and heated on the steam bath at a temperature between 75–80°. In a few minutes, the mixture had solidified and, after 20 min., water was added and the mixture was stirred and refluxed for 8 hr. to ensure dissolution of all polyphosphoric acid. The tan solid, which was isolated by filtration, crystallized from glacial acetic acid to give the product reported in Table I.

7-Hydroxy-8-methyl-3,4-cyclohexenocoumarin (IIIc). 2-Methylresorcinol (68.30 g., 0.55 mole), followed by ethyl cyclohexanone-2-carboxylate (IIc) (95.00 g., 0.56 mole), was dissolved in stirred concd. sulfuric acid (500 ml.) at such a rate as to keep the temperature below 10° (ice-salt bath). After stirring for 6 hr. the chilled solution was poured into *ca.* 8 l. of ice water with constant stirring. After standing for a few minutes, a brown solid was isolated by filtration and it crystallized from glacial acetic acid as long prisms, m.p. 279–281°. Yield and analytical data are reported in Table I.

7-Hydroxy-4-methyl-8-n-propylcoumarin (IIId). A mixture of 8-allyl-7-hydroxy-4-methylcoumarin[1] (35.94 g., 0.166 mole), pyridine (200 ml.), and 5% palladium on charcoal (1.66 g.) was shaken with hydrogen at an initial pressure of 65.2 lbs./in.[2] After 3.75 hr., 0.166 mole of hydrogen had been absorbed, and the catalyst was removed by filtration before diluting the reaction mixture to *ca.* 1.5 l. with dilute hydrochloric acid. The white precipitate, which was collected, weighed 34.28 g. and was suitable for use in the next step. Crystallization from 95% ethanol gave the material of analytical purity reported in Table I.

7-Allyloxy-3,4,8-trimethylcoumarin (IVa). A mixture of 7-hydroxy-3,4,8-trimethylcoumarin (88.00 g., 0.431 mole), anhydrous potassium carbonate (235 g., 1.7 mole), and allyl bromide (314.1 g., 2.6 mole) was stirred and heated in refluxing acetone (2 l.) for 8 hr. Evaporation of the acetone under reduced pressure left a residue, which was washed thoroughly with water, dried, and washed once with petroleum ether (b.p. 30–60°) to remove excess allyl bromide. This procedure gave 101.5 g. (96.5% yield) of product, m.p. 122–125°, free of starting material and suitable for use in the next step. Starting material, if present, can be removed by washing with 5% sodium hydroxide solution. Crystallization from 95% ethanol gave the material of analytical purity reported in Table I.

6-Allyl-7-hydroxy-3,4,8-trimethylcoumarin (Va). A solution of crude 7-allyloxy-3,4,8-trimethylcoumarin (100.5 g.) in boiling diethylaniline (275 ml.) was refluxed for 1 hr. After cooling, the product crystallized from the reaction mixture and was collected, washed with fresh diethylaniline, and then with petroleum ether (b.p. 30–60°). The crude product, m.p. 165–181°, weighed 78.1 g. (78% yield) and was completely soluble in 5% sodium hydroxide solution. It was suitable for use in the next step, but crystallization from benzene gave the material of analytical purity, m.p. 179–181°, reported in Table I.

6-Allyl-3-n-butyl-4,8-dimethyl-7-hydroxycoumarin (Vb). Crude 7-allyloxy-3-*n*-butyl-4,8-dimethylcoumarin (12.33 g.) was heated at 215° for 3 hr. in an oil bath. The cooled reaction mixture dissolved in boiling 95% ethanol, and the hot solution was filtered and diluted with excess water which caused the precipitation of 10.64 g. (86% yield) of crude product, m.p. 121–124°. This material was used in the acetylation step, although it was sufficiently impure that difficulty was encountered in purifying the acetate. A portion of the crude product was further purified by dissolving it in 5% sodium hydroxide solution, filtering, and reprecipitating with hydrochloric acid. The precipitate crystallized from a large volume of ligroin (*d.* 0.69–0.72) to give the material of analytical quality reported in Table I.

7-Acetoxy-6-allyl-4-methyl-8-n-propylcoumarin (Vd acetate). A mixture of 6-allyl-7-hydroxy-4-methyl-8-*n*-propyl coumarin (4.73 g.) and acetic anhydride (25 ml.) containing a few crystals of fused sodium acetate was heated under reflux for 4 hr. Excess anhydride decomposed on stirring for an hour with water (300 ml.) and the product (5.32 g., 97% yield), m.p. 112–113°, was collected by filtration. Crystallization from *n*-hexane did not change the melting point, but gave the sample of analytical purity reported in Table I.

7-Acetoxy-6-allyl-3,4,8-trimethylcoumarin (Va acetate). Acetic anhydride (35.0 g.) was added rapidly to a solution of crude (6-allyl-7-hydroxy-3,4,8-trimethylcoumarin (77.0 g., 0.317 mole) in pyridine (470 ml.) which was stirred for 1 hr. at room temperature. A mixture of ice and 5% hydrochloric acid (3.5 l.) was added and, after brief stirring to allow decomposition of excess acetic anhydride, the precipitate was collected and recrystallized from acetic acid to give 59.7 g. (66% yield) of product, m.p. 125–126.5°. Another crystallization from acetic acid gave the analytical sample reported in Table I.

7-Acetoxy-6-(2′,3′-dibromopropyl)-3,4,8-trimethylcoumarin (VIa). A solution of bromine (2.78 g., 0.0174 mole) in

chloroform (35 ml.) was added dropwise to a stirred solution of 7-acetoxy-6-allyl-3,4,8-trimethylcoumarin (5.00 g., 0.0174 mole) in chloroform (50 ml.). Evaporation of solvent left 7.6 g. (98% yield) of an off-white solid, m.p. 141–145°, which was suitable for use in the next step. Crystallization from ethanol gave the material reported in Table I.

2′,3,4,8-Tetramethylpsoralene (VIIa). A solution of crude 7-acetoxy-6-(2′,3′-dibromopropyl)-3,4,8-trimethylcoumarin (74.5 g., 0.167 mole) in ethanolic sodium ethoxide (19.2 g. sodium in 750 ml. absolute ethanol) was heated under reflux for 1.75 hr., allowed to cool for 15 min., and poured into a mixture of ice (3 kg.) and 3.5% hydrochloric acid (3 l.). The resulting precipitate was washed three times with 5% sodium hydroxide (1-l. portions) and then with water to yield 36.2 g. (89% yield) of crude product, m.p. 190–196°. Crystallization from ethanol and then from benzene gave the material reported in Table I.

3,4-Benzo-2′,8-dimethylpsoralene (VIII). A mixture of 2′,8-dimethyl-3,4-cyclohexenopsoralene (3.01 g.), 5% palladium on charcoal (3.00 g.), and diphenyl ether (25 ml.) was heated under reflux for 5 hr. The catalyst was removed from the hot solution by filtration and was washed with 10 ml. of hot diphenyl ether. On cooling, the combined filtrate and wash liquor deposited a crystalline solid, which was washed with 95% ethanol and recrystallized from benzene to yield off-white prisms, (0.75 g., 25% yield), m.p. 232–233°. Analytical data are recorded in Table I.

4′,5′-Dihydro-4,5′-dimethylisopsoralene (IX. R = CH_3). 7-Allyloxy-4-methylcoumarin[1] (212.5 g.) was heated at 215° (temperature of reaction mixture) for 3 hr. and the hot melt was poured into ethanol (1.5 l.). Addition of water (10 l.) gave a precipitate, which was treated with 5% aqueous sodium hydroxide (1.5 l.), in several portions, to obtain an alkali insoluble residue that crystallized from 95% ethanol in pale yellow needles (17.0 g., 8% yield), m.p. 117.6–117.8°. Acidification of the alkaline extracts gave crude 8-allyl-7-hydroxy-4-methylcoumarin which was purified in the manner described earlier.[1] Analytical results are included in Table I.

4,5′-Dimethylisopsoralene (X. R = CH_3). A mixture of 4′,5′-dihydro-4,5′-dimethylisopsoralene (5.41 g.), 5% palladium on charcoal (5.0 g.), and diphenyl ether (60 ml.) was heated under reflux for 5 hr., filtered, and allowed to cool. The next day, an off-white solid (1.72 g., 32.1% yield), m.p. 179.6–182.2°, was collected by filtration. Dilution of the filtrate to 300 ml. with petroleum ether (b.p. 30–60°) gave a second crop which, when combined with the first crop, crystallized from ethanol in colorless prisms (2.33 g., 43% yield), m.p. 182–183°. A mixture of this material and a sample of 4,5′-dimethylisopsoralene from another method[1] had m.p. 182–183°. The infrared spectra of the two samples were identical.

Acknowledgment. This work was made possible by financial assistance from the Paul B. Elder Co., Bryan, Ohio, and the Upjohn Co., Kalamazoo, Mich. Microcombustion analyses and spectral analyses were carried out by the Physical and Analytical Chemistry Department of the Upjohn Co. and the cooperation of Dr. James Johnson in this regard is gratefully acknowledged.

KALAMAZOO, MICH.

[CONTRIBUTION FROM THE UNITED STATES DEPARTMENT OF AGRICULTURE]

Spectral Studies on Flavonoid Compounds. II. Isoflavones and Flavanones[1a]

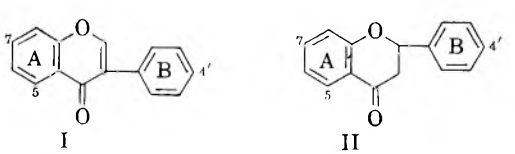
ROBERT M. HOROWITZ[1b] AND LEONARD JURD[1c]

Received October 14, 1960

The ultraviolet spectra of isoflavones and flavanones are similar. A free 7-hydroxyl group in these compounds can be detected by spectral changes observed on the addition of sodium acetate, while a free 5-hydroxyl group can be detected by addition of aluminum chloride. Certain specifically substituted flavanones are shown to form chalcones readily in dilute alkali. A number of examples are given.

Although the ultraviolet spectra of many naturally occurring isoflavones and flavanones have been reported,[2] spectral changes in the presence of basic and complexing reagents have not been extensively employed in the structural analysis of these compounds. In view of the success with which spectral shifts produced by certain reagents have been correlated with the location of hydroxyl groups in various flavonol compounds,[1] it was of interest to determine whether similar shifts might provide useful structural information in the isoflavone and flavanone series.

Isoflavones (I) and flavanones (II) differ from flavonols in that the B-ring is not conjugated with



I II

the carbonyl group. The spectral characteristics of isoflavones and flavanones are similar, therefore, and are determined primarily by absorption in the A-ring conjugated with the carbonyl group. These compounds usually have only one prominent ab-

(1) (a) Part I: L. Jurd and R. M. Horowitz, *J. Org. Chem.*, **22**, 1618 (1957). (b) Fruit and Vegetable Chemistry Laboratory, Pasadena, Calif.[1d]; (c) Western Regional Research Laboratory, Albany 10, Calif.[1d]; (d) a laboratory of the Western Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.

(2) *E.g.*, W. K. Warburton, *Quart. Rev. Chem. Soc.*, **8**, 67 (1954); N. L. Dutta, *J. Ind. Chem. Soc.*, **36**, 165 (1959); J. B. Harborne, *Chemistry and Industry*, 1142 (1954); D. H. Curnow, *Biochem. J.*, **58**, 283 (1954); P. Crabbe, P. R. Leeming, and C. Djerassi, *J. Am. Chem. Soc.*, **80**, 5262 (1958).

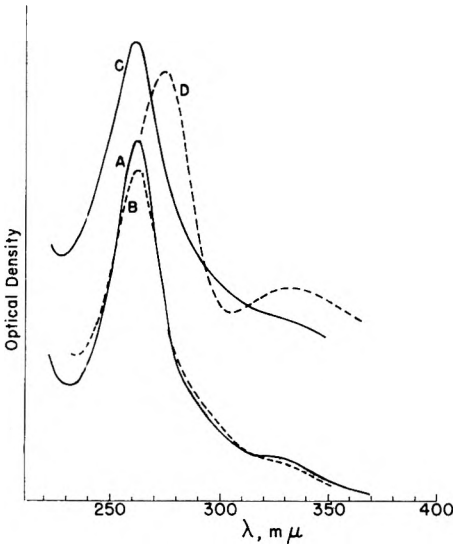


Fig. 1. Ultraviolet spectra of (A) genistin in ethanol, (B) genistin in ethanolic sodium acetate, (C) sophoricoside in ethanol, (D) sophoricoside in ethanolic sodium acetate

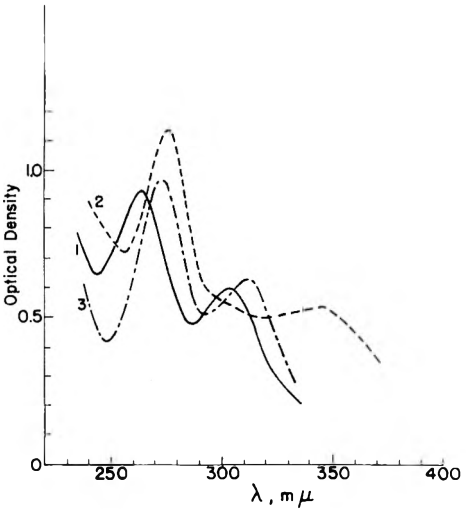
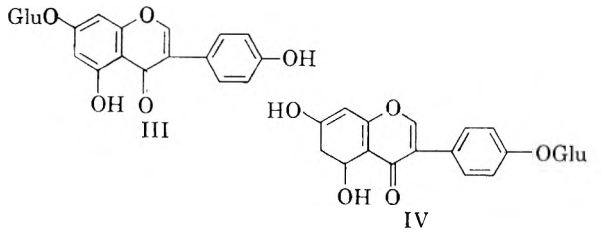


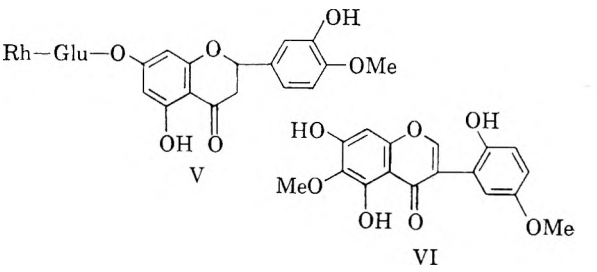
Fig. 2. Ultraviolet spectra of podospicatin in (1) ethanol, (2) sodium acetate, (3) aluminum chloride

sorption peak which occurs in the region of 250–290 mμ.

Detection of a 7-hydroxyl group. A free hydroxyl group at the 7- position of an isoflavone is sufficiently acidic to be ionized by fused sodium acetate. Ionization of a 7-hydroxyl group results in a bathochromic shift of the main absorption band of about 10 mμ for isoflavones (Table I: compounds 1, 3, 5, 7, 10, and 12) and 35–60 mμ for flavanones (Table II: compounds 1, 2, 3, 4, 5, 5, 6, 7, 8, 10, and 11). No significant changes are observed in the spectra of compounds lacking a free hydroxyl group at the 7-position (Table I: compounds 2, 4, 6, and 8; Table II: compounds 9, 13, 14, 15, 16, 17, 18, 19, and 20). These observations are particularly useful in distinguishing isomers such as genistin (III) and sophoricoside (IV), which are the 7- and 4′-glucosides of the aglycone genistein (5,7,4′-trihydroxyisoflavone), respectively. These glucosides have virtually identical spectra in ethanol, but in the presence of sodium



acetate the spectrum of genistin is unchanged while that of sophoricoside shifts 13 mμ (Fig. 1). Since the spectra of both glucosides undergo a bathochromic shift with aluminum chloride (see below), it is clear that the 5-hydroxyl group is unsubstituted. Further examples are provided by the flavanone glycoside neohesperidin (V)[3] and the new isoflavone podospicatin (VI).[4] The spectrum of neohesperidin is unaffected by sodium acetate, so that it may be inferred that sugar groups are attached through the 7-hydroxyl group. This conclusion has been confirmed by chemical degradations.[5] On the other



hand, the main absorption band of podospicatin is shifted 12 mμ on the addition of sodium acetate (Fig. 2). This would be expected on the basis of the structure assigned to podospicatin by Briggs and Cebalo.[4]

Detection of 4′-hydroxy-7-alkoxyflavanones. Sodium acetate is ordinarily the preferred reagent for ionizing the 7-hydroxyl group of flavanones. The addition of dilute sodium hydroxide (one drop of 1% sodium hydroxide in a 2.5-ml. cuvette) generally gives a spectral result similar to that obtained with sodium acetate except in the case of 4′-hydroxy-7-alkoxy- or 4′-hydroxy-7-glucosidoxyflavanones. When these structural features are present the compound is rapidly converted to its chalcone which, in the ionized form, has a broad maximum in the region of 400–450 mμ. All flavanones form chalcones eventually in concentrated alkali[6] but

(3) F. Kolle and K. Gloppe, *Pharm. Zentralhalle*, **77**, 421 (1936).

(4) L. H. Briggs and T. P. Cebalo, *Tetrahedron*, **6**, 145 (1959).

(5) Unpublished data.

(6) M. Shimokoriyama, *J. Am. Chem. Soc.*, **79**, 4199 (1957).

TABLE I

INFLUENCE OF SODIUM ACETATE AND ALUMINUM CHLORIDE ON THE SPECTRA OF ISOFLAVONES

Isoflavone	λ_{max}, mμ		
	C_2H_5OH[a]	NaOAc[b]	$AlCl_3$[c]
1. 7-Hydroxy-4′-methoxyisoflavone (Formonetin)	250	260	
2. Osajin	274	274	
3. 5,7,4′-Trihydroxyisoflavone (Genistein)	262	271	274
4. 5,4′-Dihydroxy-7-glucosidoxyisoflavone (Genistin)	262	262	273
5. 5,7-Dihydroxy-4′-methoxyisoflavone (Biochanin-A)	261	271	
6. Pomiferin	276	276	
7. 5,7-Dihydroxy-4′-glucosidoxyisoflavone (Sophoricoside)	262	275	276
8. 5,3′,4′-Trihydroxy-7-methoxyisoflavone (Santal)	263		274
9. 5,2′-Dihydroxy-6,7,5′-trimethoxyisoflavone (7-*O*-methylpodospicatin) (4)	265		277
10. 5,7,3′-Trihydroxy-6,4′,5′-trimethoxyisoflavone (Irigenin)	267	277	
11. 5,3′-Dihydroxy-6,4′,5′-trimethoxy-7-glucosidoxyisoflavone (Iridin)	268	268	
12. 5,7,2′-Trihydroxy-6,5′-dimethoxyisoflavone (Podospicatin)	263	275	273
13. 5-Hydroxy-6,7,2′,5′-tetramethoxyisoflavone (4)	262		275

[a] Absolute ethanol. [b] Absolute ethanol — fused sodium acetate. [c] Absolute ethanol + 3 drops 10% aqueous aluminum chloride.

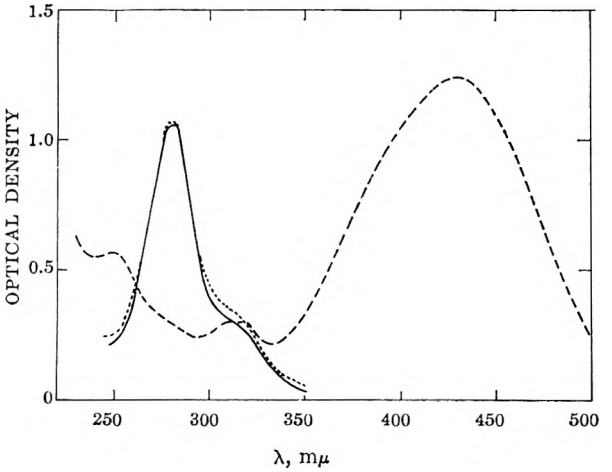


Fig. 3. Sakuranin: ——— In ethanol; _____ sodium acetate added (the curves are superimposable); ..... aluminum chloride added; - - - - 1 drop 1% sodium hydroxide added and allowed to stand ten minutes

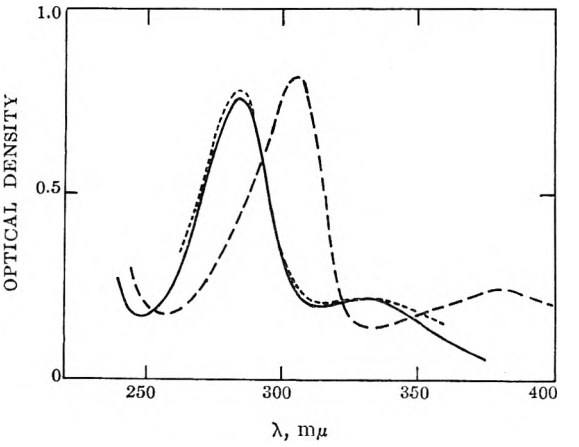
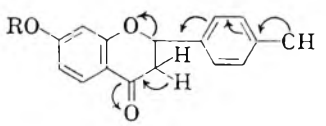


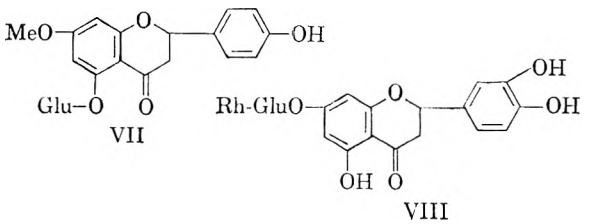
Fig. 4. Eriocitrin: ——— In ethanol; ..... sodium acetate added; - - - - aluminum chloride added

it appears that only 4′-hydroxy-7-alkoxy- or 4′-hydroxy-7-glucosidoxyflavanones form chalcones rapidly (five to ten minutes) in the very dilute alkali specified here. The susceptibility to chalcone formation in these compounds may be visualized as the result of increased acidity of the hydrogen atom *alpha* to the carbonyl group coupled with ionization of the 4′-hydroxyl group:



An example of this effect is provided by the glycoside sakuranin (VII) which is the 5-glucoside of 7-methoxy-5,4′-dihydroxyflavanone (sakuranetin). As expected, the glucoside gives no shift with sodium acetate or aluminum chloride and forms the chalcone in alkali (Fig. 3). After hydrolysis to the aglycone, a shift with aluminum chloride is observed.

Detection of a 5-hydroxyl group. It has been shown earlier that isoflavones and flavanones having a free 5-hydroxyl group form complexes with aluminum chloride and that this complex formation results in a bathochromic shift in the spectra of these compounds.[4,7,8] From the further examples reported in Tables I and II it is apparent that the principal wave length of 5-hydroxyisoflavones undergoes a remarkably constant bathochromic shift of 11–14 mμ on the addition of aluminum chloride, while that of 5-hydroxyflavanones changes by 20–30 mμ. In Fig. 4 the various



(7) T. Swain, *Chem. & Ind.*, 1480 (1954).
(8) W. J. Dunlap and S. H. Wender, *Arch. Biochem. Biophys.*, 87, 228 (1960).

TABLE II

INFLUENCE OF SODIUM ACETATE, SODIUM HYDROXIDE, AND ALUMINUM CHLORIDE ON THE SPECTRA OF FLAVANONES

Compound	λ_{max}, mμ			
	C_2H_5OH[a]	NaOAc[b]	NaOH[c]	$AlCl_3$[f]
1. 7-Hydroxyflavanone	277	338	338	277
2. 7,4′-Dihydroxyflavanone (Liquiritigenin)	276	338	338	276
3. 7,3′,4′-Trihydroxyflavanone (Butin)	278	338	338	278
4. 5,7-Dihydroxyflavanone (Pinocembrin)	291	329	329	312
5. 5,7,4′-Trihydroxyflavanone (Naringenin)	290	328	328	311
6. 5,7,3′,4′-Tetrahydroxyflavanone (Eriodictyol)	289	328	328[d]	310
7. 3,5,7,3′,4′-Pentahydroxyflavanone (Taxifolin)	291	330	329[d]	314
8. 5,7-Dihydroxy-4′-methoxyflavanone (Isosakuranetin)	292	328	328	312
9. 5,3′,4′-Trihydroxy-7-methoxyflavanone	287	287	289[d]	309
10. 5,7,4′-Trihydroxy-3′-methoxyflavanone (Homoeriodictyol)	289	328	328	311
11. 5,7,3′-Trihydroxy-4′-methoxyflavanone (Hesperetin)	288	328	328	311
12. 5-Hydroxy-7,3′,4′-triacetoxyflavanone	274			303
13. Isosakuranetin 7-Rhamnoglucoside (Poncirin)	283	283	285	308
14. Eriodictyol 7-Rhamnoglucoside (Eriocitrin)	285	285	285[d]	306
15. Hesperetin 7-Rutinoside (Hesperidin)	285	285	287	308
16. Hesperetin 7-Neohesperidoside (Neohesperidin)	285	285	287	308
17. 5,4′-Dihydroxy-7-methoxyflavanone (Sakuranetin)	287	287	424[e]	310
18. Sakuranetin 5-glucoside (Sakuranin)	281	281	428[e]	281
19. Naringenin 7-glucoside (Prunin)	284	284	425[e]	308
20. Naringenin 7-rhamnoglucoside	284	284	428[e]	308

[a] Absolute ethanol. [b] Absolute ethanol saturated with fused sodium acetate. [c] 2.5 ml. absolute ethanol treated with 1 drop of 1% sodium hydroxide. [d] Solution decomposes rapidly. [e] Forms the chalcone. [f] Absolute ethanol saturated with aluminum chloride hexahydrate.

spectra of the new flavanone glycoside eriocitrin (VIII)[9] are shown. The bathochromic shift obtained with aluminum chloride shows the presence of a 5-hydroxyl group, while the lack of a shift with sodium acetate shows the presence of a sugar group at the 7-hydroxyl. The presence of free *o*-dihydroxyl groups is inferred from the instability of the compound in alkaline solution as well as from other evidence.[10]

(9) R. M. Horowitz and B. Gentili, *J. Am. Chem. Soc.*, 82, 2803 (1960).

Acknowledgment. We should like to thank Prof. L. H. Briggs for a sample of podospicatin and Dr. J. Naghski for a sample of sophoricoside. We should also like to thank Mr. Bruno Gentili for determining a number of spectra.

AGRICULTURAL RESEARCH SERVICE
WESTERN UTILIZATION RESEARCH AND DEVELOPMENT DIVISION
ALBANY 10, CALIF.

(10) The compound decomposes irreversibly in alkali before chalcone formation can be observed.

[CONTRIBUTION FROM THE INSTITUTO DE QUÍMICA AGRÍCOLA, MINISTÉRIO DA AGRICULTURA]

Chemistry of Brazilian *Leguminosae*. II.[1] Isolation and Structure of Caviunin

OTTO RICHARD GOTTLIEB AND MAURO TAVEIRA MAGALHÃES

Received June 29, 1960

Caviunin, an extractive from *Dalbergianigria* (Fr. Allem.) is shown to be 5,7-dihydroxy-2′,4′,5′,6-tetramethoxyisoflavone.

Since early Brazilian history, the wood of *Dalbergia nigra* (Fr. Allem.), a tree belonging to the *Dalbergiae* tribe of the *Leguminosae* family, has been a much valued article of export. The species is particularly abundant in the state of Espirito Santo, but occurs also in the neighbouring states of Bahia, Minas Gerais, Rio de Janeiro, and in São Paulo, where it is called jacarandá caviuna. In other countries, however, *Dalbergia nigra*[2] is known under different names, such as Brazilian rosewood[3]

(1) Paper I: O. R. Gottlieb and M. Taveira Magalhães, *Anais assoc. brasil. quim.*, 18, 89 (1959).

(2) An anatomical and dendrometric study of *Dalbergia nigra*, as well as a list of references to the botanical literature is given by A. de Mattos Filho and A. F. Coimbra Filho, *Arquivos do Serviço Florestal* (Rio de Janeiro), 11, 157 (1957).

(3) This name is an allusion to the red color of the heartwood and the species should not be confused with the essential oil-producing trees of the genus *Aniba* (family *Lauraceae*) which we have studied in several papers entitled, "The Chemistry of Rosewood." For the most recent article, Part VI in the series, see W. B. Mors, O. R. Gottlieb, and I. de Vattimo, *Nature*, 184, 1589 (1959).

(England), Palissandre (France) or Jacarandaholz (Germany). In spite of the economic importance of the jacarandá caviuna tree, the extractives of its wood do not seem to have previously received any attention.

Sapwood and heartwood[4] were investigated separately. The main crystalline constituent, which was found to be present in the benzene extract of the former, was a new substance which we have named caviunin. It was also obtained from the benzene extract of the heartwood, although it was there only a minor component. Work on its companion substances is now in progress.

Caviunin was easily isolated and purified through its sodium salt which is only slightly soluble in water. It formed colorless slender needles, having an empirical formula of $C_{19}H_{18}O_8$. Methoxyl determination revealed the existence of four such groups and the formation of a diacetate upon acetylation and a di-*O*-methyl ether derivative by methylation indicated the presence of two free hydroxyl groups in the molecule. Thus the formula could be written $C_{15}H_4O_2\cdot(OH)_2\cdot(OCH_3)_4$; it suggested a flavone or an isoflavone structure. The infrared spectrum supported this assumption; it showed the strong multiple absorption between 6 and 6.6 μ usually found in such systems. The ultraviolet spectrum also did not allow a clear distinction between flavone and isoflavone, as was demonstrated earlier in a variety of examples.[5] However, the intense band at 320–380 mμ, generally attributed to the chalcone chromophore of the flavones[6,7] was absent from the spectrum of caviunin.

Ready distinction between the two classes of substances is possible by mild alkaline treatment. Under such conditions flavones afford *o*-hydroxydibenzoylmethanes, whereas isoflavones yield benzyl-*o*-hydroxyphenyl ketones with the loss of one carbon atom (as formic acid).[8] Saponification of caviunin diacetate resulted in the formation of nearly three moles of acid instead of the two expected equivalents. The fact that a third mole of acid is formed would indicate an isoflavonic structure for caviunin. Furthermore, alkaline degradation, when applied to di-*O*-methylcaviunin, afforded in nearly quantitative yield a yellow crystalline substance, later shown to be II. Its empirical formula, $C_{14}H_6O_2(OCH_3)_6$, fitted the benzyl-*o*-hydroxyphenyl ketone which would be expected from di-*O*-methylcaviunin, if this, and hence also caviunin itself, were an isoflavone. The alternative possibility, *i.e.* a flavone structure for caviunin, was ruled out by the resistance of this degradation product to very vigorous alkaline treatment. β-Diketones, the corresponding degradation products of flavones, are unstable in alkali. The ultraviolet spectrum of II exhibited the three typical maxima of substituted desoxybenzoins.[8]

Potassium permanganate oxidation of caviunin yielded asaronic acid (2,4,5-trimethoxybenzoic acid) which was identified by direct comparison with an authentic sample. This compound could only have arisen from ring B of the isoflavone, since ring A, fused to the oxygen heterocycle, would be expected to suffer deep seated degradation under the conditions of the reaction. It was already known that carbon atom 2 of the heterocyclic ring was not substituted by an oxygen function, since, when this carbon atom was lost in the degradation of di-*O*-methylcaviunin (Ic) to the hexamethoxybenzyl *o*-hydroxyphenyl ketone (II), all oxygen atoms of the original molecule were still preserved. Thus the allocation of three methoxy groups to ring B, leaves for the remaining methoxyl and two hydroxyls only positions 5,6,7, and 8 of ring A.

The hexamethoxybenzyl *o*-hydroxyphenyl ketone (II) was very stable, even towards rather vigorous treatment with aqueous alkali. Fusion with alkali had to be employed to effect further cleavage. In this way homoasaronic acid (2,4,5-trimethoxyphenylacetic acid) (IV) and antiarol (3,4,5-trimethoxyphenol) (IIIb) were obtained. The former was identified by comparison with an authentic sample and by degradation to asaronic acid. The formation of a phenylacetic acid (besides a phenol) in this reaction is characteristic of isoflavones and was considered additional proof of such a structure for caviunin. Antiarol (IIIb) was identified by direct comparison with an authentic sample. Its formation through cleavage of di-*O*-methylcaviunin assigns to the three oxygen functions of ring A in caviunin the positions 5, 6, and 7.

Only one of the phenolic hydroxyls of caviunin was readily attacked by diazomethane. Resistance to methylation, together with a positive ferric chloride test and sparing solubility in aqueous alkali are indicative of a conjugated chelate system. Such a system would arise through hydrogen bonding in compounds of the *o*-hydroxy acetophenone type. One of the hydroxyls has, therefore, to be placed in position 5. This fact, together with the conclusion of the preceding paragraph, indicated that caviunin is a phenol with an unsubstituted *para*-position. A positive Gibbs test,[9] performed on mono-*O*-methylcaviunin, confirmed this finding.

(4) Wood samples were secured through the courtesy of Serviço Florestal and Jardim Botânico, both of the Ministério da Agricultura, Rio de Janeiro, and identified as *Dalbergia nigra* (Fr. Allem.), respectively, by Dr. Paulo Agostinho de Matos Araújo and Dr. Armando de Mattos Filho. They had been collected in the vicinity of Rio de Janeiro.

(5) F. Sondheimer and A. Meisels, *Tetrahedron*, 9, 139 (1960).

(6) K. Venkataraman in L. Zechmeister's *Progress in the Chemistry of Organic Natural Products*, Vol. 17, pp. 1–64, Springer Verlag, Wien (1959).

(7) W. K. Warburton, *Quart. Rev.*, 8, 70 (1954).

(8) For pertinent discussion and references see P. Crabbé, P. R. Leeming, and C. Djerassi, *J. Am. Chem. Soc.*, 80, 5258 (1958).

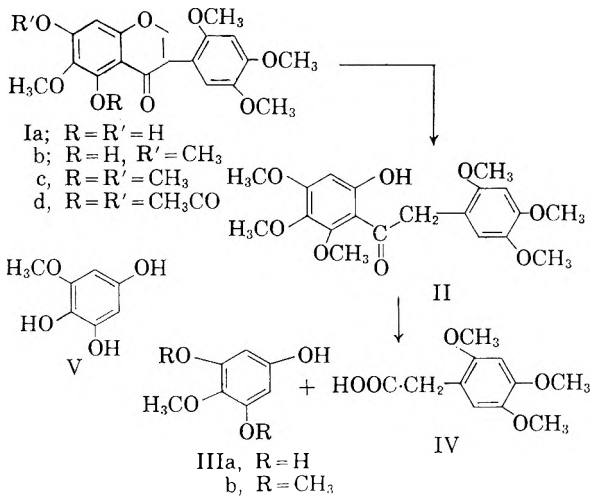
(9) F. E. King, T. J. King, and L. C. Manning, *J. Chem. Soc.*, 563 (1957).

The indophenol chromophore was found at 680 mμ.

At this stage only the relative position of a hydroxy and a methoxy group on C-6 and C-7 remained to be established. Alkaline degradation of caviunin was used to settle this question. In contradistinction to its di-*O*-methyl ether, caviunin afforded easily, by refluxing with aqueous alkali, 2,4,5-trimethoxyphenylacetic acid (IV), originating, as before, from ring B, and a phenol, m.p. 184–186°. identified as iretol, 2,4,6-trihydroxyanisol (IIIa) (lit.[10] m.p. 186°). 2,3,5-Trihydroxyanisol (V), which would have arisen from this degradation if the methoxyl and hydroxyl had the alternative orientation in caviunin, has a reported[11] m.p. of 119–125°; it readily yields a colored quinone, which was not obtained from our product.

From these facts the structure of 5,7-dihydroxy-2′,4′,5′,6-tetramethoxyisoflavone (Ia) was assigned to caviunin.

According to a recent review,[6] only thirteen isoflavones, excluding those containing additional ring systems, have so far been isolated from plants. Although, as stated, these belong to widely different families, the isoflavone skeleton seems to be rather typical of the *Leguminosae-Papilionatae*. This phytochemical regularity is accentuated further, if the results of the present research are added to the reviewer's findings. The parent plants of both substances, cabreuvin [3′,4′,7-trimethoxyisoflavone; the isolation of which from *Myroxylon balsamum* (L.) Harms and *Myrocarpus fastigiatus* (Fr. Allem.) was reported in the previous paper of this series[1]] and caviunin here presented belong to this subfamily. Thus twelve out of the fifteen known naturally occurring simple isoflavones were found in *Papilionatae* species.[12]



This relationship between taxonomy and chemistry is emphasized by the fact that almost all known isoflavonoids which contain additional furan or pyran rings, are also found in leguminous plants. The majority of substances in this latter group is oxygenated in position 2′, osajin and pomiferin being exceptions, since they occur in the family *Moraceae* and are unsubstituted in position 2′. Oxygenation in position 2′ is comparatively rare among the flavonoids[13]; it is interesting that *Dalbergia nigra* which contains caviunin, the new 2′-substituted isoflavone described in the present paper, belongs to the same tribe *Dalbergiae* of the *Papilionatae*, as do the genera *Derris*, *Dipteryx*, *Piscidia*, *Tephrosia*, *Mundulea* in which the majority of 2′-oxygenated isoflavonoid structures seem to be concentrated.

Irigenin,[10] the aglucon of iridin which occurs in *Iris* and *Belamcanda* species (*Iridaceae* family) was up to now the only known natural derivative of the hexahydroxyisoflavone skeleton. The difference between caviunin and irigenin is the presence of a 2′-methoxyl in the former, as opposed to a 3′-hydroxyl in the latter.

EXPERIMENTAL[14]

Extraction procedure. (a) *From sapwood.* The white sapwood of *Dalbergia nigra* was reduced to sawdust and 1.22 kg. were then extracted exhaustively with benzene in a Soxhlet apparatus. After concentration, small quantities of basic and acidic materials were removed from the benzene solution with dilute hydrochloric acid and concentrated sodium bicarbonate solutions respectively. Upon addition of concentrated sodium carbonate solution (or 3% sodium hydroxide solution) a sodium salt precipitated which was separated by centrifugation and washed with water and benzene. A suspension of the white mass in water was acidified and extracted with chloroform. Evaporation of the solvent yielded 750 mg. of slightly yellow, crystalline crude caviunin (Ia), melting between 185–191°. The aqueous alkaline extraction and wash solutions were united, extracted with benzene to remove suspended organic material, and acidified. Chloroform extraction removed an oil. Its ethanol solution, by slow evaporation, afforded an additional amount of 250 mg. of crystals, m.p. 185–190°.

(b) *From heartwood.* The dark red heartwood was reduced to sawdust and 2.67 kg. were extracted exhaustively with benzene in a Soxhlet apparatus. Upon concentration of the benzene solution a crystalline mass settled out and was removed by filtration. By a series of fractional crystallizations from acetone this could be separated into two components, one less soluble, called J-1, as red crystals, m.p. 186–187° (dec., variable depending upon rate of heating) and another, J-2, as yellow needles, m.p. 112–113°. Upon addition of dilute hydrochloric acid to the benzene solution a dark brown mass precipitated which was taken up in chloroform. From both organic solutions basic and acidic material was removed by further extractions with dilute hydrochloric acid

(10) G. de Laire and F. Tiemann, *Ber.*, 26, 2015 (1893).

(11) R. Robinson and C. Vasey, *J. Chem. Soc.*, 660 (1941).

(12) Since this paper was completed, several other natural isoflavones were described. *Cf.* L. H. Briggs and T. P. Cebalo, *Tetrahedron*, 6, 145 (1959); T. B. H. McMurry and C. Y. Theng, *J. Chem. Soc.*, 1491 (1960).

(13) A. J. Birch in L. Zechmeister's *Progress in the Chemistry of Organic Natural Products*, Vol. 14, pp. 186–216, Springer Verlag, Wien (1957).

(14) Melting points were taken on a Kofler hot-stage microscope. Ultraviolet absorption spectra were performed with a Beckman model DU spectrophotometer. Infrared spectral measurements were recorded on a Perkin Elmer Infracord model 137 double beam spectrometer.

and concentrated sodium bicarbonate solutions. Upon treatment with concentrated sodium carbonate solution and working up of the precipitate as described under (a), 450 mg. of crude caviunin (Ia) were obtained.

Caviunin (Ia). Two recrystallizations of crude caviunin from ethanol provided white slender needles, m.p. 191–193°,[15] $[\alpha]_D$ 0° (*c* 1.0, chloroform). The substance sublimed unchanged. With alcoholic ferric chloride a violet color passing into dark green was observed. Infrared bands (in Nujol mull) occured *inter al.*, at 2.95, 6.00, 6.15, 6.30, 6.56, 8.25, 10.35, and 12.08 μ. The ultraviolet absorption spectrum in 95% ethanol solution (neutral and acidic conditions) exhibited maxima at 263 mμ (log ϵ 4.37) and 297 mμ (log ϵ 4.25), minima at 245 mμ (log ϵ 4.23) and 232 mμ (log ϵ 4.15). Upon addition of alkali the maxima were shifted to higher wavelength: λ_{max} 271 mμ (log ϵ 4.32) and 339 mμ (log ϵ 4.14); λ_{min} 254 (log ϵ 4.17) and 315 mμ (log ϵ 4.05).

Anal. Calcd. for $C_{19}H_{18}O_8$: C, 60.96; H, 4.85; 4 OCH_3, 33.16. Found: C, 61.23; H, 4.98; OCH_3, 32.95.

7-O-Methylcaviunin (Ib). Caviunin (Ia) (150 mg.) in ether solution was left overnight in presence of excess diazomethane. After evaporation, crystalline material, m.p. 181–186°, remained. Recrystallization from boiling ethanol afforded yellow needles, m.p. 185.5–187.5°. The ferric chloride test was positive. A blue-green color, λ_{max} 680 mμ was obtained with 2,6-dichlorobenzoquinone when the Gibbs test was performed according to the procedure of King, King, and Manning[9] in borate buffered solution of *p*H 9.3. The ultraviolet absorption spectrum in 95% ethanol solution (unchanged by acid) was practically identical with that of caviunin: λ_{max} 265 mμ (log ϵ 4.40) and 295 mμ (log ϵ 4.27); λ_{min} 246 mμ (log ϵ 4.24) and 283 mμ (log ϵ 4.20). In alkaline solution: λ_{max} 275 mμ (log ϵ 4.31) and 370 mμ (log ϵ 3.60); λ_{min} 255 mμ (log ϵ 4.19); and 332 mμ (log ϵ 3.30).

Anal. Calcd. for $C_{20}H_{20}O_8$: C, 61.85; H, 5.19; 5 OCH_3, 39.95. Found: C, 61.53; H, 5.13; OCH_3, 39.70.

5,7-Di-O-methylcaviunin (Ic). Caviunin was dried at 70° *in vacuo* and 250 mg. were dissolved in 15 ml. of acetone (dried over freshly ignited potassium carbonate). Purified dimethyl sulfate (0.3 ml.) and 0.8 g. of the ignited potassium carbonate were added. After the mixture had been heated for 14 hr. under reflux, 0.2 ml. of dimethyl sulfate and 0.4 g. of potassium carbonate were added and reflux time brought to a total of 40 hr. After cooling, the reaction mixture was treated with water and extracted with chloroform. Upon evaporation of the solvent white crystals, m.p. 152.5–153.5°, remained. By recrystallization from methanol the m.p. rose to 154.5–155.5°. The ferric chloride test was negative. The infrared spectrum in Nujol mull showed the absence of hydroxyl functions, λ_{max}, *inter al.*, at 6.09, 6.25, 7.83, 8.28, 8.70, 8.87, and 9.67 μ.

Anal. Calcd. for $C_{21}H_{22}O_8$: C, 62.68; H, 5.51; 6 OCH_3, 46.27. Found: C, 62.62; H, 5.70; OCH_3, 45.10.

5,7-Di-O-acetylcaviunin (Id). Caviunin was dried at 70° *in vacuo* and 50 mg. was dissolved in a mixture of dry pyridine (1 ml.) and acetic anhydride (1 ml.). After 8 min. boiling and cooling to room temperature, water was added and the mixture extracted with chloroform. The organic solution was washed with dilute hydrochloric acid and sodium hydroxide solutions. Evaporation of the chloroform and recrystallization from cyclohexane-benzene 2:1 afforded 26.3 mg. of white crystals, m.p. 198–200°. The ferric chloride test was negative. The infrared spectrum showed the absence of hydroxyl functions and absorption maxima at 5.8 μ (ester) and 6.2 μ (α,β-unsaturated ketone), *inter al.*

Anal. Calcd. for $C_{23}H_{22}O_{10}$: C, 60.26; H, 4.84. Found: C, 59.97; H, 4.80. The substance (3.772 mg.) was refluxed with *N* methanolic sodium hydroxide during 90 min. The volatile acids were distilled and, upon titration, consumed 2.09 ml. 0.01 *N* sodium hydroxide, equivalent to 0.706 mg. CH_3CO— (calcd. for $2CH_3CO$—) and 0.131 mg. HCO— (calcd. by difference). Theoretically 0.238 mg. HCO— are available by decomposition of the isoflavone.

2,4,5-Trimethoxybenzyl 2-hydroxy-4,5,6-methoxyphenyl ketone (II). To 150 mg. of 5,7-di-*O*-methylcaviunin (Ic) 10 ml. of water were added and a slow current of nitrogen was passed through the mixture. After 5 ml. of a 10% aqueous sodium hydroxide solution had been admitted, the mixture was refluxed for 100 min., cooled to room temperature and the yellow solution extracted with chloroform. Upon evaporation of the solvent 145 mg. of crystalline material, m.p. 128.5–131°, was obtained. Recrystallization from methanol afforded pure 2,4,5-trimethoxybenzyl 2-hydroxy-4,5,6-methoxyphenyl ketone (II), yellow crystals, m.p. 129.5–131°. The ferric chloride test was positive. The same product (II) was obtained when 150 mg. of 5,7-di-*O*-methylcaviunin (Ic) were refluxed for 16 hr. under nitrogen with 10 ml. of a 22% aqueous solution of potassium hydroxide. Infrared bands (in Nujol mull) occurred *inter al.*, at 6.22, 8.28, 8.67, 9.10, and 9.62 μ. The ultraviolet absorption spectrum in 95% ethanol solution exhibited maxima at 220 mμ (log ϵ 4.19), 285 mμ (log ϵ 4.08) and 332 mμ (log ϵ 3.56); minima at 253 mμ (log ϵ 3.53) and 318 mμ (log ϵ 3.51). In alkaline solution λ_{max} 232 mμ (log ϵ 4.12), 285 mμ (log ϵ 3.70) and 353 mμ (log ϵ 3.47); λ_{min} 270 mμ (log ϵ 3.60) and 312 mμ (log ϵ 3.25).

Anal. Calcd. for $C_{20}H_{24}O_8$: C, 61.21; H, 6.17; 6 OCH_3, 47.44. Found: C, 61.05; H, 6.04; OCH_3, 47.13.

Iretol (IIIa) *and homoasaronic acid* (IV). To 150 mg. of caviunin 10 ml. of water were added and a slow current of nitrogen was passed through the mixture. After 5 ml. of a 10% aqueous solution of potassium hydroxide had been admitted, the mixture was refluxed for 3 hr. After cooling to room temperature, the current of nitrogen was replaced by one of carbon dioxide which was allowed to pass until saturation of the solution. Ether (free from peroxides) extraction afforded 39 mg. of oily material which was only slightly soluble in chloroform. After several days crystals slowly started to appear. These were separated and purified by vacuum sublimation providing colorless crystals of iretol (IIIa), m.p. 184–186° (lit.[10] m.p. 186°). The substance is not very stable.

Anal. Calcd. for $C_7H_8O_4$: C, 53.84; H, 5.16; 1 OCH_3, 19.88. Found: C, 53.33; H, 5.20; OCH_3, 19.98.

The aqueous solution was acidified and extracted again with ether. Upon evaporation of the solvent a cream colored solid remained which, by vacuum sublimation, afforded white crystals of 2,4,5-trimethoxyphenylacetic acid (IV), melting partially above 70°, recrystallizing and melting finally at 84–87° (lit.[15,17] m.p. 87°). A sample of 2,4,5-trimethoxyphenylacetic acid which was synthetized by hydrolysis of 2,4,5-trimethoxyphenylacetonitrile[18] showed the same melting behavior and did not depress the melting point of the degradation product IV.

Anal. Calcd. for $C_{11}H_{14}O_5 \cdot H_2O$: C, 54.09; H, 6.60; 3 OCH_3, 38.12. Found: C, 54.36; H, 6.55; OCH_3, 37.92.

Upon oxidation of the degradation product IV with alkaline potassium permanganate (by the procedure outlined under the heading "Asaronic acid"), 2,4,5-trimethoxybenzoic acid, m.p. and mixture m.p. with an authentic sample 144–145.5°, was obtained. The infrared spectra of both samples were superimposable. Nitration yielded 1-nitro-2,4,5-trimethoxybenzene, m.p. 128–130° (lit.[16] m.p. 129°).

Antiarol (IIIb) *and homoasaronic acid* (IV). 2,4,5-Trimethoxybenzyl 2-hydroxy-4,5,6-methoxyphenyl ketone (II) (145 mg.), 5% methanolic potassium hydroxide solution (3 ml.) and water (0.5 ml.) were heated slowly to 180° in a platinum crucible. The temperature was maintained at

(15) During several melting point determinations of caviunin samples a second melting point followed at 197–198°.

(16) S. Takei, S. Miyajima, and M. Ono, *Ber.*, 65, 288 (1932).

(17) The literature records also different melting points, which is due, probably, to the existence of hydrates; *cf.* ref. 18.

(18) A. Robertson and G. L. Rusby, *J. Chem. Soc.*, 1371 (1931).

180° during 15 min. After cooling to room temperature, the product was taken up in water and washed with chloroform. The aqueous solution was saturated with carbon dioxide and again extracted with chloroform. Upon evaporation of the solvent an oily mass remained which was submitted to vacuum sublimation at 120°, 0.005 mm. Two resublimations yielded colorless crystals of antiarol (IIIb) (5 mg.), m.p. 144–146° (lit.[3] m.p. 145.5–146°). Identity with an authentic sample was established by mixture melting point determination and by infrared spectral comparison; λ_{max} (in Nujol mull) 3.03, 6.16, 12.16, and 12.84 μ.

The degradation product IIIb was treated with boiling acetic anhydride and anhydrous sodium acetate. Crystallization from ethanol afforded colorless prisms of *O*-acetylantiarol, m.p. 73–74° (lit.[19] 74°).

The above aqueous solution was now acidified with dilute hydrochloric acid and extracted with ether. Evaporation of the solvent afforded a crystalline mass which was purified by three vacuum sublimations to yield colorless crystals of homoasaronic acid (IV), melting partially at 78°, resolidifying and melting finally at 84–87° (lit.[16] m.p. 87°). Identity of this product was established as outlined above.

Asaronic acid. A solution of caviunin (Ia) (90 mg.) in 5 ml. of 3% aqueous sodium hydroxide was treated at 50° with small portions of potassium permanganate solution until the consumption of the oxidant subsided. The excess permanganate was reduced with sodium sulfite, the precipitate separated by filtration and washed with 3% sodium hydroxide solution. The combined filtrates were acidified and extracted with chloroform. The organic layer was washed with concentrated sodium bicarbonate solution. This yielded, after acidification and extraction with chloroform, 40 mg. of a slightly yellow solid which was washed with a little ethanol. Vacuum sublimation afforded white crystals of asaronic acid, m.p. 144–145° (lit.[16] m.p. 144–145.5°). Identity with an authentic sample of 2,4,5-trimethoxybenzoic acid was established by mixture melting point determination and infrared spectral comparison; λ_{max} (in Nujol mull), *inter al.*, 5.80, 6.00, 7.77, 8.23, 9.26, and 9.80 μ. Nitration yielded 1-nitro-2,4,5-trimethoxybenzene,[16] m.p. and mixture m.p. with an authentic sample 128–130°.

Oxidation of caviunin (Ia) with alkaline hydrogen peroxide[20] also yielded asaronic acid.

Acknowledgment. The authors wish to record their appreciation of the valuable help afforded by Dr. B. Gilbert. They are indebted to Dr. E. J. Eisenbraun (Stanford University), Dr. W. D. Ollis (Bristol University), and Dr. T. R. Govindachari (Presidency College, Madras) who kindly remitted the model substances. Finally, they wish to thank the Conselho Nacional de Pesquisas, Brazil, for financial aid.

RIO DE JANEIRO, BRAZIL

(19) E. Chapmann, A. G. Perkin, and R. Robinson, *J. Chem. Soc.*, 3028 (1927).

(20) O. A. Stamm, H. Schmid, and J. Büchi, *Helv. Chim. Acta*, 41, 2006 (1958).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLLEGE OF SCIENCE AND TECHNOLOGY, BRISTOL, AND THE DEPARTMENT OF ORGANIC CHEMISTRY, UNIVERSITY OF BRISTOL]

Synthesis of Isoflavones. Part III.[1] Caviunin

S. F. DYKE, W. D. OLLIS, AND M. SAINSBURY

Received September 16, 1960

The synthesis of caviunin (5,7-dihydroxy-2′,4′,5′,6-tetramethoxyisoflavone) using the ethoxalylation method is described.

At the suggestion of Dr. Gottlieb and Dr. Magalhães, whose interest we are pleased to acknowledge, we have investigated the synthesis of caviunin whose determination of structure is described in the preceding paper.[2] Of the various methods which are available for the synthesis of isoflavones,[3] the method due to Baker and Ollis[4] involving the reaction of benzyl *o*-hydroxyphenyl ketones with ethoxalyl chloride is particularly suitable for the synthesis of isoflavones bearing several hydroxyl groups.

Caviunin is one of the more unusual types of isoflavone in that it is a derivative of 5,7-dihydroxy-6-methoxyisoflavone. This class includes tectorigenin (I), irigenin (II), and podospicatin[5] (III) as well as caviunin (IV). Previously the synthesis of isoflavones in this class has presented some difficulty but recently it was shown that the ethoxalylation method could be used for the synthesis of tectorigenin and irigenin.[6] By a similar method, the followed synthesis of caviunin has been achieved.

Hoesch condensation of iretol and 2,4,5-trimethoxybenzyl cyanide yielded the benzyl *o*-hydroxyphenyl ketone (VII). This ketone was treated with ethoxalyl chloride in pyridine solu-

(1) Part II. W. Baker, J. B. Harborne, and W. D. Ollis, *J. Chem. Soc.*, 1860 (1953).

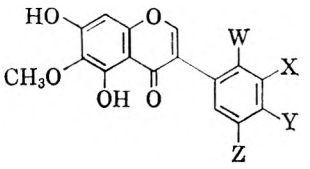
(2) O. R. Gottlieb and M. T. Magalhães, *J. Org. Chem.*, 26, 2449 (1961).

(3) W. K. Warburton, *Quart. Revs. (London)*, 8, 67 (1954), K. Venkataraman in L. Zechmeister's *Fortschritte der Chem. Org. Nat.*, Vol. 17, p. 1, Springer Verlag, Wien (1959); W. Baker and W. D. Ollis, *Sci. Proc. Roy. Dublin Soc.*, 27, No. 6, 119 (1956). W. D. Ollis in *The Chemistry of Flavonoids*, ed. by T. A. Geissman (Pergamon Press). In press.

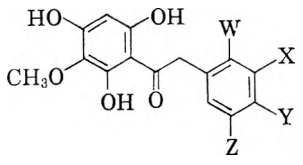
(4) W. Baker and W. D. Ollis, *Nature*, 169, 706 (1952); W. Baker, J. Chadderton, J. B. Harborne, and W. D. Ollis, *J. Chem. Soc.*, 1852 (1953).

(5) L. H. Briggs and T. P. Cebalo, *Tetrahedron*, 6, 143 (1959).

(6) W. Baker, D. F. Downing, A. J. Floyd, B. Gilbert, W. D. Ollis, and R. C. Russell, *Tetrahedron Letters*, No. 5, 6 (1960).

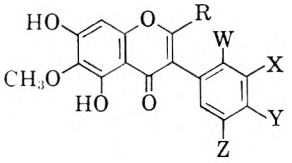


I. W = H; X = H; Y = OH; Z = H
II. W = H; X = OH; Y = OCH_3, Z = OCH_3
III. W = OH; X = H; Y = H; Z = OCH_3
IV. W = OCH_3; X = H; Y = OCH_3; Z = OCH_3

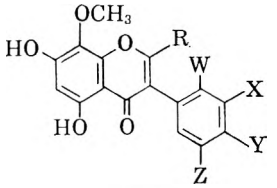


V. W = H; X = H; Y = OH; Z = H
VI. W = H; X = OH; Y = OCH_3; Z = OCH_3
VII. W = OCH_3; X = H; Y = OCH_3; Z = OCH_3

tion and the total ethoxalylation product was hydrolyzed with alkali and thermally decarboxylated. The decarboxylation reaction product was purified by chromatography on thick paper and yielded the isoflavone (IV) which was identical with caviunin. The synthetic isoflavone was characterized as its diacetate and both these compounds gave very detailed infrared spectra which were identical with the infrared spectra of caviunin and its diacetate.



VIII



IX

It was expected from our experiences with the synthesis of tectorigenin and irigenin[6] that this synthesis would have yielded both caviunin (VIII. R = X = H; W = Y = Z = OCH_3) and its isomer (IX. R = X = H; W = Y = Z = OCH_3). However, chromatographic examination of the total ethoxalylation product from the ketone (VII) did not indicate that it was a mixture of the two possible products (VIII and IX. R = $CO_2C_2H_5$; X = H; W = Y = Z = OCH_3). Furthermore, the isomer (IX. R = X = H; W = Y = Z = OCH_3) of caviunin was not present in detectable amounts in the total product obtained by hydrolysis and decarboxylation of the crude 2-carbethoxyisoflavone. This result certainly contrasts with our earlier experiences in synthetical approaches to tectorigenin (I) and irigenin (II), when the 2-carbethoxy-Ψ-tectorigenin (IX. R = $CO_2C_2H_5$; W = X = Z = H; Y = OH) and 2-carbethoxy-Ψ-irigenin (IX. R = $CO_2C_2H_5$; W = H; X = OH; Y = Z = OCH_3) were the compounds which were more easily isolated from the mixture produced in the ethoxalylation reaction. Clearly the relative proportions of the two possible products (see VIII and IX. R = $CO_2C_2H_5$) which could be formed from a ketone of the type derived from iretol (see V–VII) are controlled by subtle features.

EXPERIMENTAL

2,4,5-Trimethoxybenzyl 2,4,6-trihydroxy-3-methoxyphenyl ketone (VII). A mixture of iretol[7] (4.2 g.), 2,4,5-trimethoxybenzyl cyanide[8] (6.0 g.) and anhydrous zinc chloride (5.0 g.) in anhydrous ether (150 ml.) was saturated with dried hydrogen chloride during 5 hr. at 0° and after keeping at 0° for 1 week, the ether solution was decanted from the oily layer of ketimine hydrochloride–zinc chloride complex which had separated. The oily layer was shaken twice with dry ether (250 ml.) then heated (nitrogen atmosphere) on a steam bath with water (400 ml.) which had been previously boiled with a stream of nitrogen bubbling through it. After cooling and standing, the product was collected and recrystallized from aqueous ethanol giving the ketone (VII) (5.9 g., 60%) as almost colorless rhombs, m.p. 211–212°. The ultraviolet spectrum in 95% ethanol showed a maximum at 291 mμ (log ε 3.39), an inflection at 340 mμ (log ε 2.54) and a minimum at 253 mμ (log ε 2.13).

Anal. Calcd. for $C_{18}H_{20}O_8$: C, 59.46; H, 5.50. Found: C, 59.45; H, 5.79.

Caviunin (IV). The above ketone (VII) (2.48 g.) was dissolved in dry pyridine (50 ml.) and ethoxalyl chloride (4.5 ml.) added with shaking at 0°. After keeping at 0° for 3 days, it was poured into water and extracted with chloroform. The extract was washed with dilute sulfuric acid and with water, dried (magnesium sulfate), and evaporated to yield the 2-carbethoxyisoflavone (3.18 g.) as an oil which showed one main spot (R_f = 0.86) by chromatography[9] on Whatman No. 3 paper.

This oil (3.10 g.) was dissolved in acetone (150 ml.) and added to a mixture of air free water (750 ml.) and 2N aqueous sodium hydroxide (33 ml.). After keeping at room temperature for 12 hr., acidification and extraction with chloroform yielded the isoflavone-2-carboxylic acid as a light brown amorphous solid (2.9 g.). Chromatography[9] on Whatman No. 1 paper gave one main spot (R_f 0.79) when examined under ultraviolet light.

A portion (860 mg.) of this crude isoflavone-2-carboxylic acid was divided into 40 small portions (*ca.* 20 mg.). Each small portion was placed in an ignition tube and heated at 295° for 3–3.5 min., when decarboxylation was completed. The product was removed from the ignition tubes with warm ethanol giving a gum (649 mg.) which was chromatographed on silica and eluted with chloroform. The chloroform eluate (438 mg.) was chromatographed[9] on Whatman (No. 3 MM) thick paper and the strip bearing the major band (R_f = 0.75–0.90) was cut out and eluted with ethanol yielding a crystalline compound (222 mg.). This material showed R_f %. Asin 0.72 identical with that of caviunin on paper chromatography.[9] Recrystallization of this fraction from chloroform and from ethanol gave caviunin as colorless needles, m.p. and mixed m.p. 191–192°.

Anal. Calcd. for $C_{15}H_6O_4$ $(OCH_3)_4$: C, 60.96; H, 4.85; OCH_3, 33.16. Found: C, 60.46; H, 5.48; OCH_3, 32.67.

(7) R. E. Damschroder and R. L. Shriner, *J. Amer. Chem. Soc.*, **59**, 931 (1937).

(8) A. Robertson and G. L. Rusby, *J. Chem. Soc.*, 1371 (1935).

(9) The solvent used in paper chromatography was the top layer of a mixture of benzene, acetic acid, formic acid, and water in the proportions 8:2:1:1 by volume.

The synthetic caviunin was characterized as its diacetate, colorless crystals from ethanol, m.p. and mixed m.p. 197.5°.

Anal. Calcd. for $C_{19}H_{16}O_6$ $(OCH_3)_4$; C, 60.26; H, 4.84; OCH_3, 27.1. Found: C, 59.91; H, 5.18; OCH_3, 28.7.

The natural and synthetic caviunin gave identical infrared (Nujol mull) and ultraviolet spectra. The infrared spectra (Nujol mull) of the diacetates were also identical.

BRISTOL 8, ENGLAND

[CONTRIBUTION FROM THE ARTHRITIS RESEARCH LABORATORY, DEPARTMENTS OF MEDICINE AND BIOCHEMISTRY, UNIVERSITY OF ALABAMA MEDICAL CENTER]

Methyl Derivatives of D-Mannosamine

WOLFGANG ROTH AND WARD PIGMAN

Received October 12, 1960

By replacement of a *p*-tolylsulfonyloxy group with hydrazine and subsequent reductions, 2-amino-2-deoxy-3-*O*-methyl-D-mannose hydrochloride and crystalline 2-amino-2-deoxy-3,5,6-tri-*O*-methyl-D-mannose hydrochloride and their crystalline methyl β-glycosides were prepared. Other new amorphous intermediates are reported.

The interest in the preparation of methylated derivatives of 2-amino-2-deoxy-D-mannose arises from the finding of D-mannosamine as a structural entity of the biochemically important neuraminic acid.[1] The methods for the preparation of 2-amino-2-deoxy-D-mannose[2–6] require the separation of this sugar from its epimeric isomer in one step of the procedure. We are reporting the preparation of methyl ethers of D-mannosamine by a method which avoids such a separation and leads unambiguously only to compounds with a 2-amino-2-deoxy-D-mannose configuration.

It has been shown that the replacement of a *p*-tolylsulfonyloxy group with hydrazine[7] in appropriately substituted sugars proceeds with Walden inversion.[8–10] The application of this reaction to 2-*O*-*p*-tolysulfonyl-D-glucose derivatives should therefore yield compounds with a 2-hydrazino-2-deoxy-D-mannose configuration in which the hydrazino group should be reducible to an amino group.[8,11]

In an effort to get the unsubstituted D-mannosamine, we prepared the methyl 2-*O*-*p*-tolylsulfonyl-3,5,6-tri-*O*-benzyl-α,β-D-glucofuranoside by tosylation of methyl 3,5,6-tri-*O*-benzyl-α,β-D-glucofuranoside[12] in pyridine. The replacement of the *p*-tolylsulfonyloxy group with hydrazine, however, was not achieved even after a prolonged period of refluxing (four days). The steric effect of a large benzyl group in the 3- position or even in the 5- and 6- positions seems the probable basis for this lack of reactivity.

In order to test this supposition, the reaction was then carried out on the corresponding 3-*O*-methyl-5,6-di-*O*-benzyl derivative. This compound was prepared by benzylation of 1,2-*O*-isopropylidene-3-*O*-methyl-D-glucofuranose (I)[14] with benzyl chloride and potassium hydroxide, yielding 1,2-*O*-isopropylidene-3-*O*-methyl-5,6-di-*O*-benzyl-D-glucofuranose (II). With methanolic hydrogen chloride the isopropylidene group was split off, and a mixture of the α- and β-glycosides (III) was formed. Tosylation of III in pyridine yielded methyl 2-*O*-*p*-tolylsulfonyl-3-*O*-methyl-5,6-di-*O*-benzyl-α,β-D-glucofuranoside (XV). For this compound, also, a replacement of the *p*-tolysulfonyloxy group with hydrazine could not be achieved.

To show whether benzyl groups in the 5- or 6-positions would prevent a back-side displacement by hydrazine of the *p*-tolylsulfonyloxy group, the methyl 2-*O*-*p*-tolylsulfonyl-3,5,6-tri-*O*-methyl-β-D-glucofuranoside was prepared by tosylation of the known methyl 3,5,6-tri-*O*-methyl-β-D-glucofuranoside.[13] This compound was found to react with hydrazine. On subsequent hydrogenation with Raney nickel catalyst the methyl 2-amino-2-deoxy-3,5,6-tri-*O*-methyl-β-D-mannofuranoside was isolated as a crystalline hydrochloride. Hydrolysis with hydrochloric acid yielded the crystalline 2-amino-2-deoxy-3,5,6-tri-*O*-methyl-D-mannose hydrochloride.

---

(1) D. G. Comb and S. Roseman, *J. Am. Chem. Soc.*, **80**, 497, 3166 (1958).

(2) P. A. Levene, *J. Biol. Chem.*, **36**, 73 (1918); **39**, 69 (1919).

(3) R. Kuhn and W. Kirschenlohr, *Ann.*, **600**, 115 (1956); R. Kuhn and W. Bister, *Ann.*, **602**, 217 (1957); R. Kuhn and J. C. Jochims, *Ann.*, **628**, 172 (1959).

(4) C. T. Spivak and S. Roseman, *J. Am. Chem. Soc.*, **81**, 2403 (1959).

(5) A. N. O'Neill, *Can. J. Chem.*, **37**, 1747 (1959).

(6) J. C. Sowden and M. L. Oftedahl, *J. Am. Chem. Soc.*, **82**, 2303 (1960).

(7) K. Freudenberg, O. Burkhart, and E. Braun, *Ber.*, **59**, 714 (1926).

(8) R. U. Lemieux and P. Chu, *J. Am. Chem. Soc.*, **80**, 4745 (1958).

(9) M. L. Wolfrom, F. Shafizadeh, R. K. Armstrong, and T. M. Shen, *J. Am. Chem. Soc.*, **81**, 3716 (1959).

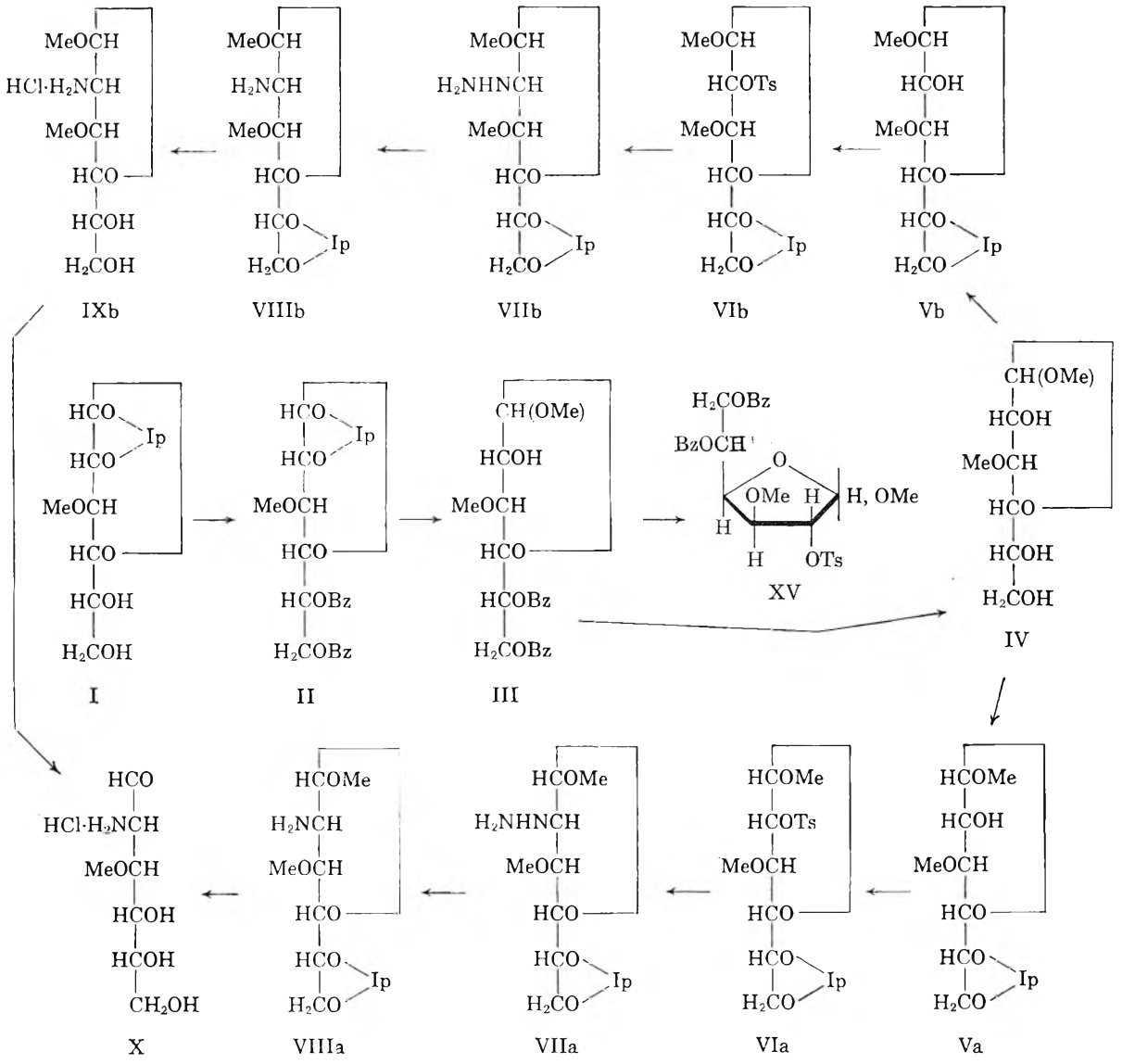
(10) R. Kuhn and G. Baschang, *Ann.*, **628**, 193 (1959).

(11) M. L. Wolfrom, F. Shafizadeh, and R. K. Armstrong, *J. Am. Chem. Soc.*, **80**, 4885 (1958).

(12) F. Weygand and O. Trauth, *Ber.*, **85**, 57 (1952).

(13) P. A. Levene and G. M. Meyer, *J. Biol. Chem.*, **70**, 343 (1926); **74**, 701 (1927).

(14) E. Vischer and T. Reichstein, *Helv. Chim. Acta*, **27**, 1332 (1944).



To prepare the corresponding 2-amino-2-deoxy-3-*O*-methyl-D-mannose, the methyl 3-*O*-methyl-5,6-di-*O*-benzyl-α,β-D-glucofuranoside (III) was hydrogenated with palladium catalyst to eliminate the benzyl groups (IV). By treatment with acetone and cupric sulfate, an isopropylidene group was introduced, and high vacuum distillation of the resulting compound (V) allowed the separation of the α- and β-glycosides (Va, Vb) which subsequently were tosylated in pyridine to yield VIa and VIb.

These compounds were subjected to hydrazine treatment and the resulting products (VIIa and VIIb) were hydrogenated with Raney nickel catalyst to yield the amino compounds VIIIa and VIIIb. Attempts to isolate VIIIb as a hydrochloride failed, caused the elimination of the isopropylidene group and produced the crystalline methyl 2-amino-2-deoxy-3-*O*-methyl-β-D-mannofuranoside hydrochloride (IXb). Acid hydrolysis of VIIIa and IXb yielded the same compound (X) which could only be isolated as an amorphous hydrochloride. *N*-Acetylation[15] of X did not lead to a crystalline compound.

The different optical rotations of the hydrochlorides of X and 2-amino-2-deoxy-3-*O*-methyl-D-glucose ($[\alpha]_D^{20}$ − 23.3°, final, compared with +91.0° final,[16] and their different chromatographic properties (Rg value 1.09 compared with 1.19 in 1-butanol–pyridine–water, 6:4:3) seems reasonable evidence that the replacement of the *p*-tolysulfonyloxy group had proceeded with Walden inversion. In the presence of the blocking groups, the reaction of VIa and VIb could only yield these two compounds.

EXPERIMENTAL

Methyl 2-O-p-tolylsulfonyl-3,5,6-tri-O-benzyl-α,β-D-glucofuranoside (XI). To a solution of 12 g. of methyl 3,5,6-tri-*O*-benzyl-α,β-D-glucofuranoside[12] in 60 ml. of dry pyridine, a

(15) S. Roseman and J. Ludowieg, *J. Am. Chem. Soc.*, **76**, 301 (1954).

(16) A. Neuberger, *J. Chem. Soc.*, 50 (1941).

solution of 7.5 g. of *p*-tolylsulfonyl chloride in 15 ml. of chloroform was added at 0°. After the reaction mixture had been kept at room temperature for 12 hr., 1.5 ml. of water was added and the solution was vigorously stirred for 1 hr. Subsequently, chloroform (150 ml.) was added, and the solution was poured in 1 l. of water. The chloroform layer was separated, washed twice with 10% sulfuric acid, twice with saturated sodium bicarbonate solution, and finally with water. The chloroform layer was then dried with calcium chloride and evaporated. The colorless sirup could not be distilled in high vacuum without decomposition.

Anal. Calcd. for $C_{25}H_{38}O_8S$: C, 67.94; H, 6.19; S, 5.18. Found: C, 68.13; H, 6.35; S, 5.11.

Methyl 2-O-p-tolylsulfonyl-3,5,6-tri-O-methyl-β-D-glucofuranoside (XII). Methyl 3,5,6-tri-*O*-methyl-β-D-glucofuranoside[13] was treated with tolylsulfonyl chloride as described for the benzyl derivative (XI). The product could not be distilled in high vacuum without decomposition.

Anal. Calcd. for $C_{17}H_{26}O_8S$: C, 52.29; H, 6.71; S, 8.21. Found: C, 52.03; H, 6.66; S, 7.96.

Methyl 2-amino-2-deoxy-3,5,6-tri-O-methyl-β-D-mannofuranoside hydrochloride (XIII). A mixture of 25 g. of XII and 50 g. of anhydrous hydrazine (95 + %) was heated under reflux (bath temperature 140°) for 36 hr. After cooling, the final homogeneous solution was extracted four times with 100-ml. portions of ether. The combined ether fractions were then extracted with 200 ml. of water. Subsequently the water phase was treated with Raney nickel catalyst (*ca.* 3–4 g.) for 6 hr. at room temperature and then hydrogenated for 20 hr. at 3 atm. pressure, using Raney nickel catalyst added before. The catalyst was filtered off, and the solution evaporated *in vacuo*. The remaining sirup was dissolved in ether. When methanolic hydrogen chloride was added, a crystalline compound precipitated, which was recrystallized from alcohol. Yield 15 g.; m.p. 227–232° dec. $[\alpha]_D^{20}$ −57.2° (*c*, 1, water).

Anal. Calcd. for $C_{10}H_{22}O_5NCl$: C, 44.30; H, 8.16; N, 5.16. Found: C, 44.31; H, 8.29; N, 5.24.

2-Amino-2-deoxy-3,5,6-tri-O-methyl-D-mannose hydrochloride (XIV). A solution of 12 g. of XIII in 50 ml. of 2.5*N* hydrochloric acid was heated on a steam bath for 2 hr. and then evaporated *in vacuo*. The residue was recrystallized from alcohol, yield 10 g.; m.p. > 300°, turns dark at 190°; $[\alpha]_D^{20}$ −13.0° final (*c*, 1, water); +16.7° (extrap.) → −87° (*c* 1, pyridine).

Anal. Calcd. for $C_9H_{20}O_5NCl$: C, 41.94; H, 7.82; N, 5.44. Found: C, 41.74; H, 7.76; N, 5.50.

Methyl 2-O-p-tolylsulfonyl-3-O-methyl-5,6-di-O-benzyl-α,β-D-glucofuranoside (XV). Compound III was treated with tolylsulfonyl chloride as described for the preparation of XI. The resulting sirup could not be distilled without decomposition, even in high vacuum (10^{-3} mm.).

Anal. Calcd. for $C_{29}H_{34}O_8S$: C, 64.19; H, 6.32; S, 5.91. Found: C, 63.70; H, 6.10; S, 5.61.

1,2-O-Isopropylidene-3-O-methyl-5,6-di-O-benzyl-D-glucofuranose (II). In a three-necked flask provided with a mechanical stirrer and a condenser, 90 g. of 1,2-*O*-isopropylidene-3-*O*-methyl-D-glucofuranose (I) was dissolved in 1 l. of dry, freshly distilled benzyl chloride, and 250 g. of powdered potassium hydroxide was added with vigorous stirring. The reaction mixture was heated to 100° while the stirring was continued. After 30 min., another portion of 250 g. powdered potassium hydroxide was added, and the heating and stirring was extended 4 more hours. After cooling, water was added, and the water phase when separated was extracted twice with ether. The extracts were combined with the benzyl chloride phase, dried with potassium hydroxide and evaporated *in vacuo*, finally at 5×10^{-3} mm. and 100°. The residue, free of benzyl chloride and benzyl alcohol, was then distilled in a molecular still at 3×10^{-3} mm. at 140°, yield 85%; $[\alpha]_D^{20}$ −32.4° (*c*, 1, chloroform).

Anal. Calcd. for $C_{24}H_{30}O_6$: C, 69.54; H, 7.30. Found: C, 69.88; H, 7.49.

Methyl 3-O-methyl-5,6-di-O-benzyl-α,β-D-glucofuranoside (III). A solution of 132 g. of II in 1 l. of methanol containing 0.5% hydrogen chloride was heated for 6 hr. under reflux. After cooling the solution was neutralized with lead carbonate, filtered, and evaporated *in vacuo;* yield of the remaining sirup, 95%.

Anal. Calcd. for $C_{22}H_{28}O_6$: C, 68.02; H, 7.26. Found: C, 67.89; H, 7.31.

Methyl 3-O-methyl-α,β-D-glucofuranoside (IV). A solution of 118 g. of III in 500 ml. tetrahydrofuran was hydrogenated with hydrogen using palladium black catalyst (*ca.* 1 g.) at 3 atm. pressure for 12 hr., and 2 moles of hydrogen was absorbed. The catalyst was removed by filtration, the solution evaporated *in vacuo*, the residue dissolved in acetone and the solution again evaporated; yield of the remaining sirup, 95%.

Anal. Calcd. for $C_8H_{16}O_6$: C, 46.15; H, 7.75. Found: C, 45.90; H, 7.67.

Methyl 3-O-methyl-5,6-O-isopropylidene-α and β-D-glucofuranosides (V). To a solution of 69 g. of IV in 2 l. of acetone, 30 g. of anhydrous cupric sulfate was added, and the reaction mixture was stirred for 10 days. The precipitate was removed by filtration, and the yellow solution evaporated *in vacuo*. Subsequently, the residue was fractionated by high vacuum distillation. At 90–92° and 5×10^{-3} mm. a fraction (Va) was collected as a colorless sirup, yield 39%, $[\alpha]_D^{20}$ +67.2° (*c*, 2, chloroform).

Anal. Calcd. for $C_{11}H_{20}O_6$: C, 53.21; H, 8.12. Found: C 53.12; H, 8.07.

At 114–116° and 5×10^{-3} mm., another compound (Vb) was isolated as a light yellow sirup; yield 42%, $[\alpha]_D^{20}$ −54.1° (*c*, 1, chloroform).

Anal. Calcd. for $C_{11}H_{20}O_6$: C, 53.21; H, 8.12. Found: C, 53.43; H, 8.01.

Methyl 2-O-p-tolylsulfonyl-3-O-methyl-5,6-O-isopropylidene-α-D-glucofuranoside (VIa). Compound Va was treated with *p*-tolylsulfonyl chloride as described for the preparation of XI, yield 85% of light yellow sirup, $[\alpha]_D^{20}$ + 75.8 (*c*, 1, chloroform).

Anal. Calcd. for $C_{18}H_{26}O_8$ S: S, 7.97. Found: S, 7.73.

Methyl 2-O-p-tolylsulfonyl-3-O-methyl-5,6-O-isopropylidene-β-D-glucofuranoside (VIb). Compound Vb was treated with *p*-tolylsulfonyl chloride as described for the preparation of XI; yield 90% of light yellow sirup, $[\alpha]_D^{20}$ −28.5 (*c*, 1, chloroform).

Anal. Calcd. for $C_{18}H_{26}O_8S$: S, 7.97. Found: S, 8.07.

Methyl 2-amino-2-deoxy-3-O-methyl-β-D-mannofuranoside hydrochloride (IXb). Compound VIb (20 g.) was treated with hydrazine and afterwards hydrogenated, as described for the preparation of XIII. The solvent was evaporated and the residue dissolved in ether, then methanolic hydrogen chloride was added and after 15 min. petroleum ether. The precipitated sirup was separated and dissolved in alcohol. On the addition of ether, crystallization occurred. The reaction product was recrystallized from alcohol; yield 65%, m.p. 180–185° dec., $[\alpha]_D^{20}$ −90.7° (*c*, 2, water).

Anal. Calcd. for $C_8H_{18}O_5NCl$: C, 39.43; H, 7.45; N, 5.75. Found: C, 39.80; H, 7.57; N, 5.77.

2-Amino-2-deoxy-3-O-methyl-D-mannose hydrochloride (X) (A) A solution of 2 g. of IXb in 2*N* hydrochloric acid was heated on a steam bath for 1 hr. and then evaporated *in vacuo*. The residue was dissolved in methanol, treated with activated carbon, and precipitated with acetone. The resulting sirup was dissolved two more times in methanol and precipitated with acetone $[\alpha]_D^{20}$ −23.3° final (*c*, 5, water).

Anal. Calcd. for $C_7H_{16}O_5NCl$: C, 36.60; H, 7.02; N, 6.10. Found: C, 36.41; H, 6.81; N, 6.39.

(B) Compound VIa was treated with hydrazine and subsequently hydrogenated as described for the preparation of XIII. The reduction product was dissolved in 2*N* hydrochloric acid and heated on the steam bath for 1 hr. and then

worked up as described under (A). The resulting product showed the same properties as listed under (A).

Chromatography on Whatman No. 1 paper with 1-butanol–pyridine–water, 6:4:3 resulted in a single spot, Rg value 1.09. The substance is ninhydrin positive.

Acknowledgment. This work was supported by the U. S. Public Health Service, National Institute of Arthritis and Metabolic Diseases (Grant A-3555).

BIRMINGHAM, ALA.

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, PURDUE UNIVERSITY]

Reaction of Amylose with 1-Acrylamido-1-deoxy-D-glucitol to Introduce Extended Branches[1]

ROY L. WHISTLER AND HUGH J. ROBERTS

Received November 28, 1960

Amylose reacts with 1-acrylamido-1-deoxy-D-glucitol in aqueous base. Ten molar lithium chloride solution as solvent permits a completely homogeneous reaction and suppresses amide hydrolysis. The product of the reaction is given the trivial name "glucamidoethylamylose." Fractionation of glucamidoethylamylose by ethanol precipitation yields fractions having degrees of molar substitution ranging from 0.20 to 0.82. Solubility in water increases with the amount of substitution. The solutions give a blue color with iodine, but do not show complex formation on titration with iodine. These derivatives of amylose are hydrolyzed by acid and by α-amylase, but are much less susceptible to the action of β-amylase than is amylose. They show no tendency toward retrogradation, nor do they complex with butanol.

A structure consisting of an amylose main chain with grafted poly(1-deoxy-1-β-oxypropionamido-D-glucitol) branches is consistent with these findings and is supported by chromatographic analysis of an acid hydrolyzate.

Introduction of a small amount of neutral substituent into a linear polysaccharide tends to increase its water solubility and its stability in solution. Solubility is further enhanced if the substituent group is hydrophilic. Hydroxyethylation and carbamylethylation are familiar examples of substitution by neutral, hydrophilic groups. The introduction of a sugar or an open-chain polyol as a substituent might provide a still greater enhancement of solubility and solution stability.

Sugar-substituted polysaccharides have recently been prepared by Husemann and Reinhardt,[2] who used the modified Koenigs-Knorr method of Bredereck and co-workers[3] wherein a carbohydrate trityl ether is treated with an acetobromo sugar in the presence of silver perchlorate. The synthesis in this laboratory[4] of 1-acrylamido-1-deoxy-D-glucitol (*N*-acryloyl-D-glucamine) has provided a sugar-substituted acrylamide which has now been shown to undergo reaction, through its activated double bond, with the hydroxyl groups in the linear polysaccharide, corn amylose. The product of the reaction is an *N*-substituted carbamylethylamylose to which the trivial name "glucamidoethylamylose" is given.

In preliminary investigations *N*-acryloyl-D-glucamine reacted with a dispersion of amylose in dilute sodium hydroxide solution. Base concentrations between 0.1 and 1.0*M*, temperatures between 50° and 100° and reaction periods between one half and twelve hours were investigated for mixtures containing one mole of *N*-acryloyl-D-glucamine per D-glucose residue of the amylose. Maximum incorporation of nitrogen to 0.85% *N*, or a molar substitution[5] of 0.12, occurs without the appearance of carboxyl groups in 0.3*M* base at 70° for two hours. An increase in either base strength, temperature, or time brings about partial hydrolysis of amide linkages. Since amylose is not readily soluble in 0.3*M* sodium hydroxide solution, the reaction mixture is not always completely homogeneous. Dissolution of the amylose in 10*M* lithium chloride solution provides a homogeneous reaction mixture, and at the same time reduces the amount of water available for hydrolysis of amide bonds. Consequently, base concentrations up to 0.6*M* in 10*M* lithium chloride solution may be used without the appearance of carboxyl groups in the product. Nitrogen contents up to 2.15%, corresponding to an M.S.[5] of 0.39, are obtained when four moles of *N*-acryloyl-D-glucamine are treated per D-glucose residue of the amylose in this manner.

Fractionation of glucamidoethylamylose on the basis of its solubility in water-ethanol mixtures gives rise to fractions having different nitrogen contents (Table I). As the concentration of ethanol is increased, fractions containing an increasing amount of nitrogen are obtained. The fractions are soluble in water, and their solubility increases with increasing amounts of substitution.

---

(1) Presented before the Division of Cellulose Chemistry at the 138th Meeting of the American Chemical Society, New York, September 1960; Journal Paper No. 1689 of the Purdue Agricultural Experiment Station.

(2) E. Husemann and M. Reinhardt, *Angew. Chem.*, **71**, 429 (1959); Abstracts of Papers, 138th Meeting, American Chemical Society, September 1960, 8D.

(3) H. Bredereck, A. Wagner, G. Faber, H. Ott, and J. Rauther, *Chem. Ber.*, 92, 1135 (1959).

(4) R. L. Whistler, H. P. Panzer, and H. J. Roberts, *J. Org. Chem.*, 26, 1583 (1961).

(5) Molar substitution (M.S.) is defined as the number of moles of substituent introduced per D-glucose residue.

TABLE I

FRACTIONATION OF GLUCAMIDOETHYLAMYLOSE

Fraction No.[a]	Ethanol Concentration Range Where Precipitation Occurred, % V/V	Yield[b] G./G. Amylose	Nitrogen %	Nitrogen M.S.
1-1	35–40	0.69	1.35	0.20
1-2	40–50	0.21	1.85	0.31
1-3	50–60	0.30	2.73	0.58
2-0	—	—	2.15	0.39
2-1	35–40	0.68	1.75	0.29
2-2	40–50	0.88	2.19	0.40
2-3	50–60	0.10	3.23	0.82

[a] Fractions 1-1, 1-2, and 1-3 are from glucamidoethylamylose prepared with 0.4*M* base in 10*M* lithium chloride solution. The other fractions are from a preparation in which 0.6*M* base was used. Fraction 2-0 is the material from the latter preparation prior to fractionation. None of the fractions contain carboxyl groups. [b] Grams of product per one gram of amylose.

Glucamidoethylamylose fractions 2-1 and 2-2 (Table I) are compared with amylose in tests for retrogradation, butanol complexing ability, iodine binding capacity, and susceptibility to both acid and enzyme hydrolysis.

The tendency of amylose solutions to retrograde is well known. Glucamidoethylamylose fractions unlike amylose[6] are not precipitated by 1-butanol.

Solutions of glucamidoethylamylose give a blue color with iodine. However, when they are titrated with iodine potentiometrically, no inflection is observed in the plot of E.M.F. versus amount of iodine added. In this respect glucamidoethylamylose resembles amylopectin. The wave length of maximum absorption (λ_{max}) and the intensity of the glucamidoethylamylose-iodine color lie between the corresponding values for amylose and amylopectin. Thus, the absorbance of 0.005% solutions at λ_{max} for amylose-, glucamidoethylamylose-, and amylopectin-iodine colors are 0.905 at 630 mμ, 0.180 at 590 mμ, and 0.072 at 565 mμ, respectively. Husemann and Reinhardt[2] report that their sugar-substituted amyloses give no color with iodine above a degree of substitution (D.S.) of 0.2, and yellow to red-brown colors when the D.S. is lower.

A marked difference exists between the abilities of amylose and glucamidoethylamylose to serve as substrates for the enzyme β-amylase. Glucamidoethylamylose fractions are hydrolyzed much less extensively than is amylose. On the other hand, α-amylase hydrolyzes amylose and glucamidoethylamylose fractions to the same extent (Table III).

TABLE II

RETROGRADATION OF AMYLOSE AND GLUCAMIDOETHYLAMYLOSE FRACTIONS

Polysaccharide	Concentration of Solution Before Test, %	Concentration of Solution After Test, %	Remarks
Amylose	0.50	0.015	Heavy white precipitate
Fraction 2-1	0.49	0.50	Trace of precipitate
Fraction 2-2	0.51	0.51	No precipitate

TABLE III

ACTION OF α- AND β-AMYLASE ON AMYLOSE AND GLUCAMIDOETHYLAMYLOSE FRACTIONS

Milligrams of Reducing Sugars as Maltose

Polysaccharide	Per 100 Mg. of Substrate α-Amylase	Per 100 Mg. of Substrate β-Amylase	Per 162 Mg. of Amylose α-Amylase	Per 162 Mg. of Amylose β-Amylase
Amylose	31.8	77.1	51.5	125.
Fraction 2-1	25.4	2.6	49.3	5.9
Fraction 2-2	20.3	2.8	51.9	7.1

The rates of hydrolysis of amylose and glucamidoethylamylose in dilute sulfuric acid solution, as measured by the change in reducing power of the solutions, are similar. However, the extent of hydrolysis appears to be somewhat less in the case of glucamidoethylamylose. Thus, after two and a half hours in 1.4*N* sulfuric acid at reflux temperature the hydrolyses are nearly complete. The dextrose equivalents of the hydrolyzates indicate 86% conversion for amylose, but only 60% and 78% for the two glucamidoethylamylose fractions. A reaction between reducing groups of the sugars and free amino groups from the hydrolysis of amide linkages might explain the apparent difference.

Three courses for the reaction between amylose and *N*-acryloyl-D-glucamine may be envisaged. Homopolymerization of *N*-acryloyl-D-glucamine through a reaction between one of the hydroxyl groups of the D-glucamine moiety and the double bond, with no participation of the amylose, would result in a mixture of amylose and homopolymer. Homopolymerization with accompanying reaction of hydroxyl groups on the amylose molecule would result in the grafting of extended branches onto the amylose chain. Reaction between hydroxyl groups on the amylose molecule and *N*-acryloyl-D-glucamine without homopolymerization would result in single-unit substitution. That the amylose does react is demonstrated by performance of the reaction in the absence of amylose and, after neutralization, addition of amylose in a solution of 10*M* lithium chloride. Precipitation of this known mixture by methanol results in a product which contains 0.94% nitrogen, an apparent M.S. of 0.13. However, this mixture is not soluble in water, whereas glucamidoethylamylose preparations having a M.S. greater than 0.1 are water soluble.

(6) T. J. Schoch, *J. Am. Chem. Soc.*, **64**, 2957 (1942).

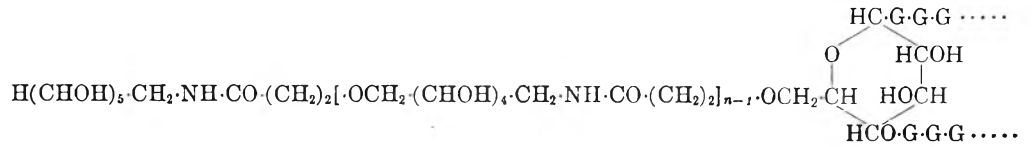


Fig. 1. Suggested repeating unit of glucamidoethylamylose. G = anhydro-D-glucose unit; n = average branch length

These results support a course of reaction involving concurrent homopolymerization and substitution.

Several additional facts indicate that substitution of amylose occurs. No amylose is detected in glucamidoethylamylose by potentiometric iodine titration. Very little reducing sugar is obtained when glucamidoethylamylose is subjected to the action of β-amylase, while α-amylase hydrolyzes glucamidoethylamylose and amylose to the same extent. No amylose is obtained from solutions of glucamidoethylamylose by retrogradation or upon butanol precipitation.

The variation in composition of glucamidoethylamylose fractions (Table I) is consistent with a course of reaction involving concurrent homopolymerization and substitution. In this homogeneous reaction the number of hydroxyl groups substituted should be the same for each amylose molecule, but the nitrogen content of the substituted molecules will depend upon whether the substituent is a polymer chain or a single *N*-acryloyl-D-glucamine molecule. The isolation of fractions of glucamidoethylamylose which range in M.S. from 0.20 to 0.82 (Table I) is thus explainable on the basis of a distribution of branch lengths. A glucamidoethylamylose molecule in agreement with these observations would consist of an amylose main chain with grafted poly(1-deoxy-1-β-oxypropionamido-D-glucitol) branches (Fig. 1).

One measure of the average branch length, n, is the ratio M.S./D.S. It might be expected that the D.S. of a glucamidoethylamylose fraction could be obtained by alkaline hydrolysis of all amide linkages and determination of the carboxyl groups in the resultant carboxyethylamylose salt. However, when conditions sufficiently vigorous to give a nitrogen-free product are used, the product is also devoid of carboxyl groups. It is suggested that, as is the case with the closely related Michael reaction,[7] the reaction of *N*-acryloyl-D-glucamine with a hydroxyl group is reversible, and that an excess of base favors the reverse reaction. As a result, treatment of glucamidoethylamylose with strong base merely regenerates the amylose.

The D.S. of a glucamidoethylamylose fraction may also be obtained by measurement of the ratio of carboxyethyl-D-glucose to D-glucose in an acid hydrolyzate. Quantitative paper chromatography indicates a ratio of 1:50 in glucamidoethylamylose fraction 2-1. The average branch length, n, of this fraction is thus 0.29/0.02 or 14–15 units.

(7) E. S. Gould, *Mechanism and Structure in Organic Chemistry*, Henry Holt and Co., New York, N. Y., 1959, p. 393.

EXPERIMENTAL

Amylose. Defatted corn starch was fractionated by the butanol method of Schoch.[6] The butanol-amylose complex was recrystallized from butanol-water three times. The amylose was obtained by treatment of the purified complex first with acetone and then with absolute ethanol. Ethanol was finally removed under reduced pressure in the presence of calcium chloride. The product was a fine, white powder.

1-Acrylamido-1-deoxy-D-glucitol. 1-Acrylamido-1-deoxy-D-glucitol (*N*-acryloyl-D-glucamine) was synthesized from acryloyl chloride and D-glucamine as described earlier.[4]

Glucamidoethylamylose. A solution of amylose in 10*M* lithium chloride was prepared by addition of 10 ml. of the lithium chloride solution per g. of polysaccharide, followed by stirring for 15–20 min. at 70°. The solution was blanketed with nitrogen. In this solution 4 mmoles of *N*-acryloyl-D-glucamine per 162 mg. of amylose was then dissolved, and sufficient 10*M* sodium hydroxide solution was added to give the desired base concentration (0.4 or 0.6*M*).[8] Stirring was continued at 70° for 2 hr., with the nitrogen atmosphere maintained. The reaction mixture was diluted with water and neutralized to phenolphthalein with acetic acid. Hydrochloric acid was added to *p*H 2, and the solution was poured into 5–6 volumes of methanol. After 2 hr. the turbid supernatant liquid was poured off and discarded, and the white precipitate either redissolved in water for fractionation (see below) or washed free from lithium chloride with methanol, washed once with anhydrous ether, and dried under reduced pressure in the presence of phosphorus pentoxide.

Fractionation of glucamidoethylamylose. An aqueous solution of glucamidoethylamylose was prepared using 100 ml. of water for each g. of amylose present. Ethanol, 99.5%, was added slowly with stirring until a precipitate was visible. There was no precipitate up to an ethanol concentration of 35% by volume. At 40% ethanol the suspension was centrifuged to yield the first fraction. Second and third fractions were obtained similarly at ethanol concentrations of 50% and 60%, respectively. No additional precipitate formed up to an ethanol concentration of 80%.

Analyses. Nitrogen analyses were performed according to a micro-Kjeldahl technique.[9]

A semimicro potentiometric titration was devised for the determination of carboxyl groups. A 20–50-mg. sample was dissolved, by heating on a steam bath if necessary, in 10*M* lithium chloride solution previously adjusted to *p*H 5.5–6.0. This solution was diluted to 5 ml. with water and titrated with 0.01*M* sodium hydroxide in 5*M* lithium chloride

(8) In the preliminary experiments the amylose and *N*-acryloyl-D-glucamine were triturated with a solution of sodium hydroxide of the desired concentration (0.3 to 1.0*M*) until a smooth dispersion was obtained. For each g. of amylose 12.5 ml. of base solution was used. The dispersions were then heated with stirring under nitrogen.

(9) *Official Methods of Analysis of the Association of Official Agricultural Chemists*, 7th Edition, Association of Official Agricultural Chemists, Washington, D. C., 1950, p. 745.

solution using a Radiometer automatic titration apparatus.[10] The titer was read from the inflection point on the titration curve and corrected by subtraction of the volume of base required to reach the same *p*H in a blank titration. The base was standardized by titration of 3–5-ml. aliquots of a standard solution of 0.01*M* potassium hydrogen phthalate mixed with 5 ml. of 10*M* lithium chloride solution. By this method it was possible to determine carboxyl groups in the concentration range 0.1–1% CO_2. The method is also applicable, by adjustment of sample size, to other acidic polysaccharides. Carboxymethylcellulose and two hemicelluloses have been titrated in this manner. Carboxyl contents of the hemicelluloses were identical with the values obtained by the decarboxylation method of Whistler, Martin, and Harris.[11]

Retrogradation. A solution of 250 mg. of glucamidoethylamylose in 50 ml. of 0.5*M* potassium chloride was refrigerated for 5 days at about 4°. A solution of 250 mg. of amylose in 25 ml. of 1*M* potassium hydroxide was neutralized with an equal volume of 1*M* hydrochloric acid and similarly refrigerated. The change in concentration was determined by measurement of the optical rotation of solutions after centrifugation. The specific rotations, $[\alpha]_D^{25}$, of glucamidoethylamylose fractions 2-1 and 2-2 were found to be +140° (*c*, 2.64 in water) and +121° (*c*, 2.41 in water), respectively. The specific rotation of amylose is about +200°.[12]

Iodine sorption. The potentiometric titration method of Bates, French, and Rundle[13] as modified by Wilson, Schoch, and Hudson[14] was used.

The absorption spectra of the polysaccharide-iodine colors were obtained by treatment of amylose, glucamidoethylamylose, and amylopectin according to the method of McCready and Hassid[15] and measurement, at a concentration of 0.005% polysaccharide, with a Cary recording spectrophotometer[16] in 1-cm. cells.

Enzymic hydrolysis. The amylase assay of Kneen and Sandstedt[17] was adapted as follows. Glucamidoethylamylose substrates were prepared by the dissolution of 500 mg. of the polysaccharide in 20-ml. portions of 0.5*M* potassium chloride solution, the addition of 1 ml. of acetate buffer,[17] and dilution to 25 ml. with distilled water. Amylose substrate was prepared by allowing 500 mg. to dissolve in 10 ml. of 1*M* potassium hydroxide solution under nitrogen at 4°, and adding 1 ml. of acetate buffer and 4 ml. of water. Immediately before use the amylose solution was neutralized with 10 ml. of 1*M* hydrochloric acid. Ten milliliters of each substrate was incubated for 15 min. at 30° with 10 ml. of either of the α- or β-amylase solutions described below. The reaction was stopped by the addition of 10 ml. of 1% sulfuric acid. Five-milliliter aliquots were analyzed for total reducing sugars by a macro version[18] of the alkaline ferricyanide method.[19]

The α-amylase used was prepared from commercial malt amylase. The preparation was heat-treated to destroy all β-amylase activity. By the amylase assay of Kneen and Sandstedt[17] 5 ml. of the enzyme solution converted 137 mg. of corn starch.

The β-amylase solution was prepared from crystalline sweet potato amylase.[20] Five milliliters converted[17] 208 mg. of corn starch.

Acid hydrolysis. One hundred milligrams of polysaccharide, glucamidoethylamylose, or amylose, was dissolved in 2 ml. of 72% sulfuric acid at ice bath temperature. The clear solution was diluted with 30 ml. of water. After removal of 1 ml. for analysis, the remainder was refluxed. Aliquots of 1 ml. were removed periodically for analysis. All aliquots were neutralized with the calculated amount of 1*M* sodium hydroxide solution and diluted to 25 ml. Two-milliliter portions of these dilutions were analyzed for total reducing sugars by the alkaline ferricyanide method.[19,21]

Chromatography. The acid hydrolyzate of glucamidoethylamylose fraction 2-1 was examined qualitatively and quantitatively by chromatography on Whatman No. 1 and No. 3MM papers, respectively. The solvent systems used were neutral, 1-butanol : ethanol:water (40:11:19 v/v); acidic, ethyl acetate:acetic acid:formic acid : water (18:3:1:4 v/v); and basic, ethyl acetate:pyridine:water (8:2:1 v/v). To locate the sugars on the chromatograms the silver nitrate reagent of Trevelyn, Procter, and Harrison[22] was used, but modified by the substitution of a dilute solution of sodium thiosulfate for the ammonium hydroxide. A 2.5% solution of aniline hydrogen phthalate in water-saturated 1-butanol[23] and a 1% solution of ninhydrin in 1-butanol were used to detect reducing sugars and amino sugars, respectively.

In the glucamidoethylamylose hydrolyzate three sugars were found which were not present in an amylose hydrolyzate. One of these sugars traveled more rapidly than D-glucose in the acid solvent but failed to move in the basic solvent. It gave a positive test with aniline hydrogen phthalate and a negative test with ninhydrin. On the basis of the proposed structure (Fig. 1) it is suggested that this sugar is carboxyethyl-D-glucose. Upon elution it was found[21] to be present in $^1/_{50}$th of the concentration of the D-glucose present.

The other two sugars gave negative tests with aniline hydrogen phthalate and positive tests with ninhydrin. One was present in much lower concentration than the other, and this minor component corresponded in $R_{glucose}$ value to D-glucamine in all three solvent systems. The major amino sugar was tentatively assigned the structure of carboxyethyl-D-glucamine.

Acknowledgment. The authors gratefully acknowledge grants from the Corn Industries Research Foundation and from the National Science Foundation which helped support this work.

LAFAYETTE, IND.

(10) Product of Radiometer, Copenhagen, Denmark.

(11) R. L. Whistler, A. R. Martin, and M. Harris, *J. Research Natl. Bur. Standards*, **24**, 13 (1940).

(12) J. A. Radley, *Starch and Its Derivatives*, John Wiley & Sons, Inc., New York, N. Y., 3rd Ed., 1954, Vol. II, p. 364.

(13) F. L. Bates, D. French, and R. E. Rundle, *J. Am. Chem. Soc.*, **65**, 142 (1943).

(14) E. J. Wilson, T. J. Schoch, and C. S. Hudson, *J. Am. Chem. Soc.*, **65**, 1380 (1943).

(15) R. M. McCready and W. Z. Hassid, *J. Am. Chem. Soc.*, **65**, 1154 (1943).

(16) Product of Applied Physics Corp., Pasadena, Calif.

(17) E. Kneen and R. M. Sandstedt, *Cereal Chem.*, **18**, 237 (1941).

(18) R. M. Sandstedt, *Cereal Chem.*, **14**, 603 (1937).

(19) H. C. Hagedorn and B. N. Jensen, *Biochem. Z.*, **135** 45 (1923).

(20) Kindly supplied by Professor A. K. Balls.

(21) F. J. Bates, *Polarimetry, Saccharimetry and the Sugars*, United States Government Printing Office, Washington, D. C., 1942, p. 198.

(22) W. E. Trevelyn, D. P. Procter, and J. S. Harrison, *Nature*, **166**, 444 (1950).

(23) L. Hough, *Methods of Biochem. Anal.*, **1**, 205 (1954).

[CONTRIBUTION FROM PARKE, DAVIS AND COMPANY'S MULTIPLE FELLOWSHIP IN MEDICINAL CHEMISTRY, MELLON INSTITUTE]

Acetylation of D-Ribosylamine[1]

R. STUART TIPSON[2]

Received December 2, 1960

Pure D-ribosylamine and di-D-ribosylamine have been prepared and characterized. Peracetylation of D-ribosylamine affords *N*-acetyl-tri-*O*-acetyl-D-ribosylamine which is de-*O*-acetylated to *N*-β-D-ribopyranosylacetamide. Unimolar acetylation of D-ribosylamine gives the α anomer and a mixture of the α and β anomers of *N*-D-ribopyranosylacetamide.

D-Ribosylamine is a potentially valuable intermediate in the synthesis of *N*-D-ribosylacylamides (*N*-acyl-D-ribosylamines) and other nitrogen-containing D-ribosyl derivatives. A brief description of its preparation was given by Levene and LaForge[3] in 1915. Their material had an analysis (% N) agreeing with that calculated for a pentosylamine and was a satisfactory intermediate in syntheses; for it, they recorded m.p. 137–138° dec. Later, Levene and Clark[4] mentioned that, if the initial components of the reaction mixture are dry, the yield of D-ribosylamine is 90–95% of the theoretical, but, if moist reagents are used, "the resulting product contains a certain proportion of" di-D-ribosylamine. On repeating the preparation, under conditions as close as possible to those described by Levene and LaForge,[3] it is now found that D-ribosylamine is, indeed, formed in high yield, but its melting point does not agree with that recorded by them; instead, their melting point is that of crude di-D-ribosylamine. Presumably, during the course of their "purification" for determination of melting point, they had unwittingly converted it, in part at least, to di-D-ribosylamine, a transformation readily accomplished. Precise directions for the preparation of both D-ribosylamine and di-D-ribosylamine are now given, together with a description of some of their properties.

Peracetylation of D-ribosylamine affords a crystalline *N*-acetyl-tri-*O*-acetyl-D-ribosylamine which, on de-*O*-acetylation, gives an *N*-acetyl-D-ribosylamine (*A*). On unimolar acetylation of D-ribosylamine in water,[5] the amino group is acetylated (in preference to one or more of the hydroxyl groups). Two fractions (*B* and *C*), each of which had an analysis corresponding to that for an *N*-acetylpentosylamine, were isolated, but neither had the properties of amide *A*. From the optical rotations, melting points, a study of the infrared absorption spectra, and the results of periodate oxidation of *A*, *B*, and *C*, it was decided that *A* is *N*-β-D-ribopyranosylacetamide, *C* is the corresponding α anomer, and *B* is a mixture of *A* and *C* (approx. 31:69).

Recording of infrared absorption spectra (see Fig. 1) proved particularly useful in this work.[6] The spectra are given here for comparison with those of similar derivatives of other sugars.[7]

EXPERIMENTAL[8]

D-Ribosylamine. D-Ribose (from Hoffmann-La Roche, Inc., Nutley, N. J.) was finely powdered and then dried[9]; its infrared absorption spectrum was recorded (see Fig. 1, 1). In a 250-ml. Erlenmeyer flask, closed by a rubber stopper through which passed a long inlet tube and a short outlet tube (closed by a Drierite tube), was placed 100 ml. (78.2 g.) of absolute methanol, and the assemblage was weighed. With cooling to about 5° in an ice water bath, ammonia gas (20 to 22 g.) was passed in, from a cylinder, through an empty, reversed Drechsel bottle. The stopper and tubes were then removed, 100 g. of dry, finely powdered D-ribose was rapidly added, and the flask was quickly stoppered. On gentle swirling, the D-ribose gradually dissolved and the solution became colder; after 15 min. of swirling, the sugar had all dissolved to a straw-yellow solution. After elapse of a further 30 min., the solution was nucleated with a trace of crystalline D-ribosylamine (prepared on a small scale, in a test-tube experiment), the flask was rapidly stoppered, and the solution was swirled occasionally. After 1 hr., one eighth of the volume consisted of colorless crystals (at the bottom). Crystallization now continued, with the formation of crusts of hard rosettes of needles on the walls; these were scraped off from time to time until no more crusts formed (some 6 days, stoppered, at room temperature). The crystals were then removed by suction filtration (rubber dam), collected and washed with two 20-ml. portions of absolute methanol, pressed dry, and dried[9]; yield, 90.4 g. (91.0%); colorless crystals; m.p. 123–126° dec. (softens at 122°). For purification, the dry compound was finely

(1) The work described herein was completed prior to December 26, 1956.

(2) Present address: Division of Chemistry, National Bureau of Standards, Washington 25, D. C.

(3) P. A. Levene and F. B. LaForge, *J. Biol. Chem.*, **20**, 433 (1915).

(4) P. A. Levene and E. P. Clark, *J. Biol. Chem.*, **46**, 19 (1921).

(5) K. Onodera and S. Kitaoka [*J. Org. Chem.*, **25**, 1322 (1960)] have recently described the *N*-monoacylation of certain unsubstituted glycosylamines by reaction with an acid anhydride in *N*,*N*-dimethylformamide or methanol. D-Ribosylamine is only slightly soluble in these solvents in the cold.

(6) The author is indebted to Dr. Foil A. Miller of the Department of Research in Chemical Physics, Mellon Institute, for recording the infrared spectra.

(7) R. S. Tipson and H. S. Isbell, *J. Research Natl. Bur. Standards*, **65A**, 31 (1961).

(8) Analyses by Mr. C. E. Childs, Research Division, Parke, Davis and Co., Detroit 32, Mich.

(9) At room temperature, over potassium hydroxide pellets in a vacuum desiccator (Desiguard) at 0.1 mm.

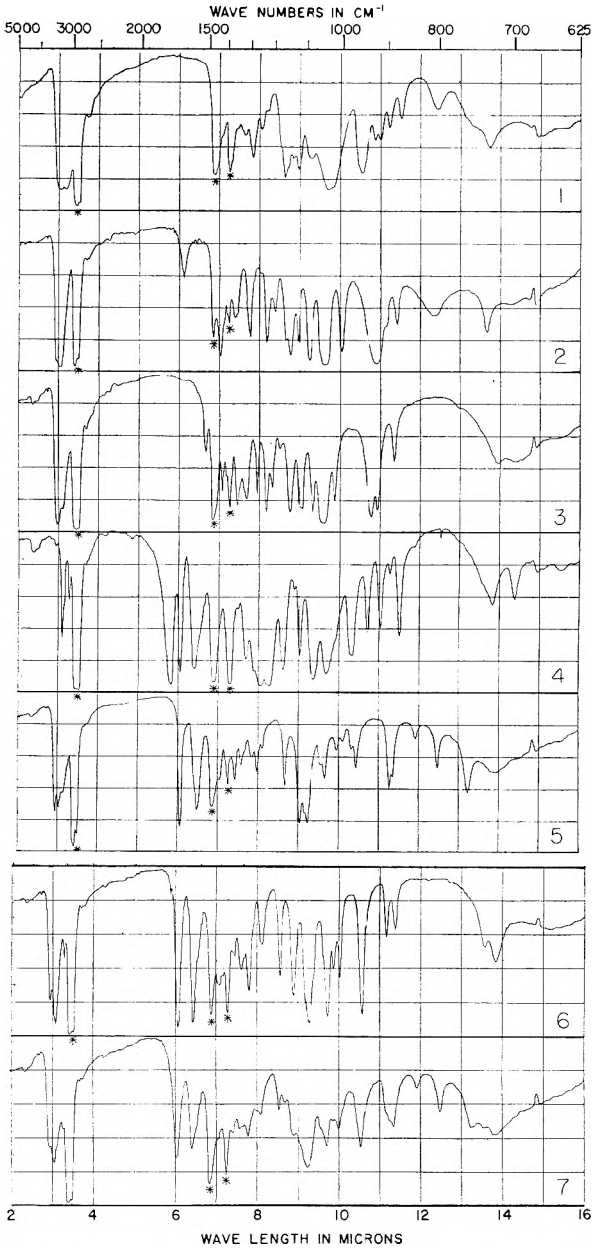


Fig. 1. Infrared absorption spectra of (1) D-ribose, (2) D-ribosylamine, (3) di-D-ribosylamine, (4) *N*-acetyl-tri-*O*-acetyl-D-ribosylamine, (5) *N*-α-D-ribopyranosylacetamide, (6) *N*-β-D-ribopyranosylacetamide, and (7) crystals *B* (of *N*-α- + *N*-β-D-ribopyranosylacetamide). (Asterisks indicate bands of Nujol)

powdered and transferred to a 500-ml. Erlenmeyer flask; absolute methanol (271.2 ml.) was added, the suspension was vigorously swirled mechanically at room temperature for 15 min., filtered with suction (rubber dam), washed with 40 ml. of absolute methanol, and dried as before; wt., 87.0 g. (88%); colorless crystals; m.p. 128–129° dec. (softens at 126°); $[\alpha]_D^{28}$ − 35.3° (2 min.) → −17.4° (43 hr.; *c*, 1.005 in water). Its infrared absorption spectrum was recorded (Fig. 1, 2).

Anal. Calcd. for $C_5H_{11}NO_4$: C, 40.26; H, 7.43; N, 9.39. Found: C, 40.56; H, 7.21; N, 9.27.

D-Ribosylamine is soluble in water or 50% aqueous ethanol. It is practically insoluble in acetonitrile, dioxane, or tetrahydrofuran; slightly soluble in 2-aminoethanol, *N*,*N*-dimethylformamide, *N*-methylpyrrolidone, or pyridine; and, on standing overnight at room temperature, it dissolves to a greater extent in either of the last solvents, or in aqueous tetrahydrofuran.

From the mother liquors (from both the preparation and the purification of D-ribosylamine), colorless, crystalline di-D-ribosylamine could be isolated by evaporation to dryness and treatment with methanol (5 vols.).

Di-D-ribosylamine. A suspension of D-ribosylamine (5 g.) in 50 mol. of absolute methanol was boiled under reflux (boiling stone; Drierite tube) until all of the compound had dissolved (4 hr.); ammonia was liberated. (In a subsequent preparation, the hot solution was filtered at this stage.) On cooling the pale yellow solution, a material crystallized which, on reboiling of the mixture for 1 hr., did not redissolve. The suspension was cooled, stoppered, kept at room temperature for a week, and then filtered with suction (rubber dam); the colorless crystals were washed with absolute methanol, pressed dry, and dried;[9] yield, 2.6 g. (55%); m.p. 142–143° dec. (softens at 136°); $[\alpha]_D^{26}$ − 58.8° (5 min) → −17.2° (53 hr.; *c*, 1.020 in water[10]). Its infrared absorption spectrum was recorded (Fig. 1, 3).

Anal. Calcd. for $C_{10}H_{19}NO_8$: C, 42.70; H, 6.81; N, 4.98. Found: C, 42.59; H, 7.03; N, 5.23.

Impure material, obtained from mother liquors in the preparation of D-ribosylamine, could be purified as follows. The crude di-D-ribosylamine was quickly dissolved, under reflux, in water (2 vols) in a bath at 75°, absolute ethanol (23 vols.) was rapidly added, followed by a small amount of Nuchar, and the hot suspension was immediately swirled and filtered. To the clear, very pale yellow filtrate, absolute ethanol (25 vols.) was added, and the solution was cooled, stoppered, and kept overnight at room temperature; crystallization had then started and was allowed to continue for several days. The purified material was isolated and dried as described above.

N-*Acetyl-tri-O-acetyl-D-ribosylamine.* D-Ribosylamine (7.5 g.) was placed in a 250-ml., three necked flask (equipped with standard-taper joints, stirrer, pentane thermometer, and pressure-equalizing dropping funnel) and was cooled in ice–salt. Dry pyridine (80 ml.) was gradually added with stirring and cooling. As soon as the temperature had reached 2°, slow addition of acetic anhydride (32 ml.) was started from the dropping funnel; addition was made during 30 min., at such a rate that the temperature of the suspension did not rise above 5°. After stirring for a further 50 min., all of the D-ribosylamine had dissolved to a very pale yellow solution which was kept overnight (stoppered) in the refrigerator. The solution was now poured slowly onto crushed ice, with stirring, but no precipitate formed. The clear solution was thoroughly extracted with three successive portions of chloroform. The chloroform extracts were combined, extracted with aqueous sodium bicarbonate solution until free from acid, dried with anhydrous sodium sulfate, filtered, and evaporated to dryness under diminished pressure at 30°, giving 11.2 g. of a pale yellow, flaky glass which crystallized on adding a little dry ether. A total of 112 ml. of dry ether was added, the suspension was stirred, and the colorless crystals were removed by suction filtration, washed with 25 ml. of dry ether, and dried; wt., 9.6 g.; m.p. 128–130°; $[\alpha]_D^{22}$ + 35.3° (*c*, 1.316 in chloroform). Its infrared absorption spectrum was recorded (Fig. 1, 4).

Anal. Calcd. for $C_{13}H_{19}NO_8$: C, 49.21; H, 6.03; N, 4.42; *N*-acetyl, 13.57; *O*-acetyl, 40.70. Found: C, 49.34; H, 6.40; *N*, 4.49; *N*-acetyl, 13.45; *O*-acetyl, 39.10.

De-O-acetylation of N-*acetyl-tri-O-acetyl-D-ribosylamine to* N-β-D-*ribosylacetamide* (*A*). *N*-Acetyl-tri-*O*-acetyl-D-ribosylamine (6 g.) was dissolved in 100 ml. of anhydrous methanol in a 500-ml., round bottomed flask; 10 ml. of 0.1*N* barium methoxide in absolute methanol was added, and the flask was stoppered and kept at room temperature for 1 hr. The solution was then evaporated to dryness under

(10) This determination was made by Miss Beverly A. Pawson.

diminished pressure at room temperature, affording a colorless crystalline mass which was dissolved in 25 ml. of distilled water. The solution was passed through a column (50 ml.) of Amberlite IR-100(H^+), washed in with 25 ml. of water, and the material eluted with five successive 50-ml. portions of water [the final aqueous wash had α − 0.04° (l, 2 dm.)]. The effluents were then passed, in the same order, through a column (50 ml.) of Amberlite IRA-400(OH^-) and six 50-ml. portions of effluent were collected [the final aqueous wash had α − 0.04 to 0.00° (l, 2 dm.)]. The effluents were combined, evaporated to dryness under diminished pressure at 30°, and dried by adding absolute ethanol and reevaporating. The resulting colorless, crystalline mass was dried at 0.1 mm.; wt., 3.6 g. This was dissolved in 117 ml. of boiling absolute ethanol under reflux, and the solution was cooled, affording colorless crystals (*A*); wt., 2.4 g.; m.p. 195–197°; $[\alpha]_D^{21}$ − 23.4° (c, 1.006 in water) with no observable mutarotation—when diluted 1:10 with water, this solution gave no peaks in the ultraviolet and no change was observed after 42 hr. at room temperature. Periodate oxidation at *p*H 7.2 indicated that compound *A* had a pyranoid structure.[11] Its infrared absorption spectrum was recorded (Fig. 1, 6).

Anal. Calcd. for $C_7H_{13}NO_5$: C, 43.98; H, 6.85: N, 7.33; *N*-acetyl, 22.51. Found: C, 44.55; H, 6,85; N, 7.51; *N*-acetyl, 22.25.

"Unimolar" acetylation of D-*ribosylamine.* Glacial acetic acid (19 ml.) and 19 ml. of distilled water were placed in a 500-ml., round bottomed flask and cooled in ice to 4°. D-Ribosylamine (7.5 g., 0.05 mole) was added and the suspension was swirled and cooled; the temperature rose to 13° and then rapidly fell to 9°. Acetic anhydride (7 ml., 0.075 mole) was now added in one portion and the mixture was swirled; no rise in temperature occurred. The cooling bath was removed and, after the mixture had been swirled for 20 min., the D-ribosylamine had all dissolved; evaporation under diminished pressure (bath temp., 30°) was immediately started and, after 35 min., a yellow sirup resulted which was immediately dried at 0.1 mm., giving (after 30 min.) a colorless, crystalline mass which was processed within 3 hr. (if not used immediately, it was refrigerated). This material was dissolved in 100 ml. of distilled water, passed through a column of 300 ml. of mixed anion- and cation-exchange resin (Amberlite MB-3, which had previously been cautiously back-washed with just enough water to remove air bubbles), and eluted with water. The first 100 ml. of effluent was evaporated to dryness and dried at 0.1 mm., giving a colorless crystalline mass (*M*), wt., 2.0 g. The next five 100-ml. effluents were combined, evaporated, and dried at 0.1 mm., giving a clorless, crystalline mass (*N*), wt., 5.4 g. The next eight 100-ml. effluents were combined, evaporated, and dried at 0.1 mm., giving a colorless mixture of sirup and crystals (*P*), wt., 1.7 g. Crystals *M* were suspended in 20 ml. of absolute ethanol and boiled under reflux; the suspension was cooled, refrigerated, and filtered, giving colorless crystals *B*, wt., 1.2 g., m.p. 172–174°, $[\alpha]_D^{23}$ +5.1° (c, 1.170 in water). Its infrared spectrum was recorded (Fig. 1, 7).

Anal. Calcd. for $C_7H_{13}NO_5$: C, 43.98; H, 6.85; N, 7.33; *N*-acetyl, 22.51. Found: C, 43.83; H, 6.79; N, 7.47; *N*-acetyl, 22.28.

Crystals *N* were treated with 54 ml. of absolute ethanol as for crystals *M*, giving colorless crystals *B*, wt., 3.2 g., m.p. 172–174°, $[\alpha]_D^{23}$ + 5.6° (*c*, 1.072 in water). Its infrared absorption spectrum was identical with that of the first crop of *B*.

Anal. Found: C, 43.92; H, 6.96; N, 7.29.

Crystals *P*, treated with 10 volumes of absolute ethanol, as above, gave colorless crystals *C*, wt., 0.3 g., m.p. 198–200° (dec., softening and browning at 195°); $[\alpha]_D^{23}$ +17.8° (*c*, 1.013 in water). Its infrared spectrum was recorded (Fig. 1, 5). Periodate oxidation at *p*H 7.2 indicated that materials *B* and *C* had a pyranoid structure.[11]

Anal. Found: C, 43.23; H, 6.73, N, 7.04; *N*-acetyl, 20.34.

PITTSBURGH 13, PA.

(11) The author thanks Dr. Calvin L. Stevens for this determination.

[CONTRIBUTION FROM THE MIDWEST RESEARCH INSTITUTE]

Interaction of Alkoxysilanes and Acetoxysilanes[1]

W. J. HAGGERTY, JR., AND L. W. BREED

Received May 6, 1960

In the presence of Lewis acid catalysts, mixtures of ethoxysilanes and acetoxysilanes give good yields of ethyl acetate. Thermal decomposition of the acetoxysilane with the intermediate formation of acetic anhydride does not have a role in the formation of the ethyl acetate. Ferric chloride was a satisfactory catalyst at temperatures as low as 130° while low yields of ethyl acetate were obtained from other catalysts, aluminum isopropylate, *p*-toluenesulfonic acid, and sodium methoxide. Although extensive redistribution of silicon-attached functional groups and cleavage of silicon-phenyl bonds occurred at elevated temperatures in the presence of acid catalysis, a transesterification reaction also took place under these conditions.

Transesterification reactions, which have been very successful in the preparation of metallosiloxanes,[2-7] offer a potentially valuable tool for the preparation of siloxanes, provided side reactions

$$R_3SiOAc + R_3'SiOEt \longrightarrow R_3SiOSiR_3' + EtOAc$$

can be avoided. Although O'Brien[8] failed to obtain such a condensation, Henglein[9] and Andrianov[10]

(1) This research was supported in whole or in part by the United States Air Force under Contract AF 33(616)-3675, monitored by the Materials Laboratory, Wright Air Development Division, Wright-Patterson Air Force Base, Ohio.

(2) K. A. Andrianov and L. M. Volkova, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk*, 303 (1957); *Chem. Abstr.*, 51, 14544.

(3) D. C. Bradley and I. M. Thomas, *Chem. & Ind.*, 1231 (1958).

(4) E. F. Gibbs, H. Tucker, G. Shkapenko, and J. C. Park, WADC TR 55-453, Part II (1957), AD 131036.

(5) F. A. Henglein, R. Lang, and K. Scheinost, *Makromol. Chem.*, 15, 177 (1955).

(6) F. A. Henglein, R. Lang, and K. Scheinost, *Makromol. Chem.*, 18–19, 102; *Chem. Abstr.*, 51, 2576 (1956).

(7) F. A. Henglein, R. Lang, and L. Schmack, *Makromol. Chem.*, 22, 103 (1957).

TABLE I

TRANSESTERIFICATION REACTION

Run No.	1	2	3	4	5	6	7	8	9	10
p-Phenylenebis(dimethylethoxysilane) (mole)			0.05							0.088
p-Phenylenebis(diethoxymethylsilane) (mole)	0.029	0.029		0.015	0.015	0.015	0.15	0.15	0.15	
Acetoxytrimethylsilane (mole)			0.10							0.18
Methyltriacetoxysilane (mole)	0.039	0.039		0.020	0.020	0.020	0.20	0.20	0.20	
Catalyst (g.)	0.3		1.0	0.15	0.15	0.15	0.15	0.15	0.15	0.75
	Al-(O*iso*Pr)$_3$		H_2SO_4	Al-(O*iso*Pr)$_3$	Al-(O*iso*Pr)$_3$	Al-(O*iso*Pr)$_3$	$FeCl_3$	*p*-Toluenesulfonic acid	$NaOCH_3$	$FeCl_3$
Temperature	160°	160°	25°	100°	120°	140°	130°	145°	145°	140°
Time, hr.	26	24	15	20	20	20	20	20	20	20
Volatiles recovered (g.)	6.0	1.7	1.7	0.10	0.50	0.80	4.6	0.6	1.0	19.0
Gas chromatography Analysis of volatiles										
					(% Peak Area)					
Ethanol	6.7	17.2	2.1		3.6	2.6	10.1	12.7	2.4	Trace
Ethyl acetate	88.1	80.0	12.8		10.0	64.0	86.9	82.2	90.5	19.4
Isopropyl acetate	5.1				Trace	Trace				
Acetic acid		1.0	3.8					5.1		Trace
Acetoxytrimethylsilane			10.3							4.3
Hexamethyldisiloxane			20.1[a]							12.2[a]
Ethoxytrimethylsilane			50.3							64.1
Ethyl ether			0.5				3.0		3.9	
Cyclohexane					86.4[b]	33.4[b]				
Unknown									3.2	

[a] Analysis of the trimethylacetoxysilane indicated it contained an equivalent amount of hexamethyldisiloxane. [b] Aluminum isopropylate was introduced in cyclohexane solution.

have reported successful condensations when Lewis acids were used as catalysts. The use of such catalysts can be expected to initiate important competing reactions, since it is well known that they catalyze redistribution of functional groups in silicon-functional compounds,[11] redistribution of siloxane linkages,[12] and at higher temperatures cause significant silicon-phenyl cleavage.[13]

DISCUSSION

A study of the effects of temperature and catalyst in the transesterification reaction is shown in Table I.

Under the conditions described by Henglein[9] (Run No. 3), the chief product was ethoxytrimethylsilane when *p*-phenylenebis(dimethylethoxysilane) and acetoxytrimethylsilane reacted in the presence of sulfuric acid. Only a small amount of ethyl acetate was formed in the reaction. When low boiling silanes could distill from the mixtures, redistribution predominated and very little ethyl acetate was recovered. Under conditions that allow the ester to be fractionally distilled from the mixture without removing any of the possible silicon-containing products, the transesterification reaction gave good yields of ethyl acetate, but the resulting silanes were derived from the complex redistribution products rather than the starting materials.

In attempts to prepare *p*-phenylenebis(1,1,3,3-tetramethyl - 3 - phenyldisiloxane) (I), methyltris(dimethylphenylsiloxy)silane (II), and phenyltris(dimethylphenylsiloxy)silane (III), only pure I was obtained in any significant yield, and this experiment represented the simple case of the reaction of a difunctional and a monofunctional silane. Substitution of phenyl for methyl did not give a less complex product in the preparation of III over II. Neither did the more thermally stable monoacetoxysilane with a triethoxysilane permit less redistribution than the triacetoxysilane and monoethoxysilane in the preparation of III.

The similarity between the ethyl acetate elimination reaction and the well known ethyl chloride elimination between a silicon chloride and a silicon ethoxide[14-16] is shown in the experimental section.

(8) J. F. O'Brien, WADC TR 57-507 (Oct. 1957). AD 142,100.

(9) F. A. Henglein and R. Schmulder, *Makromol. Chem.*, **13**, 53 (1954).

(10) K. A. Andrianov, N. N. Sokolov, and E. N. Khrustaleva, *J. Gen. Chem., U.S.S.R.*, 26, 1249 (1956).

(11) C. Eaborn, *Organosilicon Compounds*, Academic Press Inc., New York, 1960, pp. 187, 317.

(12) C. Eaborn, *Organosilicon Compounds*, Academic Press Inc., New York, 1960, p. 260.

(13) C. Eaborn, *Organosilicon Compounds*, Academic Press Inc., New York, 1960, p. 155.

(14) G. H. Wagner and C. E. Erickson, U. S. Patent **2,731,485** (Jan. 17, 1956); *Chem. Abstr.*, 50, 8247 (1956).

TABLE II

ALKYL AND ARYLACETOXYSILANES

Compound	B.P., Mm.	M.P.	Yield, %	n_D^{25}	d_4^{25}
Acetoxytrimethylsilane[17]	101–105	—	72	1.3899	0.879
Diacetoxydimethylsilane[18]	54–56 (7)	—	52	1.4020	1.050
Methyltriacetoxysilane[18]	107–109 (16)	26	61	1.4068	1.174
Tetraacetoxysilane[18]	—	108	21	—	—
Acetoxydimethylphenylsilane[19]	127–130 (44)	—	66	1.4868	1.005
Phenyltriacetoxysilane[20]	118 (0.10)	34	59	1.4738[a]	1.184[a]

[a] Super-cooled liquid.

Nearly identical yields of I and 1,3-diphenyltetramethyldisiloxane are obtained from the reaction of acetoxydimethylphenylsilane and *p*-phenylenebis(dimethylethoxysilane) and from chlorodimethylphenylsilane and *p*-phenylenebis(dimethylethoxysilane). The same result was observed in the two possible methods of preparing III.

In none of the experiments was acetic anhydride found as a volatile component of the product as might be expected from the mechanism proposed by Andrianov. He suggested that polymerization occurs through the thermal decomposition of the silicon acetates with the formation of siloxanes and acetic anhydride which, in turn, reacts with the alkoxysilane to give an ester and additional acetoxysilanes. In the presence of ferric chloride, we found that acetoxydimethylphenylsilane gave some acetic acid and acetic anhydride at 160°, but considerably less than the amount necessary to account for the ethyl acetate formed in the presence of alkoxysilanes.

The transesterification reaction is complicated by the cleavage of silicon-phenyl bonds, with the liberation of up to 8% of the available phenyl groups. A comparable amount of benzene was obtained by the action of ferric chloride on acetoxydimethylphenylsilane.

EXPERIMENTAL

In the experiments, reaction temperatures were determined by a thermometer inserted in the wall of the flask. The volatiles were allowed to distill through a short Vigreux column and were collected in a Dry Ice trap.

The composition of the volatiles wes estimated with a Perkin-Elmer Model 154B Vapor Fractometer using column "A" (diisodecyl phthalate) at 75°. All yields calculations from vapor phase chromatographic analyses were based on percentage of peak area.

Acetoxydimethylphenylsilane. To a stirred mixture of 37.0 (0.46 mole) of pyridine, 72.0 g. (0.42 mole) of chlorodimethylphenylsilane, and 250 ml. anhydrous ether was added dropwise a solution of 25.0 g. (0.42 mole) glacial acetic acid in 75 ml. of ether. When the addition was complete (4.5 hr.), the reaction mixture was stirred for an additional hour, the pyridine hydrochloride salts were removed by filtration, and the residue was washed with a little anhydrous ether. After the combined filtrate and ether washings were concentrated by downward distillation, fractional distillation of the product through a 10-in. column packed with Berl saddles gave 53.1 g. acetoxydimethylphenylsilane.

Anal. Calcd. for $C_{10}H_{14}O_2Si$: Si, 14.46, MR_D 55.49. Found: Si, 14.40, 14.33; MR_D 55.63.

The procedure, which follows one described by Étienne[17] for acetoxytrimethylsilane was particularly convenient. Yields and physical constants of the acetoxysilanes prepared by this method are shown in Table II.

p-Phenylenebis(1,1,3,3-tetramethyl-3-phenyldisiloxane). A. From acetoxydimethylphenylsilane and *p*-phenylenebis(dimethylethoxysilane): When a mixture containing 19.4 g. (0.10 mole) acetoxydimethylphenylsilane, 14.2 g. (0.05 mole) *p*-phenylenebis(dimethylethoxysilane),[21] and 0.1 g. of ferric chloride was heated at 140° for 20 hr., 8.5 g. of volatile material was obtained. The volatile components were (percentage of total peak area given): ethyl ether (0.6), ethanol (3.6), ethyl acetate (86.0), and benzene (9.6). The benzene was equivalent to the cleavage of 4.2% of the phenyl group present as acetoxydimethylphenylsilane. About 83% of the expected ethyl acetate was collected.

The nonvolatile portion of the reaction product similarly prepared from 0.90 mole acetoxydimethylphenylsilane and 0.45 mole *p*-phenylenebis(dimethylethoxysilane) was filtered to remove the ferric chloride, diluted with 50 ml. ether, washed three times with water, once with 5% sodium bicarbonate, and once again with water, and stripped to remove the ether. Distillation of the residue gave 54.5 g. (42%) of the redistribution product, 1,3-diphenyltetramethyldisiloxane, boiling 157–157.5° at 13 mm., n_D^{25} 1.5148, d_4^{25} 0.984 (reported[22] b.p. 165° at 17 mm., n_D^{25} 1.5149, d_4^{25} 0.971) and 52.4 g. (22%) *p*-phenylenebis(1,1,3,3-tetramethyl-3-phenyldisiloxane) boiling 179–189° at 0.04–0.05 mm., n_D^{25} 1.5109, d_4^{25} 0.987.

Anal. Calcd. for $C_{26}H_{38}O_2Si_4$: C, 63.05; H, 7.74; Si, 22.70; MR_D 150.60. Found: C, 63.11; H, 7.86; Si, 22.48; MR_D 150.15.

B. From chlorodimethylphenylsilane and *p*-phenylenebis(dimethylethoxysilane): A mixture of 17.1 g. (0.010 mole) of chlorodimethylphenylsilane, 14.1 g. (0.05 mole) of *p*-phenylenebis(dimethylethoxysilane), and 0.1 g. of anhydrous ferric chloride was heated at 100° for 24 hr. A total of 5.0 g. or 93% of the calculated weight was lost. The product, neutralized and washed, was distilled at reduced pressure through a 2-in. column. The following fractions were collected: A, 133–134° (4.5 mm.), 6.6 g., n_D^{27} 1.5129; B, 130–70° (0.05 mm.), 3.3 g. n_D^{27} 1.5162; C, 167–82° (0.05–0.07 mm.), 1.7 g., n_D^{27}

(15) A. Gancberg, U. S. Patent 2,768,152 (Oct. 23, 1956); *Chem. Abstr.*, 51, 10121 (1957).

(16) E. Itsugi and M. Hisazumi, Japanese Patent 3694 (May 19, 1956); *Chem. Abstr.*, 51, 10951 (1957).

(17) Y. Étienne, *Compt. rend.*, 235, 966 (1952).

(18) H. A. Schuyten, J. W. Weaver, and J. D. Reid, *J. Am. Chem. Soc.*, 69, 2110 (1947).

(19) K. A. Andrianov and N. V. Delazari, *Doklady Akad. Nauk S.S.S.R.*, 122, 393 (1958); *Chem. Abstr.*, 53, 2133 (1959).

(20) H. H. Anderson and T. C. Hager, *J. Am. Chem. Soc.*, 81, 1584 (1959).

(21) L. Breed, W. J. Haggery, Jr., and F. Baiocchi, *J. Org. Chem.*, 25, 1804 (1960).

(22) W. E. Daudt and J. F. Hyde, *J. Am. Chem. Soc.*, 74, 386 (1952); *Chem. Abstr.*, 47, 8671 (1953).

1.5156; D, residue 10.5 g. Fraction A corresponded to a 46.1% conversion to 1,3-diphenyltetramethyldisiloxane; fraction C was a 20% yield of crude *p*-phenylenebis(1,1,3,3-tetramethyl-3-phenyldisiloxane).

Phenyltris(dimethylphenylsiloxy)silane. A. From phenyltriacetoxyphenylsilane and dimethylethoxyphenylsilane: A mixture of 30.4 g. (0.169 mole) dimethylethoxyphenylsilane, 15.8 g. (0.056 mole) phenyltriacetoxysilane, and 0.1 g. of ferric chloride was heated for 24 hr. at 145–50°, then an additional 24 hr. at 150–158°. A total of 10.7 g. of distillate, which contained 67% of the expected ethyl acetate along with a small amount of ethyl alcohol and a trace of benzene, was obtained. The residue was dissolved in ether, filtered, neutralized with aqueous sodium bicarbonate, and devolatilized to give 29.4 g. of crude product. Fractional distillation gave 4.3 g. (17.7%) 1,3-diphenyltetramethyldisiloxane boiling 93–100° at 0.03–0.08 mm., n_D^{25} 1.5140, d_4^{25} 0.977, and 4.5 g. impure phenyltris(dimethylphenylsiloxy)-silane boiling 190–240° at 0.02 mm., n_D^{25} 1.529, d_4^{25} 1.076 (reported[23] b.p. 217–225° at 1.0 mm., n_D^{25} 1.528, d_4^{25} 1.060). MR_D Calcd.: 165.48. Found: 160.3.

Many small intermediate fractions indicated that the product was a complex mixture of high molecular weight compounds.

B. From acetoxydimethylphenylsilane and phenyltriethoxysilane: After 29.2 g. (0.15 mole) of acetoxydimethylphenylsilane, 12.0 g. (0.05 mole) of phenyltriethoxysilane, and 0.10 g. of ferric chloride were heated at 160° for 48 hr. and the volatiles collected in a Dry Ice trap, the residue was devolatilized at 0.02 mm. for 2 hr. at room temperature. The final weight loss of the mixture was 10.7 g. or 81% of the theoretical amount. The residue was filtered, diluted with ether, washed and dried in the manner described earlier. Fractional distillation through a 2-in. column gave the following fractions: A, 143–144° (6.2 mm.) 10.5 g., n_D^{27} 1.5124; B, 80–84° (0.02 mm.) 1.2 g., n_D^{27} 1.5131; C, 87–140° (0.02 mm.) 1.0 g.; D, 143–170° (0.03 mm.), 0.8 g. n_D^{27} 1.5176; E, residue, 12.6 g. Fraction A represented a 55% yield of 1,3-diphenyltetramethyldisiloxane, but none of the desired tri(siloxy)silane was isolated.

C. From chlorodimethylphenylsilane and phenyltriethoxysilane: When a mixture of 18.5 g. (0.108 mole) of chlorodimethylphenylsilane, 8.7 g. (0.036 mole) of phenyltriethoxysilane, and 0.1 g. of ferric chloride was heated at 100°, ethyl chloride evolution ceased after 4 hr. The crude product, 20.0 g., represented a loss of 104% of the expected weight. Benzene was identified qualitatively by gas chromatography. The neutralized residue was distilled through a 2-in. column at reduced pressure. The following fractions were collected: A, 134–135° (5.0 mm.) 2.5 g., n_D^{27} 1.5096; B, 130–160° (0.05 mm.), 1.9 g., n_D^{27} 1.5156; C, 170–80° (0.05–0.06 mm.), 1.9 g., n_D^{27} 1.5260, d_4^{27} 1.048; D, residue. 9.0 g. Fraction A corresponds to a 46% conversion to 1,3-diphenyltetramethyldisiloxane and Fraction C to a 9% yield of the tri(siloxy)silane MR_D Calcd.: 165.48. Found: 163.7.

Methyltris(dimethylphenylsiloxy)silane. From methyltriacetoxysilane and dimethylethoxyphenylsilane: When 14.1 g. (0.064 mole) of methyltriacetoxysilane, 34.0 g. (0.192 mole) of dimethylethoxyphenylsilane, and 0.1 g. of ferric chloride were heated for 20 hr. at 160°, a total of 15.5 g. of distillate was collected. The volatiles contained 83.4% of the theoretical ethyl acetate and benzene representing cleavage of 8.0% of the available phenyl groups. After the product was filtered and washed, distillation in a Hickman still gave 9.6 g. (35.2%) of 1,3-diphenyltetramethyldisiloxane, 90–95°, 0.002 mm., n_D^{25} 1.5118, d_4^{25} 0.978, a second fraction boiling 137–42° at 0.0001 mm. (2.3 g.), and 2.9 g. (7%) impure methyltris(dimethylphenylsiloxy)silane boiling 182–200° at 0.0001 mm., n_D^{25} 1.4903, d_4^{25} 1.001.

Anal. Calcd. for $C_{26}H_{36}O_3Si_4$: C, 60.42; H, 7.30; Si, 22.61, MR_D 145.66. Found: C, 58.44; H, 7.45; Si, 25.79; MR_D 143.65.

Thermal decomposition of acetoxydimethylphenylsilane. After 16.6 g. of acetoxydimethylphenylsilane was heated at 160° for 48 hr., the residue was devolatilized for 2 hr. at 0.5 mm. The volatile materials, collected in a Dry Ice trap, weighed 0.1 g. The heating of the residue at 160° was continued for 16 hr. after 0.1 g. of anhydrous ferric chloride was added, and the product was similarly devolatilized. An additional 1.0 g. of distillate was collected and the corresponding weight loss was found in the residue. Analysis indicated that benzene and acetic acid with traces of acetic anhydride and three unidentified components were present. The amount of benzene was equivalent to 7% of the available phenyl groups and the acetic acid to 7% of the available acetoxy groups.

KANSAS CITY 10, MO.

(23) J. F. Hyde, O. K. Johannson, W. H. Daudt, R. F. Fleming, H. B. Laudenslager, and M. P. Roche, *J. Am. Chem. Soc.*, 75, 5615 (1953).

[CONTRIBUTION FROM HUGHES RESEARCH LABORATORIES, HUGHES AIRCRAFT CO.]

Syntheses and Reactions of Isopropoxy and Trimethylsiloxy Titanium Dichelates[1]

H. H. TAKIMOTO[2] AND J. B. RUST

Received October 10, 1960

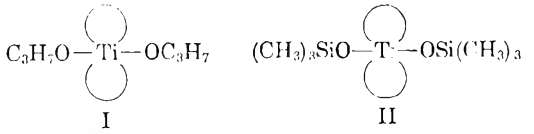
Syntheses and reactions of diisopropoxy and bis(trimethylsiloxy) titanium dichelates are described. The chelating groups are those derived from 1,3-diphenyl-1,3-propanedione, 2,4-pentanedione, and 8-quinolinol. These compounds readily replace the isopropoxy and trimethylsiloxy groups attached to a titanium atom. In cases where both groups are present, the isopropoxy groups are preferentially replaced. Hydrolyses of the dichelated titanium derivatives are also described.

Organotitanium compounds have attracted attention in recent years as intermediates for the possible synthesis of semi-inorganic polymers capable of withstanding high temperatures. The excellent thermal stability of the metal chelates is well known, and because of the interest in thermally stable polymers, particularly in organometalloxanes, we have investigated the preparations and reactions of several dichelated titanium titanium derivatives.

(1) Supported in part by the Office of Naval Research under Contract No. Nonr 2540 (OO).

(2) Hughes Research Laboratories, A Division of Hughes Aircraft Co., Malibu, Calif.

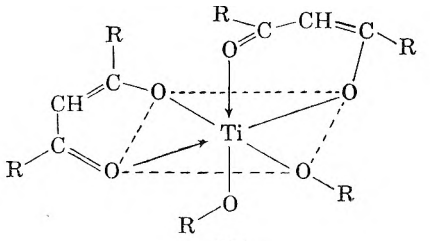
Dichelated titanium intermediates having the following structures were prepared:



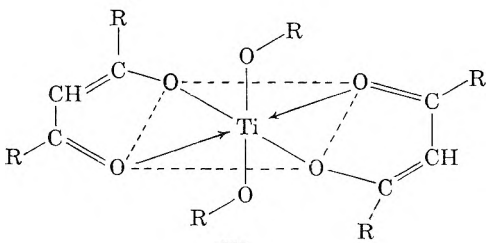
I II

where ◯ represents the chelating group derived from 1,3-diphenyl-1,3-propanedione, 2,4-pentanedione, and 8-quinolinol. Compounds having structures I and II were prepared by the reaction of the chelating agent with tetraisopropoxytitanium or with tetrakis (trimethylsiloxy)titanium, respectively. The use of a stoichiometric amount or an excess of the chelating agent resulted in the formation of the dichelated metal derivatives.

Two diasteroisomeric forms of the dichelated titanium derivatives are possible. When a β-diketone is used as the celating agent, diisopropoxy titanium derivatives may be illustrated as follows:



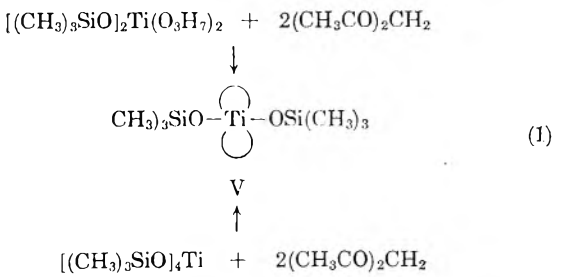
III



IV

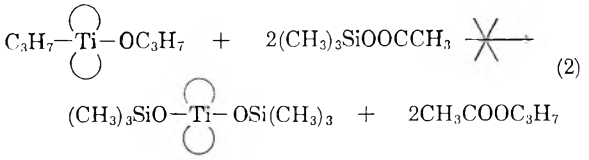
The chelating groups are shown in III to have the *cis* configuration, whereas in IV, they have the *trans* configuration.

It is interesting to note that the chelating agents such as 1,3-diphenyl-1,3-propanedione, 2,4-pentanedione, and 8-quinolinol readily replaced isopropoxy or trimethylsiloxy groups attached to titanium atom. It is of further interest that these chelating groups preferentially replaced isopropoxy groups rather than trimethylsiloxy groups. Thus, an identical product, as determined from infrared spectra and elemental analyses, was obtained from the reaction of two moles of the chelating agent with one mole of diisopropoxy bis(trimethylsiloxy)titanium, or with one mole of tetrakis (trimethylsiloxy)titanium.



(1)

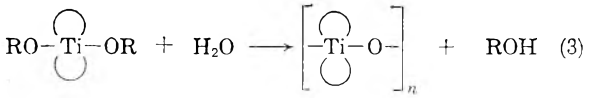
An attempt was made to obtain the siloxy titanium dichelate V by the reaction of diisopropoxy bis(2-ketopent-3-ene-4-oxy)titanium with excess trimethylacetoxysilane.



(2)

The expected ester interchange (alkoxy-acyloxy) reaction, however, did not occur under the conditions used and the desired product, bis(trimethylsiloxy) bis(2-ketopent-3-ene-4-oxy)titanium was not obtained. It may be that the alkoxy-acyloxy condensation reaction is sensitive to the steric environment around the titanium atom. In addition, electrons are not available for association with the trimethylsiloxy group in the transition state; the coordination number of six is already satisfied in the titanium dichelate. These steric and electronic effects are especially evident in view of the fact that tetraisopropoxytitanium readily undergoes the alkoxy-acyloxy reaction with trimethylacetoxysilane to give the trimethylsiloxy titanium derivatives.[3,4]

The hydrolytic stability of the dichelated titanium derivatives was investigated. The compounds containing alkoxy groups were readily hydrolyzed upon contact with moisture and were converted into high-melting solids which were insoluble or only partially soluble in common organic solvents. Thus, bis(quinolin-8-oxy) titanium oxide was obtained by the treatment of diisopropoxy bis(quinolin-8-oxy)titanium with water at room temperature.



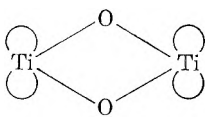
(3)

On the other hand, bis(trimethylsiloxy)bis(quinolin-8-oxy)titanium was recovered unchanged under the same conditions as above. It appears, therefore, that the bis(trimethylsiloxy) derivative of the dichelated titanium is less readily attacked by water

(3) D. C. Bradley and I. M. Thomas, *J. Chem. Soc.*, 3404 (1959).

(4) J. B. Rust, H. H. Takimoto, and G. C. Denault, "Reaction of Trimethylacetoxysilane with Tetraisopropoxytitanium," *J. Org. Chem.*, 25, 2040 (1960).

than the corresponding diisopropoxy titanium compound. Isolation of the tetrachelated product with the dimeric structure (VI) by the hydrolysis of dialkoxy bis(2-ketopent-3-ene-4-oxy)titanium has been reported.[5]



VI

This dimer could result from only one form (III) of the diasteroisomers, since in the other form (IV) the bond angles of the alkoxy groups (or trimethylsiloxy groups) attached to titanium prohibit the formation of the small ring structure. It is possible, however, that a rearrangement of the diasteroisomers may occur under hydrolytic conditions.

Infrared spectra of the dichelated titanium derivatives were taken in carbon tetrachloride. In addition, spectra of tetraisopropoxytitanium and tetrakis(trimethylsiloxy)titanium as well as those of the chelating agents, *viz.*, 1,3-diphenyl-1,3-propanedione, 2,4-pentanedione, and 8-quinolinol, were obtained for comparison purposes.

The spectra of the chelated titanium compounds of the present study all exhibited a strong, sharp absorption band at about 1375 cm.$^{-1}$ Absorption in the region of 1575 cm.$^{-1}$ and at 1520 cm.$^{-1}$ were also observed. The latter two bands were much more pronounced in the chelates prepared from β-diketone than in the 8-quinolinolates. These results agree with those of Yamamoto and his co-worker,[5] who observed two strong bands at 1376 and 1577 cm.$^{-1}$ for trialkoxy-2-ketopent-3-ene-4-oxytitanium with nearly equal intensity and a strong band at 1523 cm.$^{-1}$ Spectra of various metal chelate compounds of 2,4-pentanedione were reported by Lecomte[6] and Bellamy[7] to exhibit two strong bands of nearly equal intensity near 1560 and 1380 cm.$^{-1}$ These investigators attributed these bands to the carbonyl group weakened by resonance between the C—O—M and C—O . . . M links. The band in the region of 1520 cm.$^{-1}$ was attributed by Lecomte to the vibration of C=C bonds of the enolic form of the β-diketone.

Diisopropoxy chelated titanium compounds showed strong broad absorption bands between 1160 and 1110 cm.$^{-1}$ and also in the region of 1000 cm.$^{-1}$ The former bands were assigned to the isopropyl skeletal vibration[8] and the latter may be a result of C—O—Ti linkage.

Chelated titanium compounds containing the trimethylsiloxy groups showed extremely strong absorption bands at about 845 and 1245 cm.$^{-1}$ These bands have been attributed to stretching and rocking vibrations, respectively, of the trimethylsilyl group.[8] The absorption band produced by C=O—Ti linkage in these compounds was shifted to a lower frequency and appeared in the region of 980 cm.$^{-1}$ instead of 1000 cm.$^{-1}$ as in the diisopropoxy titanium dichelates.

EXPERIMENTAL[9]

Materials. Commercially available tetraisopropoxytitanium and 2,4-pentane-dione were purified by fractional distillation and the fractions with b.p. 89–91°/3–4 mm. and 137–139°, respectively, were used: n_D^{25} for tetraisopropoxytitanium, 1.4608; n_D^{25} for 2,4-pentanedione, 1.4480. Commercially available 8-quinolinol melting at 75–76° and 1,3-diphenyl-1,3-propanedione melting at 76.5–78° were used.

The trimethylsiloxy derivatives of titanium were prepared by the reaction of trimethylacetoxysilane with tetraisopropoxytitanium.[4]

Reaction of tetraisopropoxytitanium with 1,3-diphenyl-1,3-propanedione in cyclohexane. 1,3-Diphenyl-1,3-propanedione (4.48 g., 0.02 mole) in 30 ml of cyclohexane was added to tetrisopropoxytitanium (2.84 g, 0.01 mole) dissolved in 15 ml. of cyclohexane. Addition of the β-diketone caused the mixture to turn bright yellow, and a precipitate of a yellow solid was observed; this solid dissolved upon heating. The refluxing was continued for 45 min. and the contents of the flask were allowed to cool to room temperature. A yellow solid again precipitated and was separated by filtration. The product, diisopropoxy bis(1,3-diphenyl-1-ketoprop-2-ene-3- oxy) titanium, weighed 5.73 g. (93.6 % yield) and melted at 170–175° after recrystallization from carbon tetrachloride.

Anal. Calcd. for $C_{36}H_{36}O_6Ti$: C, 70.59; H, 5.92. Found: C, 71.10; H, 5.09.

Reaction of diisopropoxy bis(trimethylsiloxy)titanium with 1,3-diphenyl-1,3-propanedione in cyclohexane. 1,3-Diphenyl-1,3-propanedione (4.48 g., 0.02 mole) in 30 ml. of cyclohexane was added rapidly to diisopropoxy bis(trimethylsiloxy)titanium (3.44 g., 0.01 mole) dissolved in 15 ml. of cyclohexane. The mixture turned yellow when the β-diketone was added, and a yellow solid precipitated after several minutes Upon heating, the solid dissolved (slightly cloudy) and the solution was refluxed for 20 min. A yellow solid formed on cooling. The mixture was filtered to yield 5.58 g. (83 %) of solid melting at 150–163°. Recrystallizations from cyclohexane raised the melting point to 159–165°. The infrared spectrum of this solid taken in carbon tetrachloride was identical with that of the product from the reaction of tetrakis(trimethylsiloxy)titanium with 1,3-diphenyl-1,3-propanedione.

Anal. Calcd for $C_{36}H_{40}O_6TiSi_2$: C, 64.27; H, 5.99. Found: C, 64.59; H, 6.28.

Reaction of isopropoxy tris(trimethylsiloxy)titanium with 1,3-diphenyl-1,3-propanedione. 1,3-Diphenyl-1,3-propanedione (4.48 g., 0.02 mole) was added to isopropoxy tris-(trimethylsiloxy)titanium (3.74 g., 0.01 mole). The colorless clear organotitanium ester became bright yellow when the β-diketone was added. The mixture was gently heated for 30 min., during which time a volatile product was formed. This volatile product (1.43 g.) was removed by heating under reduced pressure. Recrystallization of the residual material from cyclohexane yielded 3.42 g. (50.9 %) of a solid melting at 160–167°. The infrared spectrum of this product taken in carbon tetrachloride was identical with the spectrum of the

(5) A. Yamamoto and S. Kambara, *J. Am. Chem. Soc.*, 79, 4344 (1957).

(6) J. Lecomte, *Disc. Faraday Soc.*, 9, 125 (1950).

(7) L. J. Bellamy and R. F. Branch, *J. Chem. Soc.*, 4491 (1954).

(8) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, 2nd ed., John Wiley & Sons, Inc., New York, 1958, pp. 26 and 274.

(9) All melting points are uncorrected. Microanalyses by Elek Micro Analytical Laboratories, Los Angeles, Calif.

product obtained from the reaction of tetrakiskis(trimethylsiloxy)titanium with 1,3-diphenyl-1,3-propanedione.

Reaction of tetrakis(trimethylsiloxy)titanium with 1,3-diphenyl-1,3-propanedione. 1,3-Diphenyl-1,3-propanedione (4.48 g., 0.02 mole) dissolved in 25 ml. of cyclohexane was added to tetrakis(trimethylsiloxy)titanium (4.04 g., 0.01 mole) dissolved in 10 ml. of cyclohexane. This addition caused the solution to turn yellow and a yellow solid separated out of the reaction mixture. The solid dissolved when heated, and the refluxing was continued for 20 min. Upon cooling to room temperature the entire contents of the flask again became a yellow solid. The mixture was filtered and dried in a desiccator under vacuum to give 6.28 g. (93.5 %) of the product, bis(trimethylsiloxy)bis(1,3-diphenyl-1-ketoprop-2-ene-3-oxy titanium. This material melted at 161–170° after several recrystallizations from cyclohexane.

Anal. Calcd. for $C_{36}H_{40}O_6TiSi_2$: C, 64.27; H, 5.99. Found: C, 64.39; H, 6.06.

Reaction of tetraisopropoxytitanium with 2,4-pentanedione. 2,4-Pentanedione (20.0 g., 0.20 mole) was added to tetraisopropoxytitanium (28.4 g., 0.10 mole). The reaction mixture was heated and stirred for 30 min. to yield a clear, golden solution. The low boiling product was removed under reduced pressure and the residue was fractionated to give 23.67 g. (65 % yield) of diisopropoxy bis(2-ketopent-3-ene-4-oxy)titanium boiling at 138–140°/4–5 mm, n_D^{25} 1.5440. The pale yellow liquid produce turned dark brown on standing.

Reaction of diisopropoxy bis(trimethylsiloxy)titanium with 2,4-pentanedione. 2,4-Pentanedione (2.0 g., 0.02 mole) was added to diisopropoxybis(trimethylsiloxy)titanium (3.44 g., 0.01 mole). The solution turned yellow and heat was evolved. The contents of the flask were heated gently for 1 hr. and the volatile material (1.44 g., n_D^{25} 1.3837) was removed by heating under reduced pressure. Upon cooling, the residual material solidified to a yellow crystalline solid. During the removal of the volatile material, a solid had sublimed on the walls of the flask. This solid melted sharply at 56–57°. The total yield of the crude product, bis(trimethylsiloxy)bis(2-ketopent-3-ene-4-oxy)titanium was 3.75 g. (88.4%). An infrared spectrum of this material was identical with the spectrum of the product obtained from the reaction between tetrakis (trimethylsiloxy)titanium and 2,4-pentanedione.

Anal. Calcd. for $C_{16}H_{32}O_6Si_2Ti$: C, 45.26; H, 7.61. Found: C, 45.20; H, 7.52.

Reaction of tetrakis(trimethylsiloxy)titanium with 2,4-pentanedione. 2,4-Pentanedione (2.0 g., 0.02 mole) reacted with tetrakis(trimethylsiloxy)titanium (4.04 g., 0.01 mole). The mixture became yellow and an evolution of heat was observed. The contents of the flask were heated gently for 30 min. A volatile material refluxed on the walls of the reaction vessel during the heating. At the end of the heating period globules of immiscible liquid were seen at the bottom of the flask. The low-boiling materials (1.79 g.) were removed under vacuum and heat and collected in a Dry Ice trap. Contents of the trap consisted of two phases which were probably water and hexamethyldisiloxane; the by-product of the chelating reaction, trimethylsilanol, would be expected to condense under the reaction conditions to yield these products. The liquid remaining the reaction flask turned into a pale yellow-orange solid upon cooling to room temperature; this solid melted at 54–55° and weighed 3.55 g. (83.7% yield).

Anal. Calcd. for $C_{16}H_{32}O_6Si_2Ti$: C, 45.26: H, 7.61. Found: C, 45.78; H, 7.86.

Reaction of tetraisopropoxytitanium with 8-quinolinol in carbon tetrachloride. A solution of 8-quinolinol (5.80 g., 0.04 mole) in 30 ml. of carbon tetrachloride was added to tetraisopropoxytitanium (5.68 g., 0.02 mole) dissolved in 15 ml. of carbon tetrachloride. The clear, yellow solution was refluxed for 30 min. while stirring, and after standing for 16 hr., a yellow solid had precipitated. The mixture was filtered to yield 5.89 g. (64.9%) of the product, diisopropoxybis(quinolin-8-oxy)titanium. This material, after repeated recrystallizations from either benzene or carbon tetrachloride, melted with decomposition at 170–180°; a volatile product appeared to be evolved at this temperature.

Anal. Calcd. for $C_{24}H_{26}O_4TiN_2$: C, 63.44; H, 5.77. Found: C, 63.70; H, 6.00.

Reaction of diisopropoxybis(trimethylsiloxy)titanium with 8-quinolinol in cyclohexane. A solution of 8-quinolinol (2.90 g., 0.02 mole) dissolved in 30 ml. of cyclohexane was added to diisopropoxybis(trimethylsiloxy)titanium (3.44 g., 0.01 mole) dissolved in 15 ml. of cyclohexane. The mixture turned bright yellow upon the addition of the chelating agent. After refluxing for 20 min., the mixture was allowed to cool to room temperature yielding a bright yellow solid. The mixture was filtered to give a yellow crystalline solid (4.37 g., 85%). This product melted at 144–148° and gave an infrared spectrum identical with the product from the reaction of tetrakis(trimethylsiloxy)titanium with 8-quinolinol.

Anal. Calcd. for $C_{24}H_{30}O_4TiSi_2N_2$: C, 56.02; H, 5.88. Found: C, 54.86; H, 6.11.

Reaction of tetrakis(trimethylsiloxy)titanium with 8-quinolinol in cyclohexane. A solution of 8-quinolinol (2.90 g., 0.02 mole) in 30 ml. of cyclohexane was added to tetrakis(trimethylsiloxy)titanium (4.04 g., 0.01 mole) dissolved in 15 ml. of cyclohexane. The reaction mixture immediately turned bright yellow, and after 10 min. the entire content of the flask was converted into a yellow solid. This solid dissolved on heating, and the solution was then refluxed for 20 min. Upon cooling, the yellow solid again precipitated. The solid was separated and dried under a vacuum in a desiccator to yield 4.69 g. (91 %) of bis(trimethylsiloxy)bis(quinolin-8-oxy)titanium melting at 145–148°.

Hydrolysis of diisopropoxybis(quinolin-8-oxy)titanium. Diisopropoxybis(quinolin-8-oxy)titanium (2.27 g., 0.005 mole) was hydrolyzed by stirring with water (5 ml.) for 30 min. The yellow solid turned orange in color upon contact with water. The mixture was filtered and the solid was washed twice with water and then with benzene, yielding a product which was soluble in chloroform and acetone but insoluble in carbon tetrachloride and benzene. Yellow needles were obtained upon recrystallization of the solid from chloroform, but upon standing for several days, the needles became insoluble in the same solvent. The product did not melt below 300° but turned brown in color at about 280°.

Anal. Calcd. for $C_{18}H_{12}O_3TiN_2$: C, 61.38; H, 3.43. Found: C, 60.26; H, 3.87.

MALIBU, CALIF.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE UNIVERSITY]

Alkylation of Triphenylsilyllithium with Trialkyl Phosphates

HENRY GILMAN AND BERNARD J. GAJ

Received November 22, 1960

High yields of methyl-, *n*-butyl- and isobutyltriphenylsilane were obtained from the equimolar reactions of triphenylsilyllithium with the respective trialkyl phosphates. The 3:1 reaction of triphenylsilyllithium with tri-*n*-butyl phosphate gave *n*-butyltriphenylsilane, hexaphenyldisilane, hexaphenyldisiloxane, 4-triphenylsilylbutanol and triphenylsilanol when forced conditions were employed. A possible mechanism for the formation of these products has been proposed.

In 1915 Michaelis and Wegner,[1] while attempting to prepare the phenyl ester of diphenylphosphinic acid *via* the reaction of phenyl dichlorophosphinate with phenylmagnesium bromide, obtained an unspecified yield of triphenylphosphine oxide. Not only were the chlorine atoms displaced by the Grignard reagent, but the phenoxide group as well. Similar displacements of —O—R groupings from triphenyl phosphite, triphenyl phosphate, and tri-*p*-cresyl phosphate by phenylmagnesium bromide have also been observed.[2]

The reaction, however, is not limited to aryl esters of this type, but appears to be quite general for compounds having either alkyl or aryl groups attached through oxygen to phosphorus. To illustrate, trialkyl phosphates,[3,4] trialkyl phosphites,[3-6] dialkyl phosphites,[4,7-11] alkyl,[12,13] and aryl[5] phosphonates and phosphorochloridates,[4,14,15] have all been found to undergo similar displacements when treated with organometallic compounds.

Triphenylsilyllithium, on the other hand, reacted with tri-*n*-butyl phosphate in tetrahydrofuran to give an 83.5% yield of *n*-butyltriphenylsilane, the alkylation product[16]:

$$(C_6H_5)_3SiLi + (n\text{-}C_4H_9O)_3PO \longrightarrow (C_6H_5)_3SiC_4H_9\text{-}n + (n\text{-}C_4H_9O)_2P(O)OLi$$

Alkylation reactions involving alkyl sulfates and sulfonates with Grignard reagents are well known[17]; however, this type of reaction has not been observed for alkyl esters of acids containing phosphorus as the central element, except for the reaction involving triphenylsilyllithium and tri-*n*-butyl phosphate.[16] This study describes further investigation of the scope and limitations of this alkylation reaction.

It was found that triphenylsilyllithium reacts smoothly and promptly with trimethyl, tri-*n*-butyl, and triisobutyl phosphate in a 1:1 mole ratio to give methyl-, *n*-butyl-, and isobutyltriphenylsilane in yields of 88, 97, and 87.8%, respectively. All three products were identified by mixed melting point determinations and infrared spectra.

As it was desirable to know whether all three alkyl groups of the ester could be utilized in this reaction, the reaction of triphenylsilyllithium with tri-*n*-butyl phosphate was repeated in a 3:1 mole ratio. The *n*-butyl ester was chosen for this purpose, because it gave the best yield of alkylation product of the three esters tested, although the yields in all three cases were satisfactory.

Forced conditions were required in order to consume all of the organosilyllithium reagent, but the yield of *n*-butyltriphenylsilane was found to be only 49.5%. In addition, hexaphenyldisilane (11.6%), hexaphenyldisiloxane (2.7%), 4-triphenylsilylbutanol (6.4%), and triphenylsilanol (5.9%) were isolated from the reaction mixture. A check-run gave *n*-butyltriphenylsilane (51.5%), hexaphenyldisilane (13.8%), 4-triphenylsilylbutanol (4.5%), and triphenylsilanol (9.05%).

As forced conditions (reflux and long reaction times) were required to obtain a negative Color Test I,[18] it is apparent that the removal of the second and third alkyl groups from the ester is much more difficult than is the removal of the first. This is probably due to repulsion by the nega-

(1) A. Michaelis and F. Wegner, *Ber.*, **48**, 316 (1915).
(2) H. Gilman and C. C. Vernon, *J. Am. Chem. Soc.*, **48**, 1063 (1926).
(3) H. Gilman and J. Robinson, *Rec. trav. chim.*, **48**, 328 (1929).
(4) J. L. Willians, *Chem. & Ind.*, 235 (1957).
(5) P. W. Morgan and B. C. Herr, *J. Am. Chem. Soc.*, **74**, 4526 (1952).
(6) M. H. Maguire and G. Shaw, *J. Chem. Soc.*, 2039 (1955).
(7) G. M. Kosolapoff and R. M. Watson, *J. Am. Chem. Soc.*, **73**, 4101 (1951).
(8) R. H. Williams and L. A. Hamilton, *J. Am. Chem. Soc.*, **74**, 5418 (1952); *J. Am. Chem. Soc*, **77**, 3411 (1955).
(9) R. C. Miller, J. S. Bradley, and L. A. Hamilton, *J. Am. Chem. Soc.*, **78**, 5299 (1956).
(10) B. B. Hunt and B. C. Saunders, *J. Chem. Soc.*, 2413 (1957).
(11) R. C. Miller, C. D. Miller, Wm. Rogers, Jr., and L. A. Hamilton, *J. Am. Chem. Soc.*, **79**, 424 (1957).
(12) G. M. Kosolapoff, *J. Am. Chem. Soc.*, **72**, 5508 (1950).
(13) M. Janczewski, *Roczniki Chem.*, **33**, 185 (1959).
(14) A. Burger and N. D. Dawson, *J. Org. Chem.*, **16**, 1250 (1951).
(15) N. D. Dawson and A. Burger, *J. Org. Chem.*, **18**, 207 (1953).
(16) M. V. George, B. J. Gaj, and H. Gilman, *J. Org. Chem.*, **24**, 624 (1959).
(17) See, for example, M. S. Kharasch and O. Reinmuth, *Grignard Reactions of Nonmetallic Substances*, chapt. 21, Prentice-Hall, New York, 1954.
(18) H. Gilman and F. Schulze, *J. Am. Chem. Soc.*, **47**, 2002 (1925).

tive charge on the ester after one alkyl group has been removed. In this connection, it has also been found that the second and third alkyl groups of phosphate esters are more difficult to hydrolyze.[19]

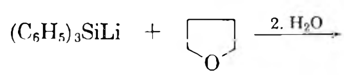
Secondly, it is apparent that all three alkyl groups of the ester are not functioning as alkylating agents, as *n*-butyltriphenylsilane was isolated in only 49.5 and 51.5% yields from these two reactions employing forced conditions. The isolation of hexaphenyldisilane also suggests that a different methanism is involved in the removal of the third alkyl group. The following reaction scheme is consistent with the observed results:

$$2(C_6H_5)_3SiLi + (n\text{-}C_4H_9O)_3PO \longrightarrow 2(C_6H_5)_3SiC_4H_9\text{-}n + \underset{\text{I}}{(LiO)_2P(O)(OC_4H_9\text{-}n)}$$

$$(C_6H_5)_3SiLi + \underset{\text{I}}{(LiO)_2P(O)(OC_4H_9\text{-}n)} \longrightarrow n\text{-}C_4H_9OLi + \underset{\text{II}}{(LiO)_2P(O)(Si(C_6H_5)_3)}$$

$$(C_6H_5)_3SiLi + \underset{\text{II}}{(LiO)_2P(O)(Si(C_6H_5)_3)} \longrightarrow (C_6H_5)_6Si_2 + \underset{\text{III}}{(LiO)_2P(O)Li}$$

$$\underset{\text{II}}{(LiO)_2P(O)(Si(C_6H_5)_3)} + 3H_2O \longrightarrow (C_6H_5)_3SiOH + (HO)_2P(O)H + 2LiOH$$



$$(C_6H_5)_3Si(CH_2)_4OH + LiOH$$

The first two alkyl groups of the ester react with triphenylsilyllithium to form I and *n*-butyltriphenylsilane. Although not indicated as such, this reaction probably occurs stepwise. Triphenylsilyllithium then reacts with I to give the silylphosphorus intermediate (II) by displacement of the *n*-butoxide group. Apparently after two of the alkyl groups have been removed from the ester, the steric hindrance around phosphorus is reduced sufficiently for the organolsilyllithium compound to attack the central phosphorus atom in the manner usually observed with compounds of this type.

Subsequent cleavage of the silylphosphorus intermediate (II) by triphenylsilyllithium leads to the formation of hexaphenyldisilane and lithium phosphite (III). Cleavages of this type have been used to explain the formation of hexaphenyldisilane from reactions of triphenylsilyllithium with halides of group V-B elements.[16] Similar reactions involving silicon-sulfur,[20] silicon-oxygen,[21] and silicon-mercury[22] bonds are also known.

As care was taken to exclude moisture from these reactions, the triphenylsilanol probably was formed *via* hydrolysis of the silylphosphorus compound (II). Compounds containing silicon-phosphorus bonds are known to undergo ready hydrolysis.[23] The hexaphenyldisiloxane isolated in the first reaction employing forced conditions was formed by dehydration of triphenylsilanol, and the 4-triphenylsilylbutanol, *via* cleavage of the solvent by triphenylsilyllithium.[24]

It would appear that steric requirements of the triphenylsilyl group are largely responsible for the occurrence of alkylation in these reactions. The large size of this anion prevents its attack on the ester at the central phosphorus atom. Apparently there is not too much difference, energywise, between these two possible reactions (alkylation *vs.* displacement), and the more favored displacement reaction gives way to the alkylation reaction when the organometallic compound is sufficiently hindered. An investigation to test this hindrance hypothesis employing Grignard reagents and organolithium compounds is presently being carried out. The results of this work will be reported later.

EXPERIMENTAL[25]

Reaction of triphenylsilyllithium with trimethyl phosphate (1:1). A solution of 0.04 mole of triphenylsilyllithium[26] in 75 ml. of tetrahydrofuran was added dropwise to a stirred solution of 5.6 g. (0.04 mole) of trimethyl phosphate in 50 ml. of the same solvent. Color Test I[18] was negative immediately after the addition was completed. Work-up by hydrolysis, addition of 100 ml. of diethyl ether, separation of the layers, extraction of the aqueous layer with diethyl ether, drying of the organic layer and removal of the solvents left an oil which was poured on a column of dry alumina.

Elution with 400 ml. of petroleum ether (b.p. 60–70°) gave 7.8 g. (71%) of methyltriphenylsilane, m.p. 63–65°, and an oil which contained triphenylsilane as the main constituent, as evidenced by strong absorption bands at 4.75 and 8.97 μ in its infrared spectrum, characteristic of the Si-H and sili-

(19) G. M. Kosolapoff, *Organophosphorus Compounds*, chapt. 9, Wiley, New York, 1950.

(20) H. Gilman and D. Wittenberg, *J. Am. Chem. Soc.*, **79**, 6339 (1957); D. Wittenberg, T. C. Wu, and H. Gilman, *J. Org. Chem.*, **23**, 1898 (1958); D. Wittenberg, H. A. McNinch, and H. Gilman, *J. Am. Chem. Soc.*, **80**, 5418 (1958).

(21) D. Wittenberg, M. V. George, and H. Gilman, *J. Am. Chem. Soc.*, **81**, 4812 (1959); H. Gilman and T. C. Wu, *J. Org. Chem.*, **25**, 2251 (1960).

(22) M. V. George, G. D. Lichtenwalter, and H. Gilman, *J. Am. Chem. Soc.*, **81**, 978 (1959).

(23) See, for example, G. Fritz, *Z. Naturforsch.*, **8b**, 776 (1953); G. Fritz, *Z. anorg. u. allgem. chem.*, **280**, 332 (1955); W. Keeber and H. W. Post, *J. Org. Chem.*, **21**, 507 (1956); G. Fritz and H. O. Berkénhoff, *Z. anorg. u. allgem. chem.*, **289**, 250 (1957); F. Fehér, G. Kuhlbörsch, A. Blüneke, H. Keller, and K. Lippert, *Chem. Ber.*, **90**, 134 (1957); G. W. Parshall and R. V. Lindsey, *J. Am. Chem. Soc.*, **81**, 6273 (1959).

(24) D. Wittenberg, D. Aoki, and H. Gilman, *J. Am. Chem. Soc.*, **80**, 5933 (1958).

(25) Melting points are uncorrected. All reactions were carried out in an atmosphere of dry, oxygen-free nitrogen in oven-dried glassware. The tetrahydrofuran was dried and purified by refluxing over sodium wire for at least 24 hr., followed by distillation into a refluxing suspension of lithium aluminum hydride under dry nitrogen. It was distilled immediately before use from this suspension.

(26) Prepared according to the procedure of H. Gilman and G. D. Lichtenwalter, *J. Am. Chem. Soc.*, **80**, 608 (1958).

con-phenyl bond, respectively. Recrystallization of the solid from methanol raised the melting point to 65–66°. The product was identified by the method of mixed melting points and by a comparison of its infrared spectrum, as a carbon disulfide solution, with that of an authentic sample.

The reaction was repeated using the same quantities of triphenylsilyllithium and freshly distilled trimethyl phosphate. Hydrolysis and work-up as in the previous reaction gave 9.6 g. (88%) of methyltriphenylsilane, m.p. and mixed m.p. 67–68°, after crystallization from methanol.

Reaction of triphenylsilyllithium with tri-n-butyl phosphate (1:1). The addition of one-third of a solution of 0.04 mole of triphenylsilyllithium in 90 ml. tetrahydrofuran to a stirred solution of 3.99 g. (0.015 mole) of tri-*n*-butyl phosphate in 30 ml. of the same solvent gave a negative Color Test I and discharged the color of the silyllithium reagent. The addition of another 0.0133 mole of the organometallic compound resulted in a brown solution which gave a positive Color Test I even after stirring for 1 hr. An additional 6.65 g. (0.025 mole) of tri-*n*-butyl phosphate in 30 ml. of tetrahydrofuran was added and the remaining triphenylsilyllithium reagent then was added dropwise. Color Test I became negative and the mixture developed a pale pink coloration.

Hydrolysis with water, and the addition of 100 ml. of diethyl ether produced an emulsion which was cleared by the addition of a small amount of dilute hydrochloric acid. Work-up in the manner described for trimethyl phosphate gave 12.3 (97%) of *n*-butyltriphenylsilane, m.p. 85–87°, identified by mixed melting point and infrared spectra.

Reaction of triphenylsilyllithium with tri-n-butyl phosphate (3:1) *at reflux. Run 1.* A solution of 0.08 mole of triphenylsilyllithium in 160 ml. of tetrahydrofuran was added to a stirred solution of 7.1 g. (0.0267 mole) of freshly distilled tri-*n*-butyl phosphate in 50 ml. of the same solvent. The dark mixture was stirred for 2.5 hr. at room temperature (Color Test I positive), then at reflux for 18 hr. Hydrolysis, filtration, and washing of the insoluble material with water and diethyl ether left 2.2 g. of hexaphenyldisilane, m.p. and mixed m.p. 364–366°.

The filtrate, which had a strong phosphine-like odor, was acidified and the aqueous layer extracted with diethyl ether. Removal of the solvents from the dried organic phase left an oily solid which was washed with petroleum ether (b.p. 60–70°) and crystallized from benzene to give 0.1 g. of impure hexaphenyldisilane, identified by mixed melting point.

The petroleum ether extract was chromatographed on a column of alumina to give 12.5 g. (49.5%) of *n*-butyltriphenylsilane, 0.1 g. (2.7%) of hexaphenyldisiloxane (eluted with benzene), 0.1 g. of hexaphenyldisilane (total yield, 2.4 g., 11.6%), 1.7 g. (6.4%) of 4-triphenylsilylbutanol (eluted with ethyl acetate), and 1.3 g. (5.9%) of triphenylsilanol. All products were identified by mixed melting points.

Run 2. A solution of 0.06 mole of triphenylsilyllithium in 70 ml. of tetrahydrofuran was added to 5.3 g. (0.02 mole) of tri-*n*-butyl phosphate in a mixture of 40 ml. of tetrahydrofuran and 30 ml. of diethyl ether, and refluxed gently for 5 days with continuous stirring. At the end of this time, Color Test I was negative. Hydrolysis with 100 ml. of water and filtration gave 2.15 g. (13.8%) of hexaphenyldisilane, m.p. and mixed m.p. 363–365°. The filtrate had a strong phosphine-like odor.

Chromatographic separation of the organic layer gave 9.8 g. (51.5%) of *n*-butyltriphenylsilane, m.p. 86–88°. (mixed m.p.); 0.85 g. (4.5%) of 4-triphenylsilylbutanol, m.p. 107–109° (mixed m.p. and infrared spectra); and 1.5 g. (9.05%) of triphenylsilanol, m.p. 152–154° (mixed m.p.).

Reaction of triphenylsilyllithium with triisobutyl phosphate (1:1) *Run 1.* A mixture of 0.06 mole of triphenylsilyllithium and 16 g. (0.06 mole) of triisobutyl phosphate[27] in 170 ml. of tetrahydrofuran gave, after the initial heat of reaction had dissipated, a negative Color Test I. The pink solution was hydrolyzed with 50 ml. of half-saturated ammonium chloride, and 100 ml. of diethyl ether was added. Drying of the separated organic layer followed by removal of the solvents and boiling of the residue with 150 ml. of absolute ethanol gave upon filtration 0.3 g. (2%) of hexaphenyldisilane, m.p. 357–360° (mixed m.p.).

The ethanolic filtrate yielded upon concentration, two crops of isobutyltriphenylsilane (13.75 g., 72.3%), m.p. 75–76°. The product was identified by a mixed melting point with a sample prepared from the reaction of isobutyl chloride with triphenylsilyllithium,[28] and by infrared spectra.

Run 2. The previous reaction was repeated using 0.04 mole of each reactant in 110 ml. of tetrahydrofuran. Hydrolysis and removal of the solvents from the dried organic layer was accomplished as described in Run 1. The residue was purified by passing it through a column of alumina as a petroleum ether (b.p. 60–70°) solution. Removal of the solvent left 11.1 g. (87.8%) of isobutyltriphenylsilane, m.p. and mixed m.p. 74–76°. Elution with ethyl acetate gave, after crystallization from cyclohexane, 0.5 g. (4.5%) of triphenylsilanol, m.p. 151–153° (mixed m.p.).

Acknowledgment. This research was supported in part by the United States Air Force under Contract AF 33(616)-3510 monitored by the Materials Laboratory, Directorate of Laboratories, Wright Air Development Center, Wright-Patterson AFB, Ohio. Infrared spectra were obtained through the courtesy of the Institute for Atomic Research, Iowa State University, and special acknowledgment is made to Miss E. Conrad for preparing the spectra.

AMES, IOWA

(27) Kindly furnished by Dr. J. B. Dickey of the Tennessee Eastman Co., Kingsport, Tenn.

(28) G. Dappen. Unpublished studies.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE UNIVERSITY]

A Quantitative Estimation of Organosilylmetallic Compounds

HENRY GILMAN, ROBERT A. KLEIN, AND HANS J. S. WINKLER

Received November 10, 1960

The available methods of analysis for organometallic compounds have been evaluated in relation to their suitability for estimation of organosilylmetallic compounds. It was found that organosilylmetallic compounds reacted with *n*-butyl bromide to give an equivalent amount of metal bromide which could conveniently be estimated by a Volhard titration. A study has been made of the stability of the various available organosilyllithium compounds in tetrahydrofuran.

Various methods have been devised for the quantitative estimation of organometallic compounds. Those concerned with organomagnesium halides have been discussed in standard reference works.[1,2] Some of these methods have been used for the estimation of organoalkali metal compounds.[3] The method first studied for organomagnesium halides[4] was based on a reaction described by Bodroux.[5] This method involves the determination of the amount of iodine consumed according to equation 1:

$$RMgX + I_2 \longrightarrow RI + MgXI \qquad (1)$$

It has been found, however, that this is not the only possible reaction taking place[1,6] although it does seem to be the only one in the specific case of phenyllithium.[7] The competing reaction shown in (2) causes the consumption of only half the amount of iodine consumed by Equation 1

$$2\,RMgX + I_2 \longrightarrow R{-}R + 2\,MgXI \qquad (2)$$

Because of the interfering reaction (2) this method is not generally recommended.[1,6,8] Estimation of organometallic compounds in solvents which are not cleaved to any appreciable extent may be performed by hydrolysis and titration with acid of the total base liberated.[3,6,8,9] This method is not applicable to organometallic compounds which react with the solvent, as cleavage of an ether type solvent, for example, would yield alkoxides which would tend to increase the assay of the solution above the true value.

A double titration has been devised for this class of compounds.[10] This involves the determination of total base as described above. A second aliquot is reacted with benzyl chloride, which causes the consumption of the organometallic compounds; the alkoxides are then determined by a simple acid titration. This method has recently[11] been studied in detail. A gasometric method is useful in a limited number of cases involving low molecular weight organometallic compounds.[6]

Organoalkali metal compounds have been analyzed by a method involving their reaction with *n*-butyl bromide (3) followed by determination of the liberated alkali metal bromide according to the Volhard procedure.[12] This method is useful only for organo-metallic compounds of high reactivity (R—Li). A procedure was described for the use of this method for the estimation of less reactive organometallic compounds (R′—Li). In this procedure, dibenzylmercury was added dropwise to a mixture of the organometallic reaction and *n*-butyl bromide. Dibenzylmercury reacted with the less active organometallic compound to give a benzylmetallic intermediate (by Equation 4) which coupled readily with the *n*-butyl bromide present (Equation 5). The alkali metal halide liberated was titrated as above.

$$R{-}Li + n\text{-}C_4H_9Br \longrightarrow n\text{-}C_4H_9{-}R + LiBr \qquad (3)$$

$$R'{-}Li + (C_6H_5CH_2)_2Hg \longrightarrow C_6H_5CH_2Li + R'HgCH_2C_6H_5 \qquad (4)$$

$$C_6H_5CH_2Li + n\text{-}C_4H_9Br \longrightarrow n\text{-}C_4H_9{-}CH_2C_6H_5 + LiBr \qquad (5)$$

Halogen-metal interconversion reactions cannot be excluded, but do not interfere with these determinations as excess *n*-butyl bromide is present. It was likewise established that alkoxides did not react rapidly enough with *n*-butyl bromide to

(1) M. S. Kharasch and O. Reinmuth, *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, N. Y., 1954, p. 92–98.

(2) F. Runge, *Organo-metallverbindungen*, Wissenschaftliche Vlgs., Stuttgart.

(3) Houben-Weyl, E. Müller ed., "Methoden der Organischen Chemie," Vol. II, *Analytische Methoden*, G. Thieme, Stuttgart, 1953, p. 326.

(4) P. Jolibois, *Compt. rend.*, **155**, 219 (1912).

(5) F. Bodroux, *Compt. rend.*, **135**, 1350 (1902).

(6) H. Gilman, P. D. Wilkinson, W. P. Fishel, and C. H. Meyers, *J. Am. Chem. Soc.*, **45**, 150 (1923); H. Gilman and C. H. Meyers, *Rec. trav. chim.*, **45**, 314 (1926).

(7) A. F. Clifford and R. R. Olsen, *Anal. Chem.*, **32**, 544 (1960).

(8) H. J. S. Winkler and H. Gilman, unpublished study.

(9) H. Gilman, J. A. Beel, C. G. Brannen, M. W. Bullock, G. E. Dunn, and L. S. Miller, *J. Am. Chem. Soc.*, **71**, 1499 (1949); H. Gilman, W. Langham, and F. W. Moore, *J. Am. Chem. Soc.*, **62**, 2327 (1940); H. Gilman, E. A. Zoellner, and J. B. Dickey, *J. Am. Chem. Soc.*, **51**, 1576 (1929).

(10) H. Gilman and A. H. Haubein, *J. Am. Chem. Soc.*, **66**, 1515 (1944); H. Gilman, A. H. Haubein, and H. Hartzfeld, *J. Org. Chem.*, **19**, 1034 (1954).

(11) C. W. Kamienski and D. L. Esmay, *J. Org. Chem.*, **25**, 115 (1960); see also, K. C. Eberly, *J. Org. Chem.*, **26**, 1309 (1961).

(12) K. Ziegler, F. Crössmann, H. Kleiner, and O. Schäfer, *Ann.*, **473**, 31 (1929).

liberate excess halide which would interfere with the determination.

An oxidimetric method of analysis of aliphatic organolithium compounds has recently been reported.[13] This method is based on the reduction of vanadium pentoxide by the organometallic reagent followed by a potentiometric titration of the reduced vanadium, using potassium permanganate or preferably a cerium (Equation IV) salt as the oxidizing agent.

It was the purpose of the present study to develop a quantitative method for organosilylmetallic compounds in the presence of alkoxides. The total base method has been used for the estimation either of complete cleavage of symmetrical disilanes in the formation of organosilylmetallic compounds (Equation 6) or in the direct preparation of these from halosilanes (7)[15]:

$$R_3Si—SiR_3 + 2\,Li \longrightarrow 2\,R_3SiLi \quad (6)$$

$$R_3Si—X + 2\,Li \longrightarrow R_3SiLi + LiX \quad (7)$$

The values obtained by this method exceed the theoretical by 30–50% depending on extraneous factors. The high alkoxide content of the solutions may be assumed to have caused this error.

For this reason, the double titration has been utilized in one instance,[16] but the values were low as also shown in the present study. The values shown in Table I indicate this trend to give assays 10–20% lower than those obtained by the *n*-butyl bromide method.

TABLE I

COMPARISON OF *n*-BUTYL BROMIDE AND DOUBLE TITRATION VALUES FOR TRIPHENYLSILYLLITHIUM

Number	M by n-C_4H_9 Method	M by Double Titration Method	Theory
1	0.319	0.262	0.320
2	0.377	0.325	0.390
3	0.343	0.301	[a,b]
4	0.287	0.186	[a,c]

[a] These analyses were performed on the same sample as was used in No. 2. [b] After the solution had been standing for 48 hr. [c] After standing for 72 hr.

An attempt to use the iodine method[8] failed to give results as high as those obtained by the *n*-butyl bromide method (Table II).

These values indicate that the iodination method gives results for freshly prepared samples which

TABLE II

COMPARISON OF *n*-BUTYL BROMIDE AND IODINATION VALUES FOR TRIPHENYLSILYLLITHIUM

Number	Hours of Standing	M by n-C_4H_9 Method	% Yield by n-C_4H_9 Method	M by Iodination Method	% Yield by Iodination Method
1	24	0.314	81	0.214	55
2	48	0.323	84	0.228	59
3	72	0.256	66[a]	0.235	61
4	—	0.204	53		
5	92	0.222	57[a]	0.237	61
6	—	0.143	37	0.213	55

[a] The solution was filtered before analysis.

are 20–30% lower than those obtained by the *n*-butyl bromide method. It should be noted that the triphenylsilyllithium content did not decrease according to the iodination method, whereas the assay decreases considerably as determined by the *n*-butyl bromide method. The solution which had been filtered was more stable than that which had not (Nos. 3–6).

The failure of the iodination method may be attributed to the extensive reaction of type (2). That this reaction does take place was established by isolation of hexaphenyldisilane from the reaction of triphenylsilyllithium with bromine by normal or inverse addition (hexaphenyldisilane was isolated in 42 and 54% yields, respectively).

$$2\,(C_6H_5)_3SiLi + Br_2 \longrightarrow (C_6H_5)_3Si—Si(C_6H_5)_3 + 2LiBr$$

No reduction of vanadium pentoxide by triphenylsilyllithium was observed. If any had taken place it would have been possible to detect a potentiometric end-point. Using potassium permanganate as the oxidizing agent there was obtained a smooth millivolts *vs.* milliliter plot with no inflection point within a reasonable range near the end-point expected from theory.

The method involving reaction of the silyllithium compound with *n*-butyl bromide and subsequent determination of lithium bromide by the Volhard procedure was investigated. The Volhard procedure is very accurate for bromides,[17] and the end-point is clearly distinguishable even in the presence of organic compounds. The reaction of triphenylsilyllithium with *n*-butyl bromide is known to take place with halogen-metal interconversion to a large extent.[18] The following reactions proceed to consumption of all the organosilylmetallic and organometallic compounds as evidenced by a negative Color Test[19]:

(13) D. L. Esmay and P. F. Collins, private communication. See P. F. Collins, C. W. Kameinski, D. L. Esmay, and R. B. Ellestad, *Anal. Chem.*, **33**, 468 (1961).

(14) H. Gilman and G. D. Lichtenwalter, *J. Am. Chem. Soc.*, **80**, 608 (1958).

(15) H. Gilman, D. J. Peterson, and D. Wittenberg, *Chem. & Ind.*, 1479 (1958); M. V. George, D. J. Peterson, and H. Gilman, *J. Am. Chem. Soc.*, **82**, 403 (1960).

(16) A. G. Brook and H. Gilman, *J. Am. Chem. Soc.*, **76**, 278 (1954).

(17) I. M. Kolthoff and V. A. Stenger, *Volumetric Analysis*, Vol. II, Interscience Publ., N. Y., 1947, p. 272.

(18) H. Gilman and D. Aoki, *J. Org. Chem.*, **24**, 426 (1959).

(19) H. Gilman and F. Schulze, *J. Am. Chem. Soc.*, **47**, 2002 (1925).

$$(C_6H_5)_3SiLi + n\text{-}C_4H_9Br \longrightarrow (C_6H_5)_3SiBr + n\text{-}C_4H_9Li \quad (9a)$$

$$(C_6H_5)_3SiLi + (C_6H_5)_3SiBr \longrightarrow (C_6H_5)_3Si\text{—}Si(C_6H_5)_3 + LiBr \quad (9b)$$

$$(C_6H_5)_3SiBr + n\text{-}C_4H_9Li \longrightarrow n\text{-}C_4H_9\text{—}Si(C_6H_5)_3 + LiBr \quad (9c)$$

$$(C_6H_5)_3SiLi + n\text{-}C_4H_9Br \longrightarrow n\text{-}C_4H_9\text{—}Si(C_6H_5)_3 + LiBr \quad (9d)$$

$$n\text{-}C_4H_9Li + n\text{-}C_4H_9Br \longrightarrow n\text{-}C_8H_{18} + LiBr \quad (9e)$$

The extent of the individual reactions may be indicated by the yields of hexaphenyldisilane (60%) and *n*-butyltriphenylsilane (10%), isolated in these laboratories during previous investigations.[18] The fact that there is such a large amount of halogen-metal interconversion does not interfere with the method of analysis, as the organometallic compound is consumed by one or more of the possible reactions. It may be expected, however, that 9d proceeds to a larger extent under the conditions of analysis than under the preparative conditions, as under the former the concentration of *n*-butyl bromide exceeds that of the latter. That part of the triphenylsilyllithium reacts by halogen-metal interconversion and that the bromotriphenylsilane thus formed reacts further by the very rapid coupling reaction (reaction 9b) is evident from the isolation of hexaphenyldisilane as the major product of the reaction. In the event that trace amounts of bromotriphenylsilane should have evaded either of the very fast coupling reactions (9b or 9c), liberation of the bromide ion, necessary for estimation, would have been effected by hydrolysis.

Two different procedures have been used in this study. The less expedient procedure involves the addition of an aliquot of the organosilylmetallic solution to excess *n*-butyl bromide. The amount of base is determined by standardized sulfuric acid using phenolphthalein indicator, and the organic layer is extracted with portions of water which are combined and diluted to volume in a volumetric flask. Aliquots of this solution are then withdrawn and their content of bromide determined by the Volhard procedure (this method will be referred to as the "extraction method").

The more expedient procedure (referred to as the "direct method") involves the same steps as above including the titration with standardized sulfuric acid. The extraction is not carried out, and the total amount of bromide is determined in the presence of the organic layer.

It was established in individual experiments, performed under the conditions of the analyses, that neither lithium silanolates (R_3SiOLi) which are formed on contact of silyllithium compounds with air,[20] nor lithium alkoxides, formed by cleavage of tetrahydrofuran by silyllithium compounds,[21] interferes with the determination.

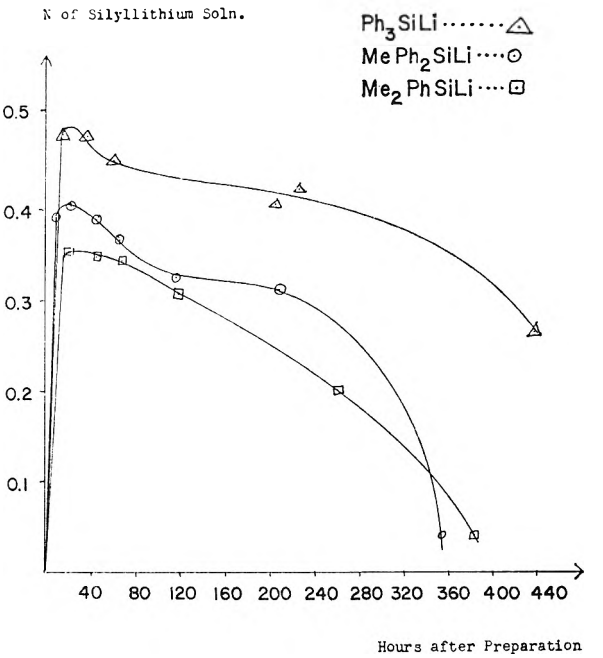


Fig. 1. Stabilities of organosilyllithium compounds in tetrahydrofuran

Figure 1 shows the results of analyses for solutions of triphenylsilyllithium, methyldiphenylsilyllithium, and dimethylphenylsilyllithium kept in volumetric flasks under a nitrogen atmosphere. The decrease in silyllithium content was paralleled by an increase in alkoxide content. The alkoxide content of the solutions of methyldiphenylsilyllithium and dimethylphenylsilyllithium had risen to 0.490 and 0.500*N*, respectively, whereas the solution of triphenylsilyllithium was 0.264*N* in alkoxide after 440 hours. It may be seen that the decrease in silyllithium content is more rapid for the more alkylated silyllithium compound, whereas the solution triphenylsilyllithium was considerably more stable. This increase in reactivity has been established in reactions of silyllithium compounds with silicon-silicon bonds.[22]

The analytical results of various solutions at the times indicated are shown in Table III with the deviation of the determinations by the particular method used. Normalities in Table III for which deviation values are given represent the average of several titrations made by one or several workers as indicated.

From the data given in Table III it is evident that the analyses obtained by the "extraction method" are consistently lower than those obtained by the "direct method" (Nos. 6, 7, and 10). This does not necessarily mean that the extraction

(20) M. V. George and H. Gilman, *J. Am. Chem. Soc.*, 81, 3288 (1959).

(21) D. Wittenberg and H. Gilman, *J. Am. Chem. Soc.*, 80, 2677 (1958).

(22) H. Gilman and G. D. Lichtenwalter, *J. Am. Chem. Soc.*, 81, 5320 (1959).

TABLE III

QUANTITATIVE ESTIMATION OF SILYLLITHIUM COMPOUNDS

No.	Silyllithium Compound	Normality	Time of Analysis, Hours after Prep.	Deviation, %	Per Cent Yield
1	$(C_6H_5)_3SiLi$	0.313[a]	24	4	97
2	$(C_6H_5)_3SiLi$	0.302[a,c]	24	1	94
3	$(C_6H_5)_3SiLi$	0.443[b]	24	3	90
4	$(C_6H_5)_3SiLi$	0.456[b,c]	24	2	91
5	$(C_6H_5)_3SiLi$	0.269[b,c]	24	2	95
6	$(C_6H_5)_3SiLi$	0.294[a]	24	—	74
		0.317[b]	24	—	79
		0.294[a]	48	—	74
		0.302[b]	48	—	75
		0.267[a]	72	—	67
		0.278[b]	72	—	70
7	$CH_3(C_6H_5)_2SiLi$	0.340[a]	24	—	88
		0.341[b]	24	—	88
		0.310[a]	48	—	81
		0.321[b]	48	—	84
8	$CH_3(C_6H_5)_2SiLi$	0.239[b]	18	1	75
		0.237[b,c]	24	4	74
		0.231[b,c]	48	4	72
9	$(CH_3)_2C_6H_5SiLi$	0.251[b]	24	3	94
10	$(CH_3)_2C_6H_5SiLi$	0.294[a]	24	—	74
		0.317[b]	24	—	79
		0.294[a]	48	—	74
		0.302[b]	48	—	75

[a] Extraction method. [b] Direct method. [c] Determined by different workers.

method gives analyses lower than theory. On the contrary, this method is considered of higher accuracy than the "direct method" which is accompanied by additional sources of error caused by adsorption phenomena.

The yields given in the last column are in good agreement with the yields of various derivatives obtained from these silyllithium compounds by reactions with chlorosilanes or tri-*n*-butyl phosphate.[23]

EXPERIMENTAL[24]

Materials. Hexaphenyldisilane, *sym*-dimethyltetraphenyldisilane, and *sym*-tetramethyldiphenyldisilane were prepared in accordance with previously reported directions.[25] The tetrahydrofuran used in the preparation of the silyllithium compounds was distilled from sodium wire into a flask containing lithium aluminum hydride. The tetrahydrofuran was redistilled from the lithium aluminum hydride as needed to insure dryness and absence of alcohols. The *n*-butyl bromide (Matheson, Coleman & Bell, reagent grade) was distilled under nitrogen through a heated, 75 cm. long helices column before use.

Direct method of analysis. Solutions of organosilylithium compounds were prepared by cleavage of the symmetrically substituted disilanes.[14] The pipettes and flasks used for the analyses were dried in an oven at 140° and flushed in a rapid stream of dry nitrogen until cool. A 5-ml. sample of the solution to be analyzed was transferred to a flask containing 5 ml. of *n*-butyl bromide under an atmosphere of dry nitrogen. The tip of the pipette was placed immediately above the surface of the *n*-butyl bromide and the organosilyllithium solution was allowed to flow freely into the *n*-butyl bromide with gentle swirling. After standing for 2 min., the solution was hydrolyzed by the addition of 5 ml. of *ca.* 0.1*N* standardized sulfuric acid, and phenolphthalein indicator was added. The excess base was neutralized by titration with the standardized sulfuric acid. It is important to note the point at which the aqueous layer becomes colorless. At this point the mixture should be shaken vigorously and the titration should be completed under slow addition of acid and good shaking. The lithium bromide content was determined by a standard Volhard procedure adding an excess of standardized silver nitrate solution and back-titrating with thiocyanate to a ferric alum end-point. The addition of a few drops of nitrobenzene may aid in the coagulation of the silver bromide but is not necessary.

Extraction method of analysis. This procedure is carried out in the same manner as the "direct method" up to and including the neutralization by standardized sulfuric acid. At this point the organic layer is extracted three times with distilled water, and the aqueous extracts are combined and diluted to volume in a 200-ml. volumetric flask. Aliquots are removed with 50-ml. pipettes and titrated for their bromide content as described under the Direct Method of Analysis.

Acknowledgment. This research was supported in part by the United States Air Force under contract AF 33(616)-6127 monitored by the Materials Laboratory Directorate of Laboratories, Wright Air Development Center, Wright-Patterson, AFB, Ohio. The authors are grateful to Gerald L. Schwebke and William J. Trepka for assistance.

AMES, IOWA

(23) D. Wittenberg and H. Gilman, *Quart. Revs.* (*London*), **13**, 119 (1959); M. V. George, B. J. Gaj, and H. Gilman, *J. Org. Chem.*, **24**, 624 (1959).

(24) All preparations and analyses were carried out in an atmosphere of dry, oxygen-free nitrogen.

(25) H. Gilman and G. E. Dunn, *J. Am. Chem. Soc.*, **73**, 5077 (1951); A. G. Smith, M.S. thesis, Iowa State University, 1953.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUQUESNE UNIVERSITY]

Cleavage Reactions of Trityl Sulfides

KURT C. SCHREIBER AND VINCENT P. FERNANDEZ

Received November 23, 1960

The cleavage reactions of trityl phenyl sufide (I) and trityl benyl sulfide (II) with iodobenzene dichoride (III), iodobenzene diacetate (IV), and *N*-bromosuccinimide are reported. The stability of I towards nucleophilic reagents (sodium ethoxide and phenylmagnesium bromide) is demonstrated.

In 1926, R. Knoll[1] reported the preparation of trityl phenyl sulfoxide, by the chromium trioxide oxidation of the sulfide, a reaction which could not be substantiated by Gregg and his co-workers.[2]

Since iodobenzene diacetate (IV) showed mild oxidizing properties toward sulfides to give sulfoxides,[3] an attempt was made to study the behavior of this compound toward phenyl trityl sulfide (I). However, no sulfoxide or sulfone could be isolated from the reaction of I or II with either IV or iodobenzene dichloride (III), but instead cleavage of the sulfides occurred to give triphenylcarbinol or triphenylmethyl chloride in good yield.

The sulfur portion from the cleavage was identified by oxidation and by reaction with mercaptan. In the reaction of II with III, the sulfur portion presumably α-phenylmethanesulfenyl chloride, reacted with benzyl mercaptan to give with the evolution of hydrogen chloride a 47% yield of dibenzyl disulfide. Oxidation of the reaction mixture with peracetic acid gave a mixture of triphenylmethyl chloride and α-phenylmethanesulfonyl chloride from which after repeated recrystallization a small amount of each of the pure compounds could be isolated.

In the reaction of I and III, the sulfur portion, presumably benzenesulfenyl chloride, reacted with phenyl mercaptan yielding with hydrogen chloride evolution diphenyl disulfide (82%).

Phenyl trityl sulfide contains a group that contributes a large steric effect and which on cleavage is stabilized by resonance. Such cleavage of these sulfides could occur through (a) a cation mechanism, (b) an anion mechanism, or (c) a free radical mechanism.

The cleavage of trityl sulfides in acidic media has been reported by several workers.[4,5]

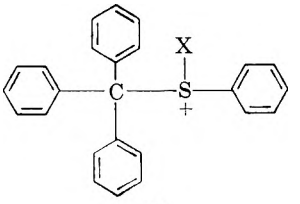
Tarbell and Harnish[5] claim that phenyl trityl sulfide is converted by alcoholic iodine at room temperature to triphenylcarbinol, diphenyl disulfide, and ethyl trityl ether. There is also a report in the literature where cleavage occurs in non-acidic medium in the oxidation with ruthenium tetroxide.[6]

To determine whether such cleavage could occur by attack of base, phenyl trityl sulfide was refluxed with an ethanolic solution of sodium ethoxide but only unchanged starting material was recovered. Reaction of phenylmagnesium bromide with phenyl trityl sulfide afforded a similar result.

It has been known that reactions of *N*-bromosuccinimide in carbon tetrachloride catalyzed by benzoyl peroxide follow a free radical mechanism.[7] For this reason a carbon tetrachloride solution of phenyl trityl sulfide was treated with an equimolar quantity of *N*-bromosuccinimide mixed with a catalytic amount of benzoyl peroxide as free radical initiator. *N*-Tritylsuccinimide and diphenyl disulfide were obtained as products.

With the above considerations in view, it could be said that the cleavage reaction of the trityl sulfides with either III or IV could follow a reaction mechanism of type (a) or (c).

However, it is suggested that the reaction with either III or *N*-bromosuccinimide occurs through the formation of intermediate V, which rapidly



V

decomposes to the triphenylmethyl cation and phenyl sulfenyl halide.

It should be noted that cleavage occurs in the case of benzyl trityl sulfide, in spite of the fact that this sulfide has two hydrogens on one of the *alpha* carbon atoms.

EXPERIMENTAL[8]

Iodobenzene dichloride (III) was prepared by the method of Lucas and Kennedy.[9] Iodobenzene diacetate (IV) m.p.

(1) R. Knoll, *J. prakt. Chem.*, **113**, 40 (1926).

(2) D. C. Gregg, K. Hazelton, and T. P. McKeon, *J. Org. Chem.*, **18**, 36 (1953).

(3) H. H. Szmant and G. Suld, *J. Am. Chem. Soc.*, **78**, 3400 (1956).

(4) D. S. Tarbell and D. P. Harnish, *Chem. Revs.*, **49**, 1 (1951).

(5) D. S. Tarbell and D. P. Harnish, *J. Am. Chem. Soc.*, **74**, 1862 (1952).

(6) C. Djerrassi and R. R. Engle, *J. Am. Chem. Soc.*, **75**, 3838 (1953).

(7) Jack Hine, *Physical Organic Chemistry*, McGraw-Hill Book Company, Inc., New York, N. Y., 1956, pp. 429–430.

157°, was prepared according to the method employed by Pausacker.[10]

Phenyltrityl sulfide (I) was prepared by the method of Finzi and Bellavita[11], m.p. 106–107°, lit.[11] m.p. 106°.

Benzyl trityl sulfide (II). To a solution of triphenylcarbinol (52.1 g., 0.2 mole) in 400 ml. of glacial acetic acid was added with constant shaking 24.8 g. (0.2 mole) of benzyl mercaptan and 20 ml. of concd. sulfuric acid. After the mixture was allowed to stand for 2 hr., it was poured into 500 g. of crushed ice. The solid that separated was filtered, washed with cold water and crystallized from petroleum ether (b.p. 30–60°) yielding needles, m.p. 82–83° (43.2 g.). Concentration of the mother liquor gave an additional 15.8 g. Total yield 80%.

Anal. Calcd. for $C_{26}H_{22}S$: C, 85.20; H, 6.05; S, 8.75. Found: C, 84.93; H, 6.04; S, 9.16.

Reaction of III *with phenyl trityl sulfide* (I). To a solution of 17.6 g. (0.05 mole) of I in 200 ml. of dry carbon tetrachloride or in dry chloroform were added 13.8 g. (0.05 mole) of III. There was no evolution of hydrogen chloride gas. The mixture was allowed to stand overnight. The solvent was removed under reduced pressure, 6.5 g. of trityl chloride separated and the supernatant liquid distilled under vacuum to give 15.0 g. of liquid. The residue in the pot solidified; crystallization from petroleum ether gave an additional 6.2 g. of trityl chloride m.p. 111–113°, lit. 113°.[12] Mixed melting point with authentic material showed no depression.

Total yield of trityl chloride was 91%. Two and two-tenths grams of the liquid distillate when treated with 1.0 g. of phenyl mercaptan reacted vigorously with the evolution of hydrogen chloride to give 1.3 g. (82%) of diphenyl disulfide m.p. 60–61°, from ethanol.

Reaction of III *with benzyl trityl sulfide* (II). To a solution of 18.3 g. (0.05 mole) of II in 200 ml. of dry carbon tetrachloride or chloroform were added 13.8 g. (0.05 mole) of III in small quantities with constant shaking. There was no apparent evolution of hydrogen chloride gas. The mixture was allowed to stand overnight.

One third of the mixture was treated with 15 ml. of 40% peracetic acid and the heterogeneous mixture was stirred overnight. The carbon tetrachloride layer was separated from the peracetic acid, the carbon tetrachloride evaporated, and the residue washed with petroleum ether to give 2.5 g. of triphenylcarbinol, m.p. 160–161°, lit. 162°. An additional 0.5 g. of triphenylcarbinol was obtained from peracetic acid layer, giving a total 69% yield of triphenylcarbinol. From the petroleum ether washings was obtained 0.3 g. (6.4%) of triphenylmethyl chloride, m.p. 111–113°, lit.[12] m.p. 113° and 0.2 g. (6.3%) of α-phenylmethanesulfonyl chloride, m.p. 92–93°.[13] Infrared spectrum was identical with the spectrum of an authentic compound. The solvent was distilled under reduced pressure from the second third of the original mixture and the residue carefully washed with petroleum ether. The remaining solid, m.p. 111–113°, represented a 95% yield of trityl chloride. The petroleum ether washings were treated with 2.0 g. of benzyl mercaptan and set aside for 3 hr. Evaporation of the petroleum ether and iodobenzene under vacuum left a solid which was crystallized from ethanol to give 1.4 g. (47.6%) of dibenzyl sulfide m.p. 71–72°, lit.[14] m.p. 69–70°.

Reaction of iodobenzene diacetate (IV) *with* I. To a solution of 3.5 g. (0.01 mole) of phenyl trityl sulfide in 100 ml. of glacial acetic acid in an Erlenmeyer flask was added IV (3.2 g., 0.01 mole) with constant swirling. The mixture was allowed to stand for 24 hr. after which it was poured into a beaker containing some crushed ice. The solid that separated was filtered, washed with cold water, and recrystallized from alcohol to yield 1.95 g. (74.9%) of triphenylcarbinol, m.p. 159–160°.[15] Mixed melting point with an authentic sample gave no depression.

Reaction of IV *with* II. A solution of 3.7 g. (0.01 mole) of II in 50 ml. of dry benzene and 3.2 g. (0.01 mole of IV was allowed to stand at room temperature for 24 hr. After concentration of the reaction mixture there was obtained triphenylcarbinol (2.1 g.) which upon recrystallization from ligroin gave no depression in melting point with an authentic sample, m.p. 160°.[15] Further concentration of the mother liquor yielded a dark brown viscous liquid from which no crystals were obtained even on prolonged cooling. No attempt was made to isolate the sulfur fraction of the sulfide; yield of triphenylcarbinol, 81%.

Reaction of N-bromosuccinimide with I. A mixture of 35.2 g. (0.1 mole) of I, 17.8 g. (0.1 mole) of *N*-bromosuccinimide and 2.4 g. of benzoyl peroxide in 150 ml. of dry carbon tetrachloride were refluxed for about 6 hr. in a water bath. The mixture was washed with a 5% solution of sodium hydroxide in order to remove the bromine and benzoic acid that was formed during the reaction. The solvent was distilled and the solid residue thus obtained was stirred well with petroleum ether and filtered. From the filtrate was obtained 7.3 g. (67%) of diphenyl disulfide. The residue (33.2 g., 97%) was recrystallized from a mixture of acetone and ligroin to give shining plates of *N*-tritylsuccinimide, m.p. 203–204°.

Anal. Calcd. for $C_{23}H_{19}NO_2$: C, 80.90; H, 5.61; N, 4.10. Found: C, 80.76; H, 5.62; N, 4.10.

In a separate run using chloroform as solvent, an aliquot quantity of the reaction mixture was taken and titrated with standard sodium thiosulfate iodometrically; the bromine titrated quantitatively. Also a 48% yield of diphenyl disulfide was obtained without washing the reaction mixture with sodium hydroxide.

Reaction of phenyl trityl sulfide with ethoxide. Phenyl trityl sulfide (17.6 g., 0.05 mole) was refluxed for 3 hr. with a solution of sodium ethoxide prepared from 5 g. of sodium and an excess of absolute ethanol. Upon cooling 14.5 g. of solid crystallized, m.p. 105–106° after one recrystallization from ethanol. This gave no depression in melting point with a sample of the starting material. An additional 1.6 g. was obtained on evaporating the ethanol, washing with water, and extracting with ether.

Reaction of phenyl trityl sulfide with phenylmagnesium bromide. To phenyl Grignard, prepared from 2.4 g of magnesium and 15.7 g. of bromobenzene in ethyl ether, was added a solution of 17.0 g. (0.05 mole) of phenyl trityl sulfide in about 100 ml. of dry benzene. After 12 hr. of stirring, the mixture was hydrolyzed with a saturated solution of ammonium chloride; the organic layer was separated and the aqueous layer was extracted several times with benzene. From the combined benzene extracts 15.3 g. of the unchanged phenyl trityl sulfide were recovered.

Hydrolysis of the reaction mixture with dilute acid solution gives cleavage products, due the reaction of the acid with phenyl trityl sulfide.

PITTSBURGH 19, PA.

(8) All microanalyses were carried out by Elek Microanalytical Laboratories, Los Angeles, Calif., or Dr. Alfred Bernhardt, Mikroanalytisches Laboratorium, Mulheim, Germany. Melting points reported are uncorrected.

(9) H. J. Lucas and R. R. Kennedy, *Org. Syntheses*, **Coll. Vol. III**, 432 (1955).

(10) K. H. Pausacker, *J. Chem. Soc.*, 107 (1953).

(11) C. Finzi and V. Bellavita, *Gazz. chim. ital.*, **62**, 699–709 (1932).

(12) W. E. Bachmann, *Org. Syn.*, **23**, 100 (1943).

(13) L. V. Pechmann, *Ber.*, **6**, 534 (1873).

(14) E. Fromm and P. Schenoldt, *Ber.*, **40**, 2870 (1907).

(15) Shriner and Fuson, *Identification of Organic Compounds*, Third Edition, John Wiley & Sons, New York, p. 282.

[CONTRIBUTION FROM THE ORGANIC CHEMICALS DIVISION, ST. LOUIS RESEARCH DEPARTMENT, MONSANTO CHEMICAL CO.]

The Preparation of Some Diaryl Sulfides and Sulfones

J. ROBERT CAMPBELL AND ROGER E. HATTON

Received November 17, 1960

Some new diaryl sulfides have been synthesized from sodium thiophenolates and aryl bromides by a simple nucleophilic displacement reaction. All were converted into the corresponding sulfones. Preparation of a bissulfide and sulfone is described.

Several new diaryl sulfides and the corresponding sulfones were prepared for study in one extensive program in this Laboratory. Preparation of the sulfides was somewhat different from published procedures. However, conversion of these sulfides to their sulfones was accomplished by the standard hydrogen peroxide oxidation.

Metal thiophenolates have often been employed to displace the halogen in aryl halides forming diaryl sulfides. Aromatic bromides react with lead thiophenolates at high temperatures.[1] A variety of sulfides has been obtained from cuprous thiophenolate and aromatic chlorides in quinoline.[2] When copper is used as a catalyst, sodium thiophenolates replace activated halogens in aromatic halides.[1] Without copper sodium thiophenolate will react with aryl halides providing the halogen is highly activated by nitro groups.[3]

All the diaryl sulfides reported here were synthesized from aryl bromides and sodium thiophenolates in dimethylformamide in the absence of any catalyst. The general procedure involves simply refluxing these reactants (thiophenolates prepared *in situ*) in dimethylformamide for several hours, distilling solvent and isolating the product. The sulfides made by this method are listed in Table I. The first column, R, denotes the substituent arising from the aryl bromide and the second column, R′, that from the thiophenolate.

Somewhat surprising is the effect R has on the reactivity of the halide. In every instance a trifluoromethyl group in the *meta* position gave good to excellent yields of the sulfide. No resonance effect can be exerted by this substituent from its position in the nucleus. The inductive effect must account for the high yields by promoting attack of the nucleophilic thiophenolate ions. The case of *m*-nitrophenyl *m*-tolyl sulfide presents an anomaly since the yield was so low. Here, a nitro group has replaced the trifluoromethyl substituent, but inductive effect should not change.

An attempt was made to prepare pentachlorophenyl α,α,α-trifluoro-*m*-tolyl sulfide from sodium pentachlorothiophenolate and *m*-bromobenzotrifluoride, but no reaction occurred. Evidently the superabundance of electronegative chlorines practically eliminates nucleophilic character in this thiophenol.

The mechanism of the reaction is probably a simple nucleophilic displacement with little, if any, occurring through a benzyne mechanism. Infrared studies of both sulfides and sulfones gave no indication of isomers which could form *via* the benzyne reaction.

A bissulfide, 4,4′-bis(α,α,α-trifluoro-*m*-toluenemercapto)biphenyl, was also synthesized by the described procedure. Starting materials were *m*-bromobenzotrifluoride and 4,4′-biphenyldithiol, which was obtained from the corresponding disulfonic acid *via* disulfonyl chloride.

EXPERIMENTAL[4]

General procedure for synthesis of diaryl sulfides. To a solution of 0.11 mole of aryl bromide and 0.15 mole of thiophenol in about 100 ml. of dimethylformamide was added 0.15 mole of sodium hydroxide in one portion. There was an initial mild exothermic reaction after which the mixture was stirred at room temperature until all sodium hydroxide had disappeared. It was then heated to reflux (145–155°) which was maintained for approximately 5 hr. Salt precipitated during this period. Dimethylformamide was distilled down to a thick residue which was treated with cold water. The oil that separated was removed with ether. The ether was washed with water, dried and evaporated to a residue, which was distilled. In Table I are given the diaryl sulfides with their properties and analyses.

2-Naphthyl α,α,α-trifluoro-m-tolyl sulfide. Following the above method 24.2 g. (0.11 mole) of *m*-bromobenzotrifluoride, 20.8 g. (0.13 mole) of 2-naphthalenethiol and 5.2 g. (0.13 mole) of sodium hydroxide yielded 30 g. (90%) of light yellow crystals. They melt at 65–66° when recrystallized from ethanol.

Anal. Calcd. for $C_{17}H_{11}F_3S$: S, 10.54. Found: S, 10.72.

4,4′Bis(α,α,α-trifluoro-m-toluenemercapto)biphenyl. A copious evolution of hydrogen chloride occurred when 83 g. (0.4 mole) of phosphorus pentachloride[5] was slowly added to 62.5 g. (0.2 mole) of 4,4′-biphenyldisulfonic acid. Following the addition, the mixture was heated slowly to 220° where homogeneity occurred. Hydrogen chloride and phosphorus oxychloride were removed under reduced pressure to a solid residue. Recrystallization of the solid from acetic acid gave 20.7 g. of 4,4′-biphenyldisulfonyl chloride, m.p. 200–202°. Literature[6] reports m.p. 203°.

(1) E. E. Reid, *Organic Chemistry of Bivalent Sulfur*, Vol. II, Chemical Publishing Co., Inc., New York, 1960, p. 28.

(2) R. Adams, W. Reifschneider, and M. D. Nair, *Croatica Chem. Acta*, **29**, 277 (1957); R. Adams and A. Ferretti, *J. Am. Chem. Soc.*, **81**, 4927 (1959).

(3) J. T. Bunnett and W. D. Merritt, Jr., *J. Am. Chem. Soc.*, **79**, 5967 (1957).

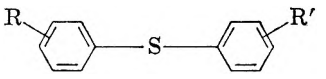
(4) All boiling points and melting points are uncorrected.

(5) Thionyl chloride failed in this reaction.

(6) S. Gabriel and A. Deutsch, *Ber.*, **13**, 390 (1880).

TABLE I

DIARYL SULFIDES

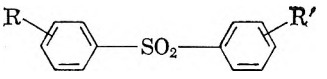


R	R′	M.P. B.P., (mm.)	Yield, %	Formula	Sulfur, % Calcd.	Sulfur, % Found
m-CF_3	H	146–158 (12–14)	93.5	$C_{13}H_9F_3S$	12.61	13.05
m-CF_3	*p*-CH_3	115 (1.5)	96.5	$C_{14}H_{11}F_3S$	11.95	11.95
m-CF_3	*m*-CH_3	99–110 (0.6)	90	$C_{14}H_{11}F_3S$	11.95	12.07
m-CF_3	*o*-CH_3	94–95 (0.5)	89.5	$C_{14}H_{11}F_3S$	—[a]	—
m-CF_3	*p*-*t*-C_4H_9	119–123 (0.7)	96.5	$C_{17}H_{17}F_3S$	10.33	10.46
m-CF_3	*m*-CF_3	93–100 (0.8)	77	$C_{14}H_8F_6S$	—[a]	—
m-CF_3	*p*-Cl	118–121 (1)	61	$C_{13}H_8ClF_3S$	11.10	11.24
CH_3	*m*-CH_3	114–116 (0.3)	—	$C_{14}H_{14}S$	14.96[b]	14.76
m-NO_2	*m*-CH_3	[a]	—	—	—	—
p-C_6H_5	*m*-CH_3	[a]	—	—	—	—
p-C_6H_5O	H	172–177 (0.5)[c]	46	$C_{18}H_{14}OS$	11.52	11.48

[a] Converted to sulfone without purification and/or identification. [b] % C: calcd.—78.46, found—78.10; % H: calcd.—6.58, found—7.09. [c] n_D^{24} 1.6440.

TABLE II

DIARYL SULFONES



R	R′	M.P.	Yield, %	Formula	Sulfur, % Calcd.	Sulfur, % Found
m-CF_3	H[a]	77–78	93	$C_{13}H_9F_3O_2S$	11.20	11.13
m-CF_3	*p*-CH_3	80–81[b] 101–102[c]	95	$C_{14}H_{11}F_3O_2S$	10.68	10.80
m-CF_3	*m*-CH_3	73–74[b]	90	$C_{14}H_{11}F_3O_2S$	10.68	11.13[d]
m-CF_3	*o*-CH_3	66–67[b]	75	$C_{14}H_{11}F_3O_2S$	10.68	10.65
m-CF_3	*p*-*t*-C_4H_9	101–102[c]	91	$C_{17}H_{17}F_3O_2S$	9.36	9.54
m-CF_3	*m*-CF_3	87–89[b]	93.5	$C_{14}H_8F_6O_2S$	9.05	9.15
m-CF_3	*p*-Cl	61–63[b]	81	$C_{13}H_8ClF_3O_2S$	10.00	9.80
m-CH_3	*m*-CH_3	94–95[c,e]	—	$C_{14}H_{14}O_2S$	14.96	14.76
m-NO_2	*m*-CH_3	95–96[f]	—	$C_{13}H_{11}NO_4S$	11.57	11.50
p-C_6H_5	*m*-CH_3	129[g]	39[h]	$C_{19}H_{16}O_2S$	10.39	10.87
p-C_6H_5O	H	92–93[i]	72	$C_{18}H_{14}O_3S$	10.33	10.57

[a] G. W. Story and C. R. Bresson, *J. Org. Chem.*, **24**, 1892 (1959), report m.p. 77–78° and 49% yield by another way. [b] From petroleum ether (b.p. 77–98°). [c] From petroleum ether (b.p. 60–70°). [d] % C: calcd.—55.99, found—55.81; % H: calcd.—3.69, found—3.88. [e] M. T. Bogert and M. R. Mandelbaum, *J. Am. Chem. Soc.*, **45**, 3045 (1923) give m.p. 94°. [f] From ether. [g] From ethanol. [h] Based on 4-bromobiphenyl. [i] From benzene–petroleum ether (b.p. 77–98°).

Following the procedure of Marvel and Caesar[7] about 21 g. (0.06 mole) of the above disulfonyl chloride and 300 g. (1.35 mole) of stannous chloride dihydrate in 1200 ml. of acetic acid yielded 12 g. (92%) of slightly impure 4,4′-biphenyldithiol, m.p. 171–174°. Marvel and Caesar's value for pure product is 179–180°.

The general procedure above with one exception was employed to prepare this dithio ether. The reflux period was increased to about 15 hr. Thus, 12 g. (0.055 mole) of the dithiol, 33.7 g. (0.15 mole) of *m*-bromobenzotrifluoride, and 4.4 g. (0.11 mole) of sodium hydroxide in 150 ml. of dimethylformamide gave 18.3 g. (66%) of 4,4′-bis(α,α,α-trifluoro-*m*-toluenemercapto)biphenyl, b.p. 235–245° (0.2 mm.), which slowly solidified to a low melting solid. No other identification was attempted, but the product was oxidized to the disulfone below.

General procedure for synthesis of diaryl sulfones. The sulfides were dissolved in acetic acid and treated with a large excess of 30% hydrogen peroxide according to standard procedures. Table II reports the diaryl sulfones prepared together with properties and analyses.

2-Naphthyl α,α,α-trifluoro-m-tolyl sulfone. In the above way there was obtained 26.1 g. (78%) of tan solid from 30 g. (0.1 mole) of 2-naphthyl α,α,α-trifluoro-*m*-tolyl sulfide and 50 ml. of 30% hydrogen peroxide. The sulfone melts at 101–103° when recrystallized from ethanol, and at 104–105° from petroleum ether (b.p. 77–98°).

Anal. Calcd. for $C_{17}H_{11}F_3O_2S$: S, 9.53. Found: S, 9.99.

4,4′-Bis(α,α,α-trifluoro-m-toluenesulfonyl)biphenyl. The general method for synthesis of sulfones was utilized to prepare 20.9 g. (98%) of white crystals, m.p. 195–200°, from 18.3 g. (0.036 mole) of 4,4′-bis(α,α,α-trifluoro-*m*-toluenemercapto)biphenyl and 20 ml. of 30% hydrogen peroxide in 100 ml. of acetic acid. Recrystallization from benzene raised the melting point of the disulfone to 201–202°.

Anal. Calcd. for $C_{26}H_{16}F_6O_4S_2$: S, 11.26. Found: S, 11.68.

ST. LOUIS 77, MO.

(7) C. F. Marvel and P. D. Caesar, *J. Am. Chem. Soc.*, **73**, 1097 (1951).

[CONTRIBUTION FROM THE DEPARTMENT OF APPLIED CHEMISTRY, COLLEGE OF ENGINEERING, UNIVERSITY OF OSAKA PREFECTURE]

Organic Polysulfides. III. Synthesis and Some Properties of Several Unsymmetrical Polysulfides[1]

TAKESHIGE NAKABAYASHI AND JITSUO TSURUGI

Received October 31, 1960

Several unsymmetrical trisulfides, RSSSR′, were prepared by condensation of alkyl hydrodisulfide RSSH with an arenesulfenyl chloride R′SCl or thiocyanate R′SSCN. Here R represents benzhydryl or benzyl groups, and R′ 2-nitrophenyl, 2-nitro-4-chlorophenyl, 2,4-dinitrophenyl, or 2-naphthyl groups. Ultraviolet absorption spectra of these unsymmetrical trisulfides were determined and compared with those of the corresponding unsymmetrical mono- and disulfides as well as with symmetrical ones.

Recently some unsymmetrical disulfides have been prepared by various investigators,[2] but only a few literature references have been found on the synthesis of unsymmetrical trisulfides. A synthetic method for unsymmetrical trisulfides is the condensation reaction of a disulfide chloride with a mercaptan

$$RSSCl + R'SH \longrightarrow RSSSR'$$

by which ethyl methyl[3] and ethyl benzyl trisulfides[4] were obtained as oily substances and 2-nitrophenyl hydroxyphenyl trisulfide[4] as a crystalline substance. More recently some liquid unsymmetrical (alkyl aryl) trisulfides were prepared by a rather complicated reaction[5] indicated below.

$$RNH{-}SO{-}SR' + 3\,R''SH \longrightarrow R''{-}SSS{-}R' + RNH_2 + R''{-}SS{-}R'' + H_2O$$

where R″ represents alkyl and R′ aryl groups. Formation of a symmetrical disulfide as well as a desired trisulfide makes it necessary to isolate the desired product by distillation.

Another probable synthetic method for unsymmetrical trisulfides may be a condensation reaction of arenesulfenyl chloride[6] (R′SCl) or thiocyanate[6] (R′SSCN) with alkyl hydrodisulfides (RSSH), which were prepared by Böhme[7] and were utilized by the present authors[8] to synthesize dialkyl pentaane hexasulfides. In the present paper some crystalline unsymmetrical trisulfides were prepared by this method.

$$RSSH + XSAr \longrightarrow RSSSAr \qquad (1)$$

where RSSH represents benzhydryl or benzyl hydrodisulfide and ArSX represents nitrobenzenesulfenyl chloride or 2-naphthalenesulfenyl thiocyanate. In order to determine some physical properties and ultraviolet spectra, it is easier to use crystalline substances.

The corresponding unsymmetrical mono- and disulfides, few of which have been reported in the literature, were prepared in the present paper to compare some of their properties and ultraviolet spectra with those of the trisulfides.

$$RSH + XSAr \longrightarrow RSSAr \qquad (2)$$

$$RX + HSAr \longrightarrow RSAr \qquad (3)$$

or

$$RSH + XAr \longrightarrow RSAr \qquad (4)$$

where X represents halogen or thiocyanate group. Table I indicates melting points and analytical data of these series of unsymmetrical mono-, di- and trisulfides, one group of which is benzhydryl or benzyl and another is one of three types of nitrophenyl groups or a 2-naphthyl group. For synthesis of the 2-naphthyl benzhydryl or benzyl di- and trisulfides, the naphthalenesulfenyl thiocyanate rather than the chloride was used, because the former is more easily prepared and more stable than the latter. Besides the series of unsymmetrical polysulfides cited in Table I the symmetrical polysulfides, 2,2′-dinaphthyl mono-, di- and trisulfides were also prepared, in order to compare some properties of the unsymmetrical polysulfides with those of the symmetrical ones. The other symmetrical polysulfides, dibenzhydryl or dibenzyl polysulfides (mono-, di- and trisulfides) were reported in Part I[8] of this series.

Ultraviolet absorption spectra of benzhydryl 2-nitrophenyl mono-, di-, and trisulfides were measured in alcoholic solution between 220 and 400 mμ and are indicated in Fig. 1. The ultraviolet absorption spectra of various unsymmetrical sul-

(1) Part II, J. Tsurugi and T. Nakabayashi, *J. Org. Chem.*, **25**, 1744 (1960).

(2) (a) G. Jacini and F. Lauria, *Gazz. chim. ital.*, **80**, 762 (1950); *Chem. Abstr.*, **46**, 4499 (1952). G. Jacini *et al.*, *Gazz. chim. ital.*, **82**, 297 (1952); *Chem. Abstr.*, **47**, 8680 (1953); (b) S. Mugnusson, J. E. Christian, and G. L. Jenkins, *J. Am. Pharm. Assoc., Sci. Ed.*, **36**, 257, 261 (1947); (c) H. Brintzinger and M. Langheck, *Chem. Ber.*, **86**, 557 (1953); **87**, 325 (1954); (d) A. Schöberl, H. Tausent, and H. Gräfji, *Angew. Chem.*, **68**, 213 (1956).

(3) H. Böhme and G. V. Ham, *Ann.*, **617**, 62 (1958).

(4) J. F. Harris, Jr., Univ. Microfilms Pub. No. 4927, 111 p.; *Chem. Abstr.*, **48**, 2636 (1954).

(5) G. Kresze and H. P. Patzschke, *Chem. Ber.*, **93**, 380 (1960).

(6) N. Kharasch, *et al.*, *Chem. Rev.*, **39**, 269 (1946).

(7) H. Böhme and G. Zinner, *Ann.*, **585**, 142 (1954).

(8) J. Tsurugi and T. Nakabayashi, *J. Org. Chem.*, **24**, 807 (1959).

TABLE I

MELTING POINTS, YIELDS, AND ANALYTICAL DATA OF UNSYMMETRICAL POLYSULFIDES

No.	Compound	Yield, %	Formula	M.P.	Calcd. C	Calcd. H	Calcd. S	Found C	Found H	Found S
			2-NITROPHENYL BENZHYDRYL SERIES							
1	Monosulfide	65.4	$C_{19}H_{15}NO_2S$	111–112	71.00	4.70	9.98	70.88	4.91	9.71
2	Disulfide	95	$C_{19}H_{15}NO_2S_2$	81–82	64.56	4.28	18.15	64.36	4.61	17.99
3	Trisulfide	70	$C_{19}H_{15}NO_2S_3$	94–96	59.19	3.92	24.95	59.35	4.29	24.73
			2-NITRO-4-CHLOROPHENYL BENZHYDRYL SERIES							
4	Monosulfide	53.6	$C_{19}H_{14}ClNO_2S$	133.5–134.5	64.13	3.97		63.81	3.97	
5	Disulfide	87.6	$C_{19}H_{14}ClNO_2S_2$	109–110	58.83	3.64		58.62	3.63	
6	Trisulfide	88	$C_{19}H_{14}ClNO_2S_3$	80–81	54.34	3.36		54.04	3.19	
			2,4-DINITROPHENYL BENZHYDRYL SERIES							
7	Monosulfide	95.6	$C_{19}H_{14}N_2O_4S$	122–123 (122–123)[a]	62.28	3.85	8.75	62.51	4.25	8.48
8	Disulfide	92.5	$C_{19}H_{14}N_2O_4S_2$	120.5–121	57.27	3.54	16.10	57.23	3.81	15.83
9	Trisulfide	98	$C_{19}H_{14}N_2O_4S_3$	129–130	53.00	3.28	22.35	53.26	3.52	22.39
			2-NITROPHENYL BENZYL SERIES							
10	Monosulfide	77.5	$C_{13}H_{11}NO_2S$	82–83 (82–83)[b]	63.65	4.52	13.36	64.12	4.77	13.27
11	Disulfide	95	$C_{13}H_{11}NO_2S_2$	53–54 (54)[c]	56.29	4.00	23.10	56.34	4.32	23.49
12	Trisulfide	53	$C_{13}H_{11}NO_2S_3$	80.5–81	50.46	3.58	31.09	50.28	3.85	31.32
			2-NITRO-4-CHLOROPHENYL BENZYL SERIES							
13	Monosulfide	56	$C_{13}H_{10}ClNO_2S$	129–130.5	55.81	3.60		55.75	4.26	
14	Disulfide	77	$C_{13}H_{10}ClNO_2S_2$	81–82	50.07	3.23		50.30	3.23	
15	Trisulfide	56	$C_{13}H_{10}ClNO_2S_3$	82.5–83.5	45.39	2.86		45.73	3.10	
			2,4-DINITROPHENYL BENZYL SERIES							
16	Monosulfide	90	$C_{13}H_{10}N_2O_4S$	128–129 (130)[d]	53.78	3.47	11.05	53.88	3.65	11.28
17	Disulfide	94	$C_{13}H_{10}N_2O_4S_2$	112–112.5	48.43	3.13	19.87	48.36	3.31	19.78
18	Trisulfide	76.5	$C_{13}H_{10}N_2O_4S_3$	112.5–113	44.05	2.84	27.14	43.85	3.00	27.07
			2-NAPHTHYL BENZHYDRYL SERIES							
19	Monosulfide	69	$C_{23}H_{18}S$	120–121	84.62	5.56	9.82	84.49	5.42	10.0
20	Disulfide	71	$C_{23}H_{18}S_2$	94–95	77.05	5.06	17.90	76.58	5.01	18.1
21	Trisulfide	90.4	$C_{23}H_{18}S_3$	69–71	70.72	4.65	24.63	71.24	4.75	24.0
			2-NAPHTHYL BENZYL SERIES							
22	Monosulfide	96.4	$C_{17}H_{14}S$	89–90 (89.8–90.5)[e]	81.55	5.64	12.81	81.35	5.33	12.5
23	Disulfide	61	$C_{17}H_{14}S_2$	60–61.5	72.29	5.00	22.71	71.60	4.86	22.6
24	Trisulfide	73	$C_{17}H_{14}S_3$	69–71	64.92	4.49	30.59	64.99	4.55	30.6

[a] J. Tsurugi and T. Nakabayashi, *Nippon Kagaku Zasshi*, 77, 581 (1956). [b] A. Sieglitz and H. Koch, *Chem. Ber.*, 58, 82 (1925). [c] H. B. Footner and S. Smiles, *J. Chem. Soc.*, 127, 2887 (1925); *Chem. Abstr.*, 20, 747 (1926). [d] R. W. Bost, J. O. Turner, and R. D. Norton, *J. Am. Chem. Soc.*, 54, 1986 (1932). [e] A. H. Weinstein and R. M. Pierson, *J. Org. Chem.*, 23, 557 (1958).

fides as well as symmetrical ones have already been interpreted by Koch.[9] However, the interpretation of the ultraviolet absorption spectra of unsymmetrical disulfides and trisulfides have never been presented. Koch[9] suggested that the weak absorption band near 350 mμ of phenyl 2-nitrophenyl sulfide may be attributed to its canonical resonance structure (I), which seems both sterically and energetically reasonable. A postulated polar excited structure of the *o*-quinoid type (II) was considered by Koch to be improbable because of the resulting interference between the van der Waals radii of oxygen and sulfur. Weak absorption bands near 350 mμ of benzhydryl 2-nitrophenyl mono-, di-, and trisulfides in Fig. 1 may be associated with the similar band of phenyl 2-nitrophenyl sulfide or with that of di-2-nitrophenyl sulfide, although intensities of the band of the unsymmetrical disulfides are a little less than those of the latter two. Absorption maxima shift to shorter wave length as the number of sulfur atoms increases from one to three. The 245 mμ absorption of the unsymmetrical monosulfide in Fig. 1 cannot be interpreted at the present time, but the similar absorption is found in (symmetrical) di-2-nitrophenyl sulfide and the similar absorption with the higher intensity is displayed by (symmetrical) di-2-nitrophenyl disulfide. However, both benzhydryl 2-nitrophenyl di-and trisulfides do not have similar absorption maxima in the same range. Generally it can be said that as compared with the spectra of (symmetrical) dibenzhydryl

(9) H. P. Koch, *J. Chem. Soc.*, 387 (*1949*).

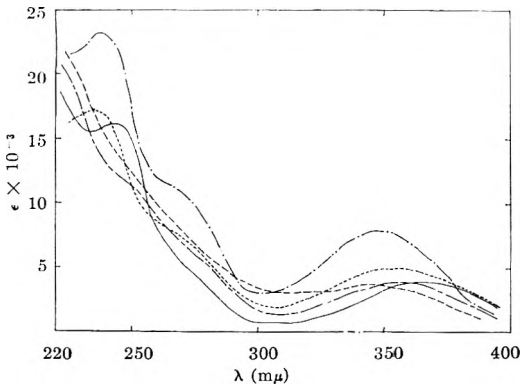
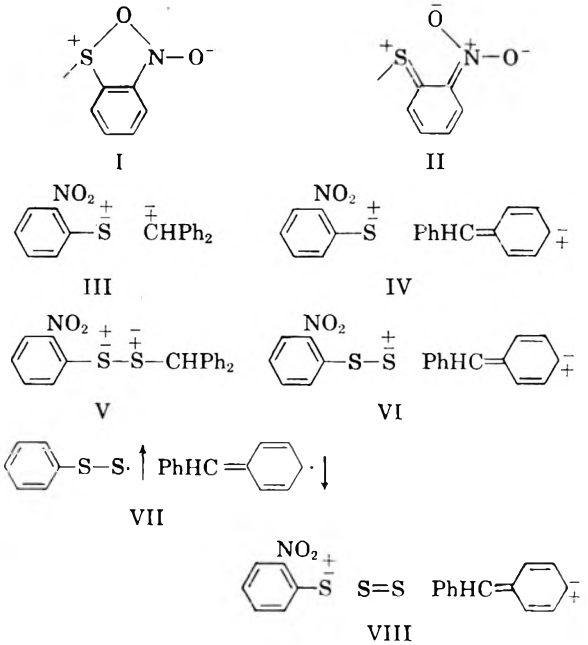


Fig. 1. Ultraviolet absorption spectra of a series of 2-nitrophenyl benzhydryl sulfides (———, mono-; — — —, di-; – – – –, trisulfides) and of di-2-nitrophenyl sulfides (- - - - - -, mono-; — · —, disulfides)

mono-, di-, and trisulfides and with that of (symmetrical) di-2-nitrophenyl sulfide, those of unsymmetrical ones seem to be the corresponding resultants of di-2-nitrophenyl sulfide and the dibenzhydryl series, except for the deficiency of the maxima in the range of shorter wave length of the unsymmetrical di- and trisulfides. Canonical structures of type III and of polar (*o*- or *p*-) quinoid type IV in addition to I make contribution to the optical excited states of benzhydryl 2-nitrophenyl monosulfide. However, the following canonical



structures V, VI, and VII besides I may contribute to the optical excited states of benzhydryl 2-nitrophenyl disulfide. The additional canonical structure VIII may be plausible for benzyhydryl 2-nitrophenyl trisulfide in addition to the ones similar to V, VI, and VII and in addition to I mentioned above. Therefore, the absorption of the unsymmetrical trisulfide in the range between 220–300 mμ becomes more intensive and shifts to longer wave lengths. Flatter curves of the unsymmetrical disulfide and trisulfide as compared to the monosulfide may result for the same reason.

Similar observations are found in a series of benzyl 2-nitrophenyl mono-, di-, and trisulfides and of benzyl 2-nitro-4-chlorophenyl mono-, di-, and trisulfides as well as in a series of benzhydryl 2-nitro-4-chlorophenyl mono-, di-, and trisulfides. The absorption maxima and their intensities are tabulated in Table II.

TABLE II

ULTRAVIOLET ABSORPTION SPECTRA OF UNSYMMETRICAL MONO-, DI-, AND TRISULFIDES

	λ_{max}, mμ	ϵ_{max}	λ_{max}, mμ	ϵ_{max}
BENZYL 2-NITROPHENYL SERIES				
Monosulfide	245	20,700	365	4,500
Disulfide	250 (shoulder)	13,500	355	4,300
Trisulfide	—	—	345	3,700
BENZYL 2-NITRO-4-CHLOROPHENYL SERIES				
Monosulfide	250	24,700	380	4,700
	270 (shoulder)	11,500		
Disulfide	240 (shoulder)	14,100	365	3,800
Trisulfide	—	—	355	3,400
BENZYL 2,4-DINITROPHENYL SERIES				
Monosulfide	—	—	330	12,900
Disulfide	—	—	320	9,200
Trisulfide	—	—	315	8,900
BENZHYDRYL 2-NITRO-4-CHLOROPHENYL SERIES				
Monosulfide	250	19,700	380	4,100
Disulfide	—	—	365	3,900
Trisulfide	—	—	360	3,800

The absorption spectra of benzhydryl 2,4-dinitrophenyl mono-, di-, and trisulfides are indicated in Fig. 2. The 330 mμ absorption maximum of the monosulfide and those of the disulfide and trisulfide near there may be ascribed to a group —S—$C_6H_4(NO_2)_2$-(2,4), because an intense absorption band of phenyl 4-nitrophenyl sulfide was found at 337,5 mμ,[9] and the corresponding *ortho* compound has the maximum near 365 mμ. Flattening of the spectra also occurs as the number of sulfur atoms increase from one to three. No further interpretation of the spectra will be attempted in view of the paucity of the reference data.

With regard to the spectra of naphthyl benzyl polysulfides shown in Fig. 3, that of the monosulfide, if it is indicated in logarithmic scale, is in complete agreement with that recorded by Weinstein and Pierson.[10] They observed a maximum similar to the 285 mμ peak of 2-naphthyl benzyl sulfide in 2-thionaphthol at 283 mμ, and ascribed it to a

(10) A. H. Weinstein and R. M. Pierson, *J. Org. Chem.*, **23**, 554 (1958).

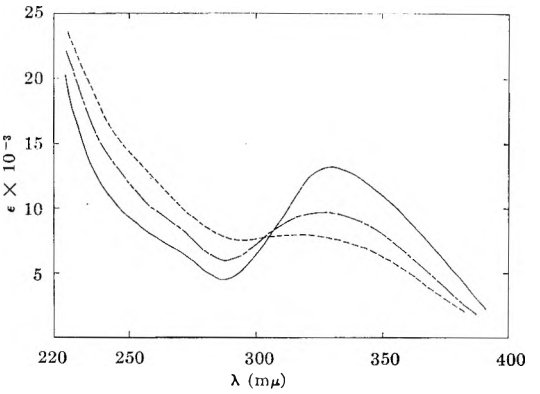


Fig. 2. Ultraviolet absorption spectra of a series of 2,4-dinitrophenyl benzhydryl sulfides (———, mono-; — — —, di-; - - - -, trisulfides)

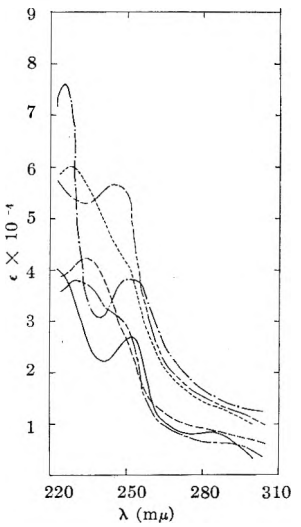


Fig. 3. Ultraviolet absorption spectra of a series of 2-naphthyl benzyl sulfides (———, mono-; — — —, di-; - - - -, trisulfides) and of di-2-naphthyl sulfides (— · —, mono-; — — —, di-; - - - - - -, trisulfides)

naphthalene chromophore bathochromically shifted by a thiol auxochrome. The 253 mμ absorption peak of 2-naphthyl benzyl sulfide resembles the absorption of 2,2′-dinaphthyl sulfide, although intensity of the former is considerably weaker than that of the latter, and may be ascribed to a modified naphthalene chromophore. As for the series of alkyl nitrophenyl polysulfides mentioned above, in this series also flattening of the curves is observed as the number of sulfur atoms increases from one to three. The same relationship was observed in ultraviolet spectra of a series of 2-naphthyl benzhydryl mono-, di- and trisulfides.

Molecular refraction of a series of unsymmetrical 2-naphthyl benzhydryl or benzyl polysulfides were determined. The results are indicated in Table III.

Calculated values of the sulfur atoms in the mono-, di-, and trisulfides in each series are in good agreement within experimental error. This confirms the existence of linear sulfur chains in each trisulfide as in the disulfide.

TABLE III

MOLAR REFRACTIONS OF 2-NAPHTHYL BENZHYDRYL OR BENZYL POLYSULFIDES AND ATOMIC REFRACTION OF SULFUR IN THESE COMPOUNDS

Unsymmetrical Sulfides R—Sn—R′	Molar Refraction MR_D (RSnR′)	Refraction of Group Sn $R_D(Sn)$	Atomic Refraction of Sulfur $R_D(Sn)/n$
2-$C_{10}H_7$—S—$CH(C_6H_5)_2$	106.7	10.2	10.2
2-$C_{10}H_7$—S_2—$CH(C_6H_5)_2$	116.8	20.3	10.1
2-$C_{10}H_7$—S_3—$CH(C_6H_5)_2$	126.0	29.5	9.8
			10.0 ± 0.2
2-$C_{10}H_7$—S—$CH_2C_6H_5$	81.1	9.8	9.8
2-$C_{10}H_7$—S_2—$CH_2C_6H_5$	92.6	21.3	10.7
2-$C_{10}H_7$—S_3—$CH_2C_6H_5$	101.3	30.0	10.0
			10.2 ± 0.5

EXPERIMENTAL

Unsymmetrical monosulfides. According to Equation 3, 0.02 mole of arenethiol (2-nitrobenzenethiol or 2-naphthalenethiol) in 50 ml. of ethanol was converted to potassium-thiolate by potassium hydroxide, and then was allowed to react with an equivalent amount of benzyl bromide in 50 ml. of dry benzene in an atmosphere of inert gas at refluxing temperature for 2 hr. under stirring. When benzhydryl bromide was used in place of benzyl bromide, not potassium arenethiolate but arenethiol itself was refluxed with benzhydryl bromide to avoid the probable hydrolysis of the bromide, and the reaction was carried out in benzene solution. The solution was washed with water and dried with anhydrous sodium sulfate. After the solvent was evaporated, compounds No. 1 and No. 19 were recrystallized from a benzene-ethanol mixture. No. 10 was recrystallized from ether, and No. 22 from ethanol.

The other unsymmetrical monosulfides were prepared by Equation 4. To an absolute alcoholic solution of potassium α-diphenylmethane- or α-toluenethiolate was added an equivalent amount of chloronitrobenzene (1,4-dichloro-2 nitrobenzene or 2,4-dinitrochlorobenzene) in ethanol in a stream of inert gas under stirring. The mixture was heated for 3 hr. at 50–70°, and diluted with 10 volumes of water. Compounds No. 4 and No. 13 were recrystallized from benzene, No. 7 and No. 16 recrystallized from a mixture of benzene and ethanol.

Unsymmetrical disulfides. To a solution of 0.01 mole of alkanethiol (α-diphenylmethane- or α-toluenethiol) in 50 ml. of dry benzene was added a soution of arenesulfenyl chloride (2-nitrobenzenesulfenyl,[11] 2-nitro-4-chlorobenzenesulfenyl,[12] or 2,4-dinitrobenzenesulfenyl chloride[13]) at room temperature. The flask was protected by a calcium chloride tube and kept standing overnight. The solution was washed with water and dried. After the solvent was evaporated under diminished pressure, the solid obtained was recrystallized from a mixture of benzene and ethanol. Compounds No. 2, 5, 8, 11, 14, and 17 were thus prepared.

2-Naphthalenesulfenyl thiocyanate[14] was used to prepare unsymmetrical naphthyl alkyl disulfides. The sulfenyl thiocyanate (0.01 mole) in 50 ml. of dry ether was added to a solution of alkanethiol (α-diphenylmethane- or α-toluenethiol) in 50 ml. of dry ether at room temperature in a stream of inert gas with stirring. The mixture was stirred for an

(11) Max H. Hubacher, *Org. Syntheses*, Coll. Vol. II, 455 (1948).

(12) Th. Zincke and J. Baeumer, *Ann.*, **416**, 86 (1918).

(13) N. Kharasch, G. I. Gleason, and C. M. Buess, *J. Am. Chem. Soc.*, **72**, 1796 (1950).

(14) H. Lecher and M. Wittwer, *Chem. Ber.*, **55**, 1474 (1922).

hour. After being washed and dried, the solvent was evaporated. The solid obtained was recrystallized from ethanol. Compounds No. 20 and 23 were prepared by the method described above.

Unsymmetrical trisulfides. To a solution of 0.02 mole of alkyl hydrodisulfide (benzhydryl or benzyl hydrodisulfide) in 50 ml. of dry ether was added a solution of arenesulfenyl chloride (2-nitrobenzenesulfenyl, 2-nitro-4-chlorobenzenesulfenyl, or 2,4-dinitrobenzenesulfenyl chloride) in 50 ml. of dry ether at room temperature in a stream of inert gas under stirring. A very slight excess of the hydrosulfide was used, otherwise diaryl disulfide was formed from the arenesulfenyl chloride. This made it difficult to isolate the unsymmetrical from the symmetrical disulfide. The reaction system was protected against moisture by a calcium chloride tube. Stirring was continued for 2 hr., and the solution was washed, dried, and concentrated by evaporation. The solid obtained was recrystallized from ether.

For the synthesis of 2-naphthyl benzhydryl or benzyl trisulfide, 2-naphthalenesulfenyl thiocyanate was used in place of the sulfenyl chloride. The procedure was the same as for the above nitrophenyl alkyl trisulfides.

2,2'-Dinaphthyl mono-, di-, and trisulfides. These were also prepared as specimens for determining the spectra. The monosulfide was obtained by pyrolysis of lead 2-naphthalenethiolate[15] at 300–320° under 100 mm., and after several recrystallizations from a benzene-ethanol mixture, m.p. 148–149° (lit.,[15] m.p. 151°), the yield was 45%.

Anal. Calcd. for $C_{20}H_{14}S$: C, 83.88; H, 4.93; S, 11.20. Found: C, 84.04; H, 5.33; S, 11.0.

The disulfide was the oxidation product of 2-naphthalenethiol by iodine,[10] recrystallized from benzene, m.p. 139° (lit.,[10] m.p. 141.8–142.6°), yield 98%.

Anal. Calcd. for $C_{20}H_{14}S_2$: C, 75.43; H, 4.43; S, 20.1. Found: C, 75.19; H, 4.33; S, 20.0.

The trisulfide was prepared by the ordinary method from the thiol and sulfur dichloride, recrystallized from benzene-ethanol mixture, m.p. 115–116° (Lit.,[16] m.p. 108–109°), yield 79%.

Anal. Calcd. for $C_{20}H_{14}S_3$: C, 68.53; H, 4.03; S, 27.45. Found: C, 68.75; H, 3.93; S, 26.8.

Determination of ultraviolet absorption spectra and molecular refraction. These were the same as those reported in Part I[8] of this series.

Acknowledgment. We wish to thank Dr. E. E. Campaigne of Indiana University for his kindness in revising the manuscript.

SAKI CITY, OSAKA, JAPAN

(15) F. Krafft and R. Schönherr, *Chem. Ber.*, **22**, 825 (1889); N. A. Lange and H. S. Haupt, *J. Am. Chem. Soc.*, **51**, 2277 (1929).

(16) T. Hornung, *J. prakt. Chem.* [2], **60**, 137 (1899).

[CONTRIBUTION 984 FROM THE CHEMISTRY LABORATORIES OF INDIANA UNIVERSITY]

The Ultraviolet Absorption Spectra of Some Unsymmetrical Disulfides[1]

E. CAMPAIGNE, J. TSURUGI,[2] AND W. W. MEYER

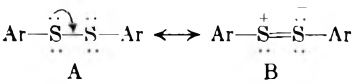
Received August 22, 1960

The ultraviolet absorption curves of certain unsymmetrical diaryl disulfides, Ar—S—S—Ar', were calculated as one-half the sum of the absorption curves of the two symmetrical disulfides, ArSSAr and Ar'SSAr'. Slight deviations from the calculated values in the observed curves were consistent with inductive effects of groups attached to sulfur in the two halves of the molecule, ArS— and Ar'S—. No transmission of electronic effects through the sulfur-sulfur bond could be detected in the ultraviolet spectra of the diaryl disulfides.

It is certain that disulfides undergo heterolytic cleavage in polar reactions. Nucleophilic cleavage of disulfide is evidenced by the reaction with organometallic reagents[3] and by Lewis-acid catalyzed electrophilic attack of disulfide on aromatic systems[4] and olefins.[5] Electrophilic cleavage may be illustrated by the reaction of disulfides with halides such as methyl iodide[6] or 2,4-dinitrochlorobenzene.[7]

The whole question of heterolytic scission of the sulfur-sulfur bond in disulfides has recently been reviewed[8] with numerous examples of both types of cleavage. Such cleavage must be initiated by polarization of the disulfide bond.

Polarization of the disulfide bond may be considered to be stabilized by resonance involving a 10-electron sulfur shell, as in A ⟷ B. One might



logically expect that placing a resonance system such as the two sulfur atoms of A ⟷ B between two chromophoric groups would be reflected in a bathochromic shift of the ultraviolet absorption of the simple chromophore. However, the opposite

(1) A Technical Report prepared under the sponsorship of the Office of Ordnance Research, United States Army, Contract DA 33-008-ORD 1916.

(2) Postdoctoral Research Associate 1959–1960, on leave from the University of Osaka Prefecture, Osaka, Japan.

(3) H. Burton and W. A. Davy, *J. Chem. Soc.*, 528 (1948).

(4) *Cf.* S. Archer and C. M. Suter, *J. Am. Chem. Soc.*, **74**, 4296 (1952); E. Campaigne and R. E. Cline, *J. Org. Chem.*, **21**, 39 (1956).

(5) *Cf.* B. Holmberg, *Arkiv Kemi, Mineral. Geol.*, **13B**, No. 14 (1939); A. Lein, D. McCauley, and A. Proell, U. S. Pat. **2,519,586**, Aug. 20, 1950 [*Chem. Abstr.*, **44**, 10728 (1950)].

(6) O. Haas and G. Dougherty, *J. Am. Chem. Soc.*, **62**, 1004 (1940).

(7) G. Leandri and A. Tundo, *Ann. Chim. (Rome)*, **45**, 832, 842 (1955).

(8) A. J. Parker and N. Kharasch, *Chem. Revs.*, **59**, 583 (1959).

effect has been observed.[9] A sulfur atom attached to an aromatic system acts as an unsaturated atom, causing a bathochromic shift of the absorption of the parent aromatic system.[10] For example, benzene shows a characteristic absorption at 202 mμ (ϵ = 7000) which is shifted to 236 mμ (ϵ = 10,000) in thiophenol.[11] Conversion of —SH to —SCH_3 causes a further shift to longer wavelength (thioanisole absorbs at 254 mμ, ϵ = 9000),[12] due to the inductive effect of the methyl group. However, oxidation to the disulfide causes a much smaller shift in absorption (diphenyl disulfide has an absorption maximum at 241 mμ, ϵ = 15,000). The effect of conversion of a thiol to a symmetrical disulfide is approximately that of bonding two identical chromophores in the same molecule by an insulating group (*i.e.*, doubling the molar intensity without shifting the wavelength of absorption). Such effects were reported on thiol and disulfide groups attached to cinnamic acid systems.[9]

In the case of a symmetrical disulfide, the resonance represented by A ⟷ B is really the sum of two equivalent resonance structures of equal but opposite polarity, C ⟷ B:

$$\underset{\text{C}}{Ar^a—\bar{S}—\overset{+}{S}—Ar^b} \longleftrightarrow \underset{\text{A}}{Ar^a—S—S—Ar^b} \longleftrightarrow \underset{\text{B}}{Ar^a—\overset{+}{S}—\bar{S}—Ar^b}$$

The resonance contribution of the polar disulfide bond to the aromatic system might therefore be presumed to be neutralized, and the absorption of an aromatic disulfide, A, should be essentially that of two moles of the simple chromophore ArS-. On the other hand, an unsymmetrical diaryl disulfide, D, in which one aryl group carried electron releasing groups while the other carried strong electron attracting groups would be expected to polarize preferentially in one way, D ⟷ E. Such an

$$\underset{\text{D}}{Ar\text{>}-\bar{S}—\overset{+}{S}\text{>}-Ar'} \longleftrightarrow \underset{\text{E}}{Ar\text{>}-\overset{+}{S}=\bar{S}\text{>}-Ar'}$$

effect might be reflected in bathochromic shifts of the ultraviolet absorption. On the other hand, a lack of transmission of resonance through the disulfide bond should be characterized by an absorption spectrum which would be the sum of one-half of the spectra of the two corresponding symmetrical disulfides:

$$\epsilon_{ArSSAr'} = {}^1/_2(\epsilon_{ArSSAr} + \epsilon_{Ar'SSAr'})$$

It is well known that the presence of an insulating group between two chromophores results in a spectrum in which the characteristic absorption of the two chromophores is generally additive.[13] The assumption is made that this relationship will not be valid if resonance is transmitted between the chromophores. This assumption is supported by the ultraviolet spectra of a series of stilbenes, where conjugation through the ethylenic linkage is well known.[14] The ultraviolet spectrum of *trans*-stilbene is characterized by a maximum at 295 mμ (ϵ = 29,000)[15] and a shoulder at 324 mμ (ϵ = 17,000)), while *trans*-4,4′-dinitrostilbene[16] has a peak at 333 mμ (ϵ = 29,000). The hypothetical spectrum, one-half the sum of the spectra of these symmetrical stilbenes, exhibits a maximum at 295 mμ (ϵ = 25,000) and a shoulder at 333 mμ (ϵ = 20,400). The actual spectrum for *trans*-4-nitrostilbene shows only one peak at 355 mμ (ϵ = 27,000).[15]

In order to examine the ultraviolet spectra of some unsymmetrical diaryl disulfides, a series of 4-nitrophenyl and 2,4-dinitrophenyl disulfides were prepared, in which the second aryl group was of the electron-rich class, phenyl, 4-tolyl, 4-anisyl, and β-naphthyl. These were chosen because they were all solids which could be purified by recrystallization. Unsymmetrical disulfides disproportionate on heating[17] or in acidic or basic solution[8] and are therefore difficult to obtain in the pure state. The compounds most commonly prepared in this class are those which are formed from treatment of the relatively stable nitrosulfenyl halides with thiols. These products are usually solids which can be purified by crystallization from cold solvents of low dielectric constant. They also contain a strong electron-attracting group, and hence are ideally suited to this study. The preparative detail and constants of these compounds are listed in Table I, parts A and B, and the syntheses described in the experimental part. Of these, the 4-methoxyphenyl and β-naphthyl derivatives are new.

As model compounds for spectral studies, the various symmetrical disulfides and corresponding methyl sulfides were prepared. Their properties are listed in Table I, parts C and D.

Discussion of the absorption spectra. The principal absorption maxima of all compounds investigated are tabulated in Table II. (All of the compounds absorb strongly in the far ultraviolet (below 220 mμ).) However, each simple methyl sulfide exhibits

(9) E. Campaigne and R. E. Cline, *J. Org. Chem.*, **21**, 32 (1956).

(10) K. Bowden, E. A. Braude, and E. R. H. Jones, *J. Chem. Soc.*, 948 (1946).

(11) *Cf. An Introduction to Electronic Absorption Spectroscopy in Organic Chemistry*, 2nd Ed., by A. E. Gillam and E. S. Stern, E. Arnold, London, 1957, p. 140.

(12) E. Fehnel and M. Carmack, *J. Am. Chem. Soc.*, **71**, 84 (1949).

(13) A. E. Gillam and E. S. Stern, *An Introduction to Electronic Absorption Spectroscopy in Organic Chemistry*, 2nd Ed., E. Arnold Ltd., London, 1957, p. 134.

(14) M. Calvin and R. E. Buckles, *J. Am. Chem. Soc.*, **62**, 3324 (1940).

(15) M. Calvin and H. W. Alter, *J. Chem. Phys.*, **19**, 765 (1951).

(16) Prepared according to the procedure of Walden and Kernbaum, *Ber.*, **23**, 1959 (1890). The spectrum was determined on a Carey Model 14 spectrophotometer. Absolute ethanol was used as a solvent in order to obtain data comparable to that of Calvin and Alter.

(17) G. Leandri and A. Tundo, *Ann. Chim.* (*Rome*), **44**, 63 (1954).

TABLE I

PHYSICAL CONSTANTS OF DIARYL DISULFIDES AND ARYL METHYL SULFIDES

Ar	M.P. Found	M.P. Reported	Formula	Sulfur, % Calcd.	Sulfur, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
			A. 4-NITROPHENYL ARYL DISULFIDES				
C_6H_5-	59–59.5	58–58.5[a]	$C_{12}H_9O_2NS_2$	24.35	24.26	5.23	5.41
4-$CH_3C_6H_4$-	63–63.5	62–62.5[a]	$C_{13}H_{11}O_2NS_2$	23.12	23.09	5.05	5.17
4-$CH_3OC_6H_4$-	72.5–73		$C_{13}H_{11}O_3NS_2$	21.86	21.86	4.77	4.89
β-$C_{10}H_7$-	85–85.5		$C_{16}H_{11}O_2NS_2$	20.46	20.47	4.47	4.59
			B. 2,4-DINITROPHENYL ARYL DISULFIDES				
C_6H_5-	87.5–88	86–87[a]	$C_{12}H_8O_4N_2S_2$	20.80	20.49	9.09	9.20
4-$CH_3C_6H_4$-	114–115	114–115[a]	$C_{13}H_{10}O_4N_2S_2$	19.89	19.76	8.69	8.65
4-$CH_3OC_6H_4$-	98		$C_{13}H_{10}O_5N_2S_2$	18.91	18.92	8.28	8.38
β-$C_{10}H_7$-	181		$C_{16}H_{10}O_4N_2S_2$	17.89	17.65	7.82	7.89
			C. SYMMETRICAL DISULFIDES				
C_6H_5-	62.5–63.5	61[b]	$C_{12}H_{10}S_2$				
4-$CH_3C_6H_4$-	48–49	46[b]	$C_{14}H_{14}S_2$				
4-$CH_3OC_6H_4$-	44–45	44–45[c]	$C_{14}H_{14}O_2S_2$				
β-$C_{10}H_7$-	143–143.5	139[d]	$C_{20}H_{14}S_2$				
4-$NO_2C_6H_4$	183–184	181[a]	$C_{12}H_8N_2O_4S_2$				

Ar	M.P. Found	M.P. Reported	n_D^{25}	B.P.
		D. ARYL METHYL SULFIDES		
C_6H_5-			1.5839 (1.5832)[e]	84/18 mm. (82/18 mm.)[f]
4-$CH_3C_6H_4$-			1.5707 (1.5730-20/D)[g]	104/20 mm. (104–105/20 mm.)[h]
4-$CH_3OC_6H_4$-	25–26	26[i]		
β-$C_{10}H_7$	59.5–60.5	60[j]		
4-$NO_2C_6H_4$-	71–72	72[g]		
2,4-$(NO_2)_2C_6H_3$-	128–129	128[k]		

[a] I. Danielsson, J. E. Christian, and G. L. Jenkins, *J. Am. Pharm. Assoc., Sci. Ed.*, **36**, 261 (1947). [b] K. W. Rosenmund and H. Harms, *Ber.*, **53B**, 2226 (1920). [c] A. J. Costanza, R. J. Coleman, R. M. Pierson, C. S. Marvel, and C. King, *J. Polymer Sci.*, **17**, 319 (1955). [d] S. S. Bhatnagar and B. Singh, *J. Indian Chem. Soc.*, **7**, 663 (1930). [e] C. M. Suter and H. L. Hansen, *J. Am. Chem. Soc.*, **54**, 4100 (1932). [f] M. P. Balfe, R. E. Darby, and J. Kenyon, *J. Chem. Soc.*, 382 (1951). [g] K. Brand and K. W. Kranz, *J. prakt. Chem.*, (2) **115**, 143 (1927). [h] H. Gilman and N. J. Beaber, *J. Am. Chem. Soc.*, **47**, 1449 (1925). [i] F. G. Bordwell and P. J. Boutan, *J. Am. Chem. Soc.*, **79**, 717 (1957). [j] H. Staudinger, H. Goldstein, and E. Schlenker, *Helv. Chim. Acta*, **4**, 342 (1921). [k] R. W. Bost, J. O. Turner, and R. D. Norton, *J. Am. Chem. Soc.*, **54**, 1985 (1932).

a characteristic peak; those of the electron-rich aromatic series in the vicinity of 255 mμ (280 mμ for the naphthyl compound), and those of the nitroaromatic series at about 335 mμ (Table II, part A). The symmetrical disulfides exhibit similar peaks of approximately twice the molar intensity, but shifted hypsochromically. This hypsochromic shift is consistent ($\Delta\lambda = -13 \pm 1$) when the aryl group has electron-releasing groups, but is nearly twice as great when the aryl group is *p*-nitrophenyl. Since the absorption maximum in this case is above 300 mμ, the magnitude of the shift would be expected to be greater. The β-naphthyl derivatives show a much more intense absorption in the 250 mμ range, but the effect of varying the sulfur function is decreased. In the case of the 2,4-dinitrophenyl derivatives, the disulfide was too insoluble in 95% ethanol to obtain a reliable absorption spectrum. The absorption of the methyl sulfide would, however, lead to a prediction of a peak at 310 mμ ($\epsilon = 18{,}000$) by analogy with the 4-nitro analogs.[18]

One-half the absorption of the symmetrical disulfide was taken as the normal absorption of the radical Ar-S-. Assuming no transmission of resonance effects by the disulfide link, as was previously indicated,[9] the absorption spectrum of the unsymmetrical disulfide was calculated as one-half the sum of the two symmetrical disulfides. The results of such calculation are shown in Figs. 1, 2, and 3, on which such a calculated curve is plotted, along with the observed absorption curves of the unsymmetrical and corresponding pair of symmetrical disulfides.

There is very close congruity of the calculated and observed curves in each of the three examples. The significant deviations are a small bathochromic shift of the *p*-nitrophenyl sulfur peak, and a larger hypsochromic shift in absorption of the electron-releasing arylsulfur moiety. These shifts are readily accounted for as inductive effects of functions attached to a sulfur atom which is in turn attached to an aromatic nucleus. For example the observed *p*-nitrophenyl sulfur peaks for the unsymmetrical

(18) G. Leandri and A. Tundo, *Ann. Chim. (Rome)*, **45**, 180 (1955) report λ_{max} 332 mμ, log ϵ 4.03 for bis-2,4-dinitrophenyl disulfide in ethanol.

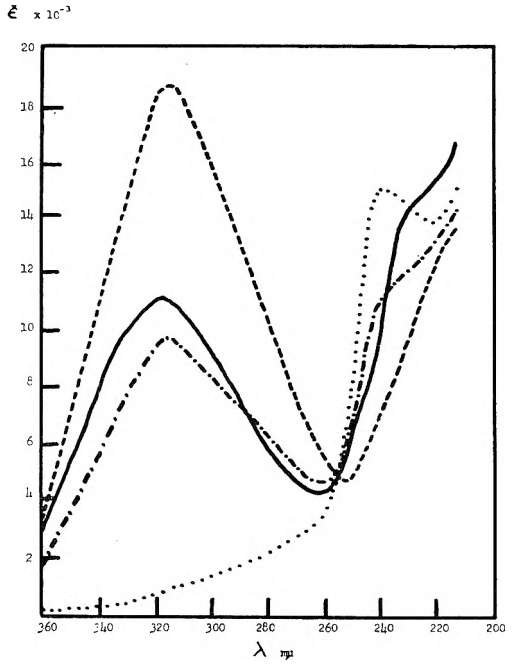


Fig. 1. ——— Absorption spectra of bis-4-nitrophenyl disulfide – – – –; diphenyl disulfide. . . .; 4-nitrophenyl phenyl disulfide (observed) ———; 4-nitrophenyl phenyl disulfide (calculated) — · —

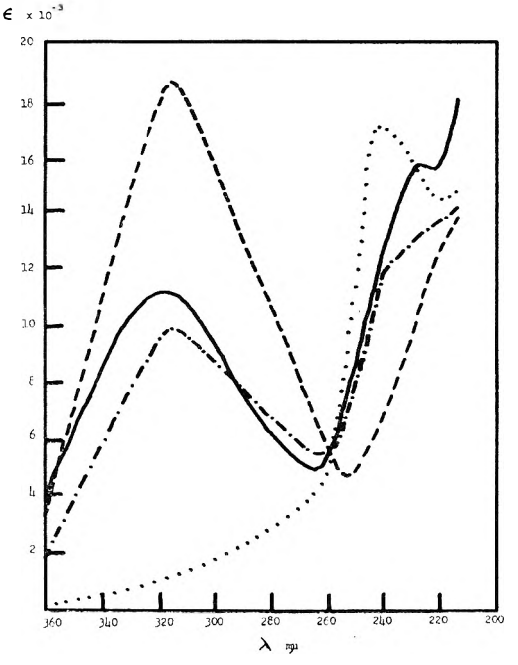


Fig. 2. ——— Absorption spectra of bis-4-nitrophenyl disulfide – – – –; bis-4-tolyl disulfide . . . .; 4-nitrophenyl 4′-tolyl disulfide (observed) ———; 4-nitrophenyl 4′-tolyl disulfide (calculated) — · —

disulfide in Figs. 1, 2, and 3 are shifted bathochromically +2, +3, and +8 mμ, corresponding to the inductive effect of increasingly higher electron density of the substituent attached to sulfur. On the other hand, the observed peaks for the electron-releasing aryl sulfur chromophore in Figs. 1, 2, and 3 are shifted hypsochromically −13, −13, and −9

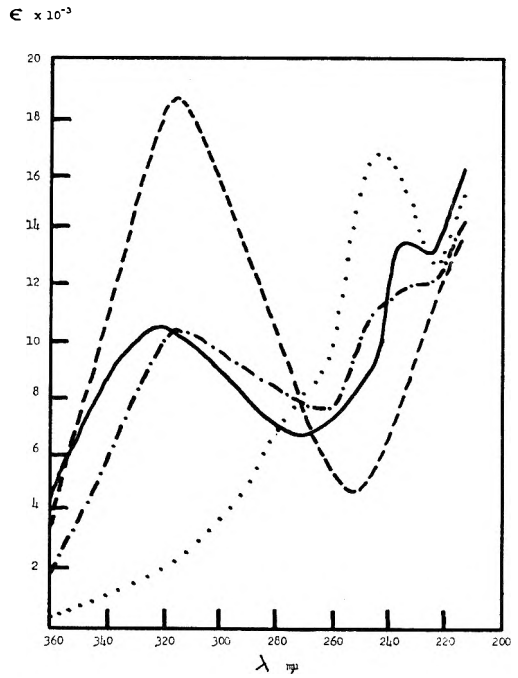


Fig. 3. ——— Absorption spectra of bis-4-nitrophenyl disulfide – – – –; bis-4-methoxyphenyl disulfide . . . .; 4-nitrophenyl 4′-methoxyphenyl disulfide (observed) ———; 4-nitrophenyl 4′-methoxyphenyl disulfide (calculated) —. —

mμ, respectively, corresponding to the inductive effect of an electronegative group attached to the sulfur atom of the chromophore.

Similar shifts occur in the spectra of the 2,4-dinitrophenyl disulfides as can be seen by comparison of the peaks shown in Table II. These are somewhat more complicated, probably due to *ortho*-effect. A similar result is also apparent in the two unsymmetrical disulfides derived from β-naphthalenethiol. Here again the picture is more complex due to the more intense absorption of the chromophore. In this case the hypsochromic shift of attaching an electronegative group to sulfur is magnified (−16 mμ for *p*-nitrophenylsulfur and −20 mμ for 2,4-dinitrophenylsulfur).

One must conclude from these results that no electronic effects are transmitted through a disulfide bond. Any stabilization of the polarized sulfur-sulfur bonds, as in D⟷E, by expansion of the valence shell of sulfur, is not reflected in the ultraviolet absorption spectra. The ultraviolet spectra are more properly explained by a simple inductive polarization as in $Ar \gtrless \overset{\delta-}{S}—\overset{\delta+}{S} \gtrless Ar'$.[19]

The absorption curves of unsymmetrical disulfides then may be approximated as the sum of the absorptions of the two halves of the molecule, ArSX and Ar′SY. The absorption of each half may be calculated as one-half the absorption of the corresponding symmetrical disulfide, with suitable

(19) For a discussion of the spectrum and properties of the elongated polarized disulfide bond, see H. P. Koch, *J. Chem. Soc.*, 394 (1949).

allowance for shifting of peaks due to the inductive effects of the groups X and Y attached to sulfur.

EXPERIMENTAL[20]

Ultraviolet absorption measurements. The ultraviolet absorption spectra were determined with a Beckman model DK-1 recording quartz spectrophotometer equipped with a hydrogen discharge tube and 1-cm. silica cells. All of the spectra were measured down to the wave-length vicinity of 215 mμ. The wave lengths and molar extinction coefficients at the absorption maxima and at prominent points of inflection are listed in Table II.

TABLE II

ULTRAVIOLET ABSORPTION SPECTRA OF DIARYL DISULFIDES AND ARYL METHYL SULFIDES[a]

Compound	Source[b]	Maxima[c] λ (mμ)	ε
A. Aryl Methyl Sulfides			
Phenyl methyl sulfide	1	254	8,700
4-Tolyl methyl sulfide	1	255	9,500
4-Methoxyphenyl methyl sulfide	2	256	8,200
β-Naphthyl methyl sulfide	1	280	7,600
		252	30,400
4-Nitrophenyl methyl sulfide	5	338	11,100
2,4-Dinitrophenyl methyl sulfide	3	331	11,100
		267	5,800
B. Symmetrical Disulfides			
Diphenyl disulfide	4	241	15,000
Bis-4-tolyl disulfide	4	242	17,000
Bis-4-methoxyphenyl disulfide	5	244	16,700
Bis-4-nitrophenyl disulfide	5	316	18,600
Bis-2,4-dinitrophenyl disulfide	6	332	10,700[d]
Di-β-naphthyl disulfide	4	248	44,300
C. Unsymmetrical Disulfides			
4-Nitrophenyl phenyl disulfide	7	318	11,200
		(228)	14,400
4-Nitrophenyl 4′-tolyl disulfide	7	319	11,200
		228	15,700
4-Nitrophenyl 4′-methoxyphenyl disulfide	5	322	10,600
		235	13,600
4-Nitrophenyl β-naphthyl disulfide	5	317	10,900
		232	36,400
2,4-Dinitrophenyl phenyl disulfide	7	311	7,200
		(265)	8,000
		(235)	12,700
2,4-Dinitrophenyl 4′-tolyl disulfide	7	310	9,300
		(265)	10,500
		(235)	17,300
2,4-Dinitrophenyl 4′-methoxyphenyl disulfide	5	311	10,000
		242	17,700
2,4-Dinitrophenyl β-naphthyl disulfide	5	(285)	26,000
		228	95,000

[a] All spectra were determined in 95% ethanol. [b] Source references: (1) prepared by methylating the corresponding thiol with dimethyl sulfate in alkali; (2) F. G. Bordwell and P. J. Boutan, *J. Am. Chem. Soc.*, **79,** 717 (1957); (3) R. W. Bost, J. O. Turner, and R. D. Norton, *J. Am. Chem. Soc.*, **54,** 1985 (1932); (4) prepared by oxidation of the appropriate thiol; (5) see section on "Preparation of Compounds"; (6) G. Leandri and A. Tundo, *Ann. Chim. (Rome)*, **45,** 180 (1955); (7) I. Danielsson, J. E. Christian, and G. L. Jenkins, *J. Am. Pharm. Assoc., Sci. Ed.*, **36,** 261 (1947); [c] The wave lengths in parentheses denote inflection points. [d] Data of Ref. b (6).

Preparation of compounds. All of the pure compounds used in this study were recrystallized or redistilled immediately before the spectra were determined. The physical constants of all the previously known compounds checked closely with reported results. These physical constants are listed in Table I.

Bis-4-nitrophenyl disulfide was prepared by a modification of the procedure in *Organic Syntheses.*[21] Sodium disulfide solution[21] (0.375 mole) was added slowly to a solution of 0.5 mole of *p*-chloronitrobenzene (78.8 g., m.p. 84–86°) in 500 ml. of 95% ethanol. The mixture was then heated on a steam bath, gently at first, then at full heat for 2 hr. After cooling, the solid was filtered, stirred thoroughly with water, filtered, and washed with ethanol.

The product was purified by the method of Zincke.[22] The crude product (51 g., 33%) was placed in 200 ml. of ethanol and the solution brought to reflux. To this solution was added a concentrated aqueous solution of 20.4 g. of crystalline sodium sulfide and 10.2 g. of sodium hydroxide. The apparatus was shaken vigorously for about 20 min., whereupon the mixture was diluted with 8–10 volumes of water, and filtered. The filtrate was acidified with dilute hydrochloric acid and oxidized with aqueous ferric chloride solution. Upon cooling, the crystals were filtered and recrystallized from glacial acetic acid to give 18 g. (12%) of yellow needles melting at 183°.

4-Methoxybenzenethiol was prepared by the method reported for *m*-thiocresol in *Organic Syntheses.*[23] Eighteen grams (0.15 mole) of powdered *p*-anisidine (m.p. 62°) was diazotized, converted to *p*-methoxyphenyl ethyl xanthate, hydrolyzed with potassium hydroxide, and then acidified with sulfuric acid. The crude thiol was distilled with steam, and then distilled under vacuum, to yield 38 g. (24%) of colorless oil, 134°/5.4 mm.

General procedure for the preparation of 4-nitrophenyl aryl disulfides. The procedure used was a modification of that by Danielsson and co-workers.[24] According to this procedure a desired unsymmetrical disulfide can be prepared without isolating the sulfenyl chloride, due to the extreme sensitivity of the sulfenyl chloride to moisture. The finely powdered bis-4-nitrophenyl disulfide (3.08 g., 0.01 mole) was suspended in 40 ml. of chloroform in a three necked flask equipped with a thermometer, gas-inlet tube, and condenser, the top of which was protected with a calcium chloride drying tube, and carbon tetrachloride bubble trap.[25] As a slow stream of chlorine gas was passed into the mixture, the color of the solution turned dark yellow, and the suspended disulfide gradually disappeared. The current of chlorine was continued for 30 min. after the solution became homogeneous. The excess chlorine was then expelled with nitrogen gas. The passage of gases was regulated by maintaining an even flow through the carbon tetrachloride trap as the temperature changed in the reaction mixture. Through a funnel, which replaced the gas-inlet tube, 0.02 mole of the arenethiol in 20 ml. of chloroform was added dropwise to the sulfenyl chloride solution under reflux. After the thiol was added, the solution was refluxed for another hour, during which time small amounts of copper-bronze were added if the color of

(20) Microanalyses were performed by Miss Joanna Dickey and Midwest Microlab, Inc. All melting points are uncorrected.

(21) M. T. Bogert and A. Stull, *Org. Syntheses,* Coll. Vol. I, 220 (1941).

(22) Th. Zincke and S. Leuhart, *Ann.*, **400,** 7 (1913).

(23) D. S. Tarbell and D. K. Fukushima, *Org. Syntheses,* Coll. Vol. III, 809 (1955).

(24) I. Danielsson, J. E. Christian, and G. L. Jenkins, *J. Am. Pharm. Assoc., Sci. Ed.*, **36,** 261 (1947).

(25) M. H. Hubacher, *Org. Syntheses,* Coll. Vol. II, 455 (1943).

the sulfenyl chloride had not disappeared. The mixture was then filtered, the solvent removed under vacuum, and the solid product recrystallized from *n*-hexane. During each recrystallization, some insoluble bis-4-nitrophenyl disulfide had to be removed before crystallization was allowed to proceed.

General procedure for the preparation of 2,4-dinitrophenyl aryl disulfides. One-hundredth mole of 2,4-dinitrobenzenesulfenyl chloride, freshly recrystallized from carbon tetrachloride (m.p. 98°) was dissolved in 100 ml. of hot, dry ether and placed in a three necked flask fitted with a thermometer, dropping funnel, and a reflux condenser, the top of which was protected with a calcium chloride drying tube. To this solution was added dropwise 0.01 mole of the arenethiol in 30 ml. of dry ether. In the case of β-naphthlenethiol, 140 ml. of dry ether was required because of the insolubility of this compound in ether. After the thiol addition was complete, the mixture was refluxed for an additional 2 hr. During this time evolution of hydrogen chloride was observed. The solution was then allowed to stand overnight without heating. The solvent was then removed and the product recrystallized from a mixture of ethanol and benzene.

4-Nitrophenyl methyl sulfide was prepared by reducing bis-4-nitrophenyl disulfide to the thiol according to the procedure of Zincke[22] as reported above. The thiol was then methylated with dimethyl sulfate in alkali. The product was recrystallized from 95% ethanol to give light yellow needles, m.p. 71–72°. The reported melting point[26] is 72.°

BLOOMINGTON, IND.

(26) K. Brand and K. W. Kranz, *J. prakt. Chem.*, (2) **115**, 143 (1927).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CORNELL UNIVERSITY]

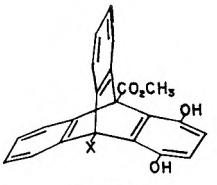
Ultraviolet Spectra of Triptycene Derivatives

CHARLES F. WILCOX, JR., AND ARNOLD C. CRAIG[1]

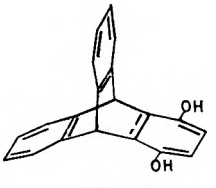
Received November 4, 1960

The preparation and ultraviolet spectra of several bridgehead derivatives of 2,5-dihydroxytriptycene are reported. It is shown that these spectra can be successfully interpreted by the model previously developed for triptycene. The bridgehead substituents have a negligible effect on the spectra.

Recently a model was developed for the interpretation of the ultraviolet spectrum of triptycene.[2] According to this model the triptycene spectrum is essentially that of an *o*-substituted benzene which, however, has been slightly displaced by interaction of the weak transition dipoles. An extension of this model to triptycenes which are substituted in one of the rings suggests that their ultraviolet spectra should be approximately the sum of the bands found in the three separate chromophores. This is only an approximation since weak interactions similar to those in triptycene should occur in such derivatives. The particular triptycene derivatives to be considered in this paper are methyl 2,5-dihydroxy-1-triptoate, Ia, methyl 6-methyl-2,5-dihydroxy-1-triptoate, Ib, methyl 6-bromo-2,5-dihydroxy-1-triptoate, Ic, as well as the simpler 2,5-dihydroxtriptyrene, II. With these molecules it should be possible to not only test the extension of the spectral model but also to determine what effect, if any, the isolated bridgehead substituents have on the spectra.

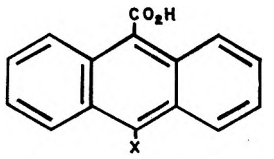


Ia X=H
Ib X=CH₃
Ic X=Br



II

Preparation of 6-bridgehead derivatives. The 6-bridgehead derivatives were prepared from the appropriately substituted anthroic acids by the same sequence employed by Bartlett and Greene[3] for Ia. Accordingly, 9-anthroic acid, IIIa, was synthesized in 80% yield by the metallation of 9-bromoanthracene with phenyllithium followed by reaction of the organometallic intermediate with carbon dioxide.



IIIa X=H
IIIb X=CH₃
IIIc X=Br

This method in our hands proved to be superior to that of the Latham, May, and Mosettig procedure[4] which gave 9-anthroic acid in 62% yield by reaction of oxaylyl chloride with anthracene. The substituted acids, IIIb and IIIc, were prepared by the procedure of Mikhaĭlov and Bronovitskaya.[5] This involved the preparation of the organo lithium

(1) Based in part on the Ph.D. dissertation of A. C. Craig, Dept. of Chemistry, Cornell University, 1959.

(2) C. F. Wilcox, Jr., *J. Chem. Phys.*, in press; Dr. Edel Wasserman has informed us that he has carried out an excition treatment of triptycene (Ph.D. dissertation, Harvard, 1958). We would like to acknowledge an enlightening discussion of this treatment with Dr. Wasserman.

(3) P. D. Bartlett and F. D. Greene, *J. Am. Chem. Soc.*, **76**, 1088 (1954).

(4) H. G. Latham, Jr., E. L. May, and E. Mosettig, *J. Am. Chem. Soc.*, **70**, 1079 (1948).

(5) B. N. Mikhaĭlov and V. P. Bronovitskaya, *Zhur. Obshcei. Khim.*, **22**, 157 (1952).

derivative of 9,10-dibromoanthracene followed either by carbonation to give IIIc or reaction with methyl iodide followed by a second carbonation reaction to give IIIb. All three acids were converted into their methyl esters with diazomethane.

The Diels-Alder adducts of the esters with *p*-benzoquinone were obtained by refluxing a benzene solution of the ester with *p*-benzoquinone under a nitrogen atmosphere for twenty-four to forty-eight hours. It is interesting to observe that, although the unsubstituted and methyl substituted adducts were formed in 58% and 65% yields, respectively, the bromo derivative was obtained in only 9–16% yield even when the quinone-ester ratio was increased threefold. Since the bromine and methyl groups have comparable size, this poorer adduction would appear to be related to either the electron withdrawing properties of the bromine atom or the loss of the bromine to ring delocalization energy in going to the adduct. Similar deleterious effects of *meso*-bromine substituents on Diels-Alder adduction of other anthracene derivatives with quinone have been observed by Theilacker and co-workers.[6]

The adducts were isomerized in hydrochloric acid-glacial acetic acid media to give the desired hydroquinones in good yield. As additional support for these structures, it can be pointed out that the three hydroquinones were easily oxidized in 72% to 85% yields with sodium bromate in acid solution into the corresponding quinones.

Infrared spectra. In the preceding reactions, the significant changes in molecular structure were reflected remarkably well by the infrared spectra. The anthroate esters had absorption near 5.80 μ typical of methyl esters of aromatic acids.[7] The benzoquinone adducts had two prominant bands at 5.72 and 5.95 μ. The shorter wave-length band is characteristic of saturated methyl esters,[8] while the longer wave-length band corresponds to α,β-unsaturated ketone absorption.[9] The related hydroquinones, Ia, Ib, Ic, all showed broad absorption at 2.90–3.00 μ and the ester carbonyl absorption was shifted to longer wave-lengths (5.77–5.80 μ). This would suggest, as Bartlett and Greene already have pointed out[3] for Ia, that in these hydroquinones a hydrogen bond is formed between the phenolic 2-hydroxy group and the carbonyl oxygen of the ester. Upon oxidation of the hydroquinones to the quinones, the ester carbonyl absorption returned to its normal position and typical quinoid bands appeared at 5.99–6.05 μ.[10]

Ultraviolet spectra. The ultraviolet spectra of alcoholic solutions of methyl 2,5-dihydroxy-1-triptoate and its 6-methyl and 6-bromo derivatives are presented in Table I along with the maxima of triptycene, 2,5-dihydroxy triptycene, and *o*-xylohydroquinone. Examination of the data in Table I yields several striking comparisons. First, the triad of bands in the ultraviolet spectrum of triptycene show up in remarkably constant positions in the four dihydroxytriptycenes. This constancy can be explained by an analysis almost identical to that developed for the ultraviolet spectrum of triptycene. This approach is based on the Longuet-Higgins and Murrell[12] model for electronic spectra which treats π-electron transitions in terms of local and charge-transfer excitations. In triptycene the longest wave length 279 mμ band is associated[2] with the doubly degenerate antisymmetrical combinations of the local $\alpha(^1L_b)$-bands, $1/\sqrt{6}$ $(2\theta_\alpha - \phi_\alpha - \Omega_\alpha)$ and $1/\sqrt{2}$ $(\phi_\alpha - \Omega_\alpha)$, where the symbols θ_α, ϕ_α and Ω_α each represent a local α transition on the θ, ϕ or Ω- benzene ring. In triptycene these transitions are bathochromically shifted relative to the symmetrical combination, $1/\sqrt{3}$ $(\theta_\alpha + \theta_\alpha + \Omega_\alpha)$, by the combined effect of neighboring ring and substituent induced mixing of higher energy transitions. This difference in behavior between the symmetric and antisymmetric combinations can be arrived at by imagining that initially the benzene rings are isolated so that each contributes an absorption spectrum characteristic of an isolated benzene ring. Then when the interaction terms are included these local transitions mix and give rise to displaced maxima. However, because the α-transitions have two components of the transition dipole which to a first approximation act in directions these interaction terms essentially cancel for triptycene. What little shift is observed can be ascribed largely to the presence of substituents (the two bridgehead C—H groups) which perturb the α-transitions so that the components of the oppositely acting dipoles are no longer exactly equal. These perturbed transitions interact in such a way as to shift the antisymmetrical combinations to longer wave lengths.

Since with each of the four dihydroxy triptycenes an analogous antisymmetrical α-transition, $1/\sqrt{2}$ $(\theta_\alpha - \Omega_\alpha)$, arises and since the electron environments are so similar it is suggested that the local pertur-

(6) W. Theilacker, U. Berger-Brose, and K. Beyer, *Ber.*, **93**, 1658 (1960).

(7) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, 2nd edition, John Wiley and Sons, Inc., New York, N. Y., 1958, p. 182.

(8) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, 2nd edition, John Wiley and Sons, Inc., New York, N. Y., 1958, p. 180.

(9) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, 2nd edition, John Wiley and Sons, Inc., New York, N. Y., 1958, p. 136.

(10) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, 2nd edition, John Wiley and Sons, Inc., New York, N. Y., 1958, p. 150.

(11) This sample was prepared by Mrs. Margaret McPhee Miano according to the method of O. H. Emerson and L. I. Smith, *J. Am. Chem. Soc.*, **62**, 141 (1940). This spectrum is consistent with that of L. Paolini and G. B. Marini-Bettolo, *Gazz. chim. ital.*, **87**, 395 (1957).

(12) H. C. Longuet-Higgins and J. N. Murrell, *Proc. Phys. Soc. A.*, **68**, 601 (1955).

TABLE I

ULTRAVIOLET SPECTRA OF ALCOHOLIC SOLUTIONS OF 6-SUBSTITUTED 2,5-DIHYDROXY TRIPTYCENES AND RELATED COMPOUNDS

Compound	λ_{max} (log ϵ in parentheses)				
Methyl 2,4-dihydroxy-1-triptoate	254 (sh) (3.24)	263 (3.25)	271 (sh) (3.29)	277 (3.57)	302 (3.65)
Methyl 6-methyl-2,4-dihydroxy-1-triptoate		261 (3.29)	269 (3.27)	278 (3.38)	304 (3.65)
Methyl 6-bromo-2,4-dihydroxy-1-triptoate		260 (sh) (3.18)	269 (3.11)	277 (3.21)	308 (3.68)
2,4-Dihydroxytriptycene	256 (3.20)	263 (3.42)	272 (3.62)	279 (3.62)	300 (3.62)
Triptycene		264 (sh) (3.3)	271 (3.55)	279 (3.67)	
o-Xylohydroquinone[11]					294 (3.46)

bations should be similar to those found in triptycene. In support for this suggestion it can be argued that on the one hand various α-substituted alkyl benzenes show little variation in their α-band positions[13] and on the other hand the extra mixing induced by the additional pair of OH groups should be small because of their distance from the pair of non-substituted benzene chromophores. Theoretical estimation of this latter effect suggests less than 0.5 mμ additional shift.[14] For these reasons it is not too surprising that the triad of bands starting at 279 mμ shows up in all five molecules.

From the data in Table I it would appear that the bands near 300 mμ are to be associated with the 294 mμ band of 2,3-dimethyl-hydroquinone. These bands also have undergone a displacement but not in as constant a way as the transitions of the *o*-xylene chromophores. The exact positions of these 300 mμ bands are more difficult to account for since little is known of the energetics of the upper excited states and it is these details in conjunction with the degree of mixing with the ground state which determine the magnitude of shift from 294 mμ. There is an approximate empirical correlation, as might be expected, between the position of this band and the inductive nature of the bridgehead substituents as measured by the sum of the Taft σ^* parameters.[15] However, with the given groups this correlation might as easily be a trivial relationship between the size of the group and its ability to interfere with solvation of the hydroxy groups.

A further point to be made from the data in Table I and the foregoing analysis is that when weak substituents[16] such as —OH are attached to only one of the benzene rings the band sequence of 279 mμ, 271 mμ, etc., should appear. Since the present data demonstrate that bridgehead substituents have little effect on these bands in the case of a pair of —OH substituents it seems reasonable that this band system should be diagnostic for triptycenes with weak substituents in one ring. When strong substituents[16] like NH_2 are included the situation is no longer clear. The strong substituents introduce considerable amounts of local charge transfer states and these depending on the number and orientation of the substituents might mix with *o*-xylene transitions to produce abnormal shifts of the 279 mμ band sequence. Such special interaction if it occurred might be turned around and used as a new measure of strong and weak substituents and the degree of local charge-transfer mixing.

(13) F. A. Matsen, Technique of Organic Chemistry, Vol. IX, Chemical Applications of Spectroscopy, A. Weissberger, Ed., Interscience Publishers, Inc., New York, 1956, p. 677.

(14) This calculation was made using theoretically evaluated penetration integrals. While the exact number is not significant the order of magnitude probably is.

(15) Chapter 13 by R. W. Taft, Jr. in M. S. Newman, *Steric Effects in Organic Chemistry*, John Wiley and Sons, Inc., New York, N. Y., 1956.

(16) J. N. Murrell, *Proc. Phys. Soc.* (*London*), **68**, 969 (1955).

EXPERIMENTAL

9-Anthroic acid (IIIa). A. The procedure of Latham, May, and Mosettig[4] was followed to give a 62% yield of a yellow powder, m.p. 209.5–215°. A small portion was recrystallized from dilute ethanol to yield pale yellow needles, m.p. 221–222°; reported, 208–212°.

B. Twenty grams (0.075 mole) of 9-bromoanthracene was added to an ethereal solution of 7 g. (0.085 mole) of freshly prepared phenyllithium and the solution was stirred under nitrogen for 45 min. at 25–35°. The reaction was cooled and then poured over a large excess (*ca.* 200 g.) of Dry Ice. The resultant slurry was allowed to stand for 20 min. after which time 500 ml. of ether and 500 ml. of water were added and the system allowed to stand overnight. The layers were separated and the ether layer then was extracted with 10% aqueous sodium carbonate solution. The carbonate extract was combined with the original aqueous layer and neutralized with 10% sulfuric acid to precipitate 12.6 g. (75.5%) of a light yellow powder, m.p. 217–218°. From the ether layer there was obtained 2.5 g. of starting material so that on the basis of consumed material the conversion to 9-anthroic acid was 80%.

9-Bromo-10-methylanthracene. This was prepared by the procedure of Mikhailov and Bronvitshaya[5] from 9,10-dibromoanthracene in 98% crude yield. Recrystallization from 95% ethanol afforded long yellow needles, m.p. 163–164°; reported m.p. 170–173°.

Anal. Calcd. for $C_{15}H_{11}Br$: C, 66.44; H, 4.09; Br 29.47. Found: C, 66.66; H, 4.17; Br 29.36.

9-Methyl-10-anthroic acid (IIIb). This was prepared from 9-bromo-10-methylanthracene by the procedure of Mikhailov

and Bronvitshaya[5] in 82% crude yield. Recrystallizations from ethanol yielded very bright yellow plates, m.p. 225–226°; reported 217–219°.

Anal. Calcd. for $C_{16}H_{12}O_2$: C, 81.33; H, 5.12; Neut. Equiv., 236. Found: C, 81.13; 81.19; H, 5.21, 5.13; Neut. Equiv., 233, 244.

9-Bromo-10-anthroic acid (IIIc). This was prepared from 9,10-dibromoanthracene by the procedure of Mikhailov and Bronvitshaya[5] in 73% yield. Recrystallization from 75% ethanol–25% benzene gave a fluffy yellow solid, m.p. 267–268°; reported 265–267°.

Anal. Calcd. for $C_{15}H_9O_2Br$: C, 59.82; H, 3.01; Br 26.54; Neut. Equiv., 301. Found: C, 60.09; 60.02; H, 3.09, 3.08; Br, 26.48, 26.63; Neut. Equiv., 286, 299.

Methyl esters. A. *Methyl 9-anthroate.* The acid (IIIa), 9.3 g. (0.042 mole) in ether, was esterified with an ethereal solution of diazomethane (0.068 mole) prepared from *N*-methyl-*N*-nitrosourea. After evaporation of the ether 7.6 g. (78%) of ester, m.p. 105–108°, was obtained. Recrystallization from ethanol gave pale yellow needles, m.p. 110–111°; reported 113°.

Anal. Calcd. for $C_{16}H_{12}O_2$: C, 81.33; H, 5.12. Found: C, 80.23, 81.51; H, 5.15, 5.17.

B. *Methyl 9-methyl-10-anthroate.* In the same manner as in part A there was obtained a 35% yield of methyl ester which when purified melted at 162–163°.

Anal. Calcd. for $C_{17}H_{14}O_2$: C, 81.57; H, 5.64. Found: C, 82.00, 80.17; H, 5.78, 5.77.

C. *Methyl 9-Bromo-10-anthroate.* In the same manner as in part A there was obtained an 85% yield of methyl ester which when purified melted at 109–110°.

Anal. Calcd. for $C_{16}H_{11}C_2Br$: C, 60.97; H, 3.52; Br, 25.36. Found: C, 60.71; H, 3.37; Br 25.32.

Diels-Alder adducts with p-benzoquinone. A. *Methyl 2,5-diketo-2,5,15,16-tetrahydro-1-triptoate.* This adduct was prepared by the method of Bartlett and Greene[3] except that the reaction was carried out under a nitrogen atmosphere. The product, obtained in 58% yield, melted at 199–200°; reported, 199–201°.

B. *Methyl 6-methyl-2,5,16,16-tetrahydro-1-triptoate.* This was prepared in 65% yield in a manner similar to that of A above except that the mixture was refluxed for only 24 hr. When the reflux time was extended to 44 hr., the yield was increased to 84%. The product melted at 196.5–197°.

Anal. Calcd. for $C_{23}H_{18}O_4$: C, 77.08; H, 5.06. Found: C, 76.81; H, 5.00.

C. *Methyl 6-bromo-2,4-diketo-2,5,15,16-tetrahydro-1-triptoate.* When the method described in part A above was applied to the bromo ester only a 4% yield was obtained. Substitution of *p*-xylene for benzene as solvent gave only intractable tars plus a trace of starting material. When the mole ratio of *p*-benzoquinone to ester was increased from 3:1 to 10:1 the yield using benzene as a solvent was 17% in one run and 10% in another run. The purified product melted at 211–211.5°.

Anal. Calcd. for $C_{22}H_{15}O_4Br$: C, 62.43; H, 3.57. Found C, 62.87, 62.99; H, 3.53, 3.61.

Conversion of the keto form to the hydroquinone. A. *Methyl 2,5-dihydroxy-1-triptoate.* The procedure of Bartlett and Greene was followed to obtain a 97% yield of fine colorless needles which sintered at 265° and melted at 272–273°; reported 265–266°.

B. *Methyl 6-methyl-2,4-dihydroxy-1-triptoate.* The procedure in part A was followed to obtain a 95% yield of fine colorless needles which melted at 274–275°.

Anal. Calcd. for $C_{23}H_{20}O_4$: C, 77.08; H, 5.06. Found: C, 77.52; H, 5.22.

C. *Methyl 6-bromo-2,5-dihydroxy-1-triptoate.* The procedure in part A was followed to obtain a 97% yield of fluffy off-white needles which melted at 286–287°.

Anal. Calcd. for $C_{22}H_{15}O_4Br$: C, 62.43; H, 3.57. Found C, 62.83; H, 3.77.

Oxidation of the triptycenehydroquinones to the triptycenequinones. A. *Methyl 2,4-diketo-2,5-dihydro-1-triptoate.* The procedure of Bartlett and Greene was followed to obtain a 72% yield of quinone which melted at 221–224°; reported 225°.

B. *Methyl 6-methyl-2,5-diketo-2,5-dihydro-1-triptoate.* In the same manner as in part A the methylhydroquinone was oxidized in 85% yield to the quinone which melted at 249–250°.

Anal. Calcd. for $C_{23}H_{16}O_4$: C, 77.51; H, 4.53. Found: C, 75.88; H, 4.57.

C. *Methyl 6-bromo-2,5-diketo-2,5-dihydro-1-triptoate.* The bromohydroquinone was oxidized by the method of part A in 85% yield to the quinone which melted at 265.5–266°.

Anal. Calcd. for $C_{22}H_{13}O_4Br$: C, 62.72; H, 3.13; Br, 18.97. Found C, 62.68; H, 3.21; Br, 19.52.

ITHACA, N. Y.

[CONTRIBUTION NO. 120 FROM THE INSTITUTO DE QUÍMICA DE LA UNIVERSIDAD NACIONAL AUTÓNOMA DE MÉXICO]

The Intensity of the Carbonyl Band in the Infrared Spectra of Methyl Benzoates

J. L. MATEOS, R. CETINA, E. OLIVERA, AND S. MEZA

Received September 28, 1960

The quantitative infrared spectra of *meta* and *para* substituted methyl benzoates were measured, and it was found that the changes of the integrated absorption intensity (A), were in full agreement with the theoretical values. No linear relation was found when plotting A *vs.* Hammett σ values.

In the study of absorption intensities of infrared bands it is now customary to report not only their frequency but also their intensity. Cole,[1] Jones,[2] Brown,[3] and others, have shown that the empirical application of the infrared data is useful for structural studies of simple and complex organic molecules. Some values of infrared intensities are reported in the literature, but much work has to

(1) A. R. W. Cole, G. T. A. Muller, D. W. Thornton, and R. S. L. Willix, *J. Chem. Soc.*, 1218 (1959).

(2) R. N. Jones, D. A. Ramsay, D. S. Keir, and K. Dobriner, *J. Am. Chem. Soc.*, **74**, 80 (1952).

(3) T. L. Brown, *J. Am. Chem. Soc.*, **80**, 794 (1958).

be done before a complete picture of the factors that control the intensity and shape of the infrared bands can be completely understood.

As a contribution in this field, we wish to report the integrated absorption values for methyl benzoates with substituents in the *meta* and *para* positions. The purpose of this work was to determine if their intensity values would follow a linear relation when plotted against Hammett σ constants. No such relation could be found for the results (Tables I and II) and this is in accordance with the findings of Brown[3] when he studied substituted benzonitriles and with Jones,[4] on substituted acetophenones. On the other hand, Califano[5] claimed that such a relation existed in the case of anilines and *N*-methylanilines, and Thompson,[6] in the case of benzonitriles.

TABLE I

CARBONYL INFRARED ABSORPTION DATA OF *para* SUBSTITUTED METHYL BENZOATES

Substituent	ν_{max} cm.$^{-1}$	ϵ	$\Delta\nu^1/_2$	A^a	σ
Nitro	1736.9	573	14.0	2.88	+1.27
Fluoro	1732.4	649	12.6	2.95	+0.062
Hydrogen	1731.9	718	11.3	2.99	0.00
Chloro	1730.6	752	11.6	3.11	+0.266
Iodo	1733.0	771	11.7	3.25	+0.276
Bromo	1734.8	666	14.3	3.45	+0.232
Methoxy	1722.1	644	15.8	3.69	−0.268
Amino	1717.2	677	15.1	3.70	−0.660
Hydroxy	1722.7	580	15.1	3.87[b]	−0.357
Methyl	1728.3	703	15.1	3.89	−0.170
Dimethyl-amino	1715.0	683	17.9	4.44	−0.600

[a] One intensity unit (A) = 1×10^4 l. mole^{-1} cm.$^{-2}$ [b] Value obtained by addition of two overlapping bands. Values of ν_{max}, ϵ, and $\Delta\nu^1/_2$ are of the stronger maximum.

TABLE II

CARBONYL INFRARED ABSORPTION DATA OF *meta* SUBSTITUTED METHYL BENZOATES

Substituent	ν_{max}, cm.$^{-1}$	ϵ	$\Delta\nu^1/_2$	A^a	σ
Chlorine	1737.3	634	12.3	2.86	+0.373
Nitro	1740.9	707	11.3	2.88	+0.710
Hydrogen	1731.9	718	11.3	2.99	0.00
Bromine	1735.9	654	12.5	2.99	+0.391
Iodine	1732.8	695	12.7	3.08	+0.352
Amino	1730.2	627	13.9	3.17	−0.161
Methyl	1731.0	705	12.9	3.22	+0.069
Dimethyl-amino	1730.4	611	14.8	3.27	−0.211
Hydroxy	1732.2	490	14.2	3.55[b]	−0.002
Methoxy	1731.3	612	15.4	3.39	+0.115

[a] One intensity unit (A) = 1×10^4 l. mole^{-1} cm.$^{-2}$ [b] Value obtained by addition of two overlapping bands. Values of ν_{max}, ϵ, and $\Delta\nu^1/_2$ are of the stronger maximum.

(4) R. N. Jones, W. F. Forbes, and W. A. Mueller, *Can. J. Chem.*, **35**, 504 (1957).

(5) S. Califano and R. Moccia, *Gazz. chim. ital.*, **87**, 58 (1959).

(6) H. W. Thompson and G. Steel, *Trans. Faraday Soc.*, **52**, 1451 (1956).

The measurement of A has many applications such as the determination of the number of carbonyl groups in a steroid[2]; in the determination of C—H present in aliphatic hydrocarbons,[7] or the determination of different types of carbonyl groups.[8,9] It was also found that this method could be used in the determination of the spacial conformation of halogens α to a carbonyl in cycloalkanones.[10] In Table III the values of A for substituted benzene compounds are collected. These data could be used to characterize the number and type of substituents in aromatic rings.

EXPERIMENTAL

The infrared spectra were measured with a double beam single pass Perkin-Elmer Model 21 spectrophotometer, equipped with sodium chloride prism and cells. In order to plot 1 μ in 40 cm. of the chart two number 45 gears were installed in the A and C positions.[11] The solutions (in 10 ml. of carbon tetrachloride), were approximately 0.015M depending on the band intensity, and in each case at least five independent measurements were made. The average results are reported on Table I and II. A pair of matched cells 1 mm. thick was used and all the measurements were made under the same experimental conditions in order to minimize errors. The slit width used was 49 μ and the spectral slit width 7 cm.$^{-1}$ The error in the infrared measurements is ± 0.1 for the A value and ± 2 cm.$^{-1}$ in the wave number.

Methyl esters of substituted benzoic acids. The methyl esters were prepared from the acids by esterification with methanol and hydrogen chloride by the usual technique. The acids were prepared by standard methods reported in the literature. The physical constants of the esters were in good agreement with literature values.

The values ν_{max}, molecular extinction coefficient, half band width and integrated absorption areas of the 19 methyl esters studies, are given in Tables I and II.

DISCUSSION

The values of ν_{max} of the *para* substituted methyl benzoates (Table I) are between 1715 and 1737 cm.$^{-1}$ Since the value of ν_{max} indicates the energy needed to produce a dipolar excited state, one can assume that a variation of ν_{max} is directly related to the increase or decrease in energy produced by the introduction of the substituent in the molecule. For example, ν_{max} of methyl benzoate was 1732 cm.$^{-1}$ while the value for *p*-dimethylaminobenzoic acid methyl ester was 1715 cm.$^{-1}$, 17 cm.$^{-1}$ lower. The sequence in which the substituents increase ν_{max} was $p - N(CH_3)_2$, $p - NH_2$, $p - CH_3O$, $p - OH$, $p - CH_3$, $p - Cl$, $p - H$, $p - F$, $p - I$, $p - Br$, $p - NO_2$.

In some cases it is possible to ascribe the change in energy to a specific effect: For example, in the

(7) S. A. Francis, *J. Chem. Phys.*, **18**, 861 (1950); **19**, 942 (1951).

(8) G. M. Barrow, *J. Chem. Phys.*, **21**, 2008 (1953).

(9) J. Wenograd and R. Spurr, *J. Am. Chem. Soc.*, **79**, 5844 (1957).

(10) R. Cetina and J. L. Mateos, *J. Org. Chem.*, **25**, 704 (1960).

(11) For a more complete description consult the Perkin-Elmer Manual.

TABLE III

INTEGRATED ABSORPTION AREAS OF SUBSTITUTED AROMATIC COMPOUNDS[a]

R—C_6H_4-	—CHO[b]	—CN[c]	—$COCH_3$[d]	—OH[e]	—CN[f]	—CO_2CH_3[g]	—NH_2[h]	—OH[i]
	(CCl_4)	(CCl_4)	(CCl_4)	(CCl_4)	($CHCl_3$)	(CCl_4)	(CCl_4)	(CCl_4)
R = H	2.25	0.20	2.20	0.99	0.37	2.99		1.15
m-F			1.66					
m-Cl			1.90	1.31		2.86	0.45	1.5
m-Br				1.29		2.99	0.50	
m-I						3.08		
m-NO_2	1.91		2.02		0.17	2.88	0.58	2.42
	2.41[j]							
m-NH_2			2.15		0.47	3.17		
m-$N(CH_3)_2$						3.27		
m-CH_3		0.20				3.22	0.30	1.37
m-OCH_3	2.50					3.39		
m-OH	2.90[j]				0.47	3.35		
p-F		0.20	2.17			2.95	0.32	
p-Cl	2.55	0.20	2.25	1.19		3.11	0.42	1.46
p-Br			2.24	1.23		3.45	0.46	1.45
p-I			2.39			3.25		
p-NO_2	1.85		1.93		0.13	2.88	1.13	2.36
p-NH_2		0.82	2.38		1.48	3.70		
p-$N(CH_3)_2$	2.25					4.44		
p-CH_3	2.37	0.28	2.44			3.89	0.29	1.16
p-OCH_3	2.88	0.44	1.06			3.69		1.27
p-OH	3.22[j]				0.91	3.77		

[a] One intensity unit (A) = 1×10^4 l. mole^{-1} cm.$^{-2}$ [b] Unpublished results of this laboratory. [c] Ref. 3. [d] Ref. 4. [e] T. L. Brown, *J. Chem. Phys.*, **65**, 821 (1957). [f] P. Sensi and G. G. Gallo, *Gazz. chim. ital.*, **85**, 235 (1955). [g] This paper. [h] S. Califano and R. Moccia, *Gazz. chim. ital.*, **87**, 58 (1957). [i] R. Moccia and S. Califano, *Gazz. chim. ital.*, **88**, 342 (1958). [j] Measured in chloroform.

case of the *p*-dimethylamino and similar groups containing $p\pi$ electrons, the delocalization of the $p\pi$ electrons of the substituent stabilize the molecule in the basal state and probably it stabilizes too the dipolar excited state. The *p*-methyl group facilitates the dipolar structure by hyperconjugation. On the other hand, the *p*-nitro reduces the carbonyl dipole formation due to its inductive and resonance effect, increasing the force constant of the carbonyl, and therefore ν_{max}. However, in the case of the halogens, the effect produced is not related to their electronegativity or to their polarizability.

In Table I, the half band width is also given. It increased with the substituents bromo, methyl, amino, methoxy, and dimethylamino. All these groups are electron donors. It seems that this is one factor which contributes to the increase of the band width. The *p*-dimethylamino benzoic ester has the largest set of values. It is probable that in this case the substituent effect may decrease the energy of the molecule in the excited state, increasing, therefore the probability of transitions among different energy levels. If more rotational transitions are allowed, the band width will increase. The substituents in the *meta* position, affect the carbonyl by their inductive effect, which can be positive or negative, while the same substituent in the *para* position affects the carbonyl by the inductive and resonance effects.

Since the value of A was greater when *para* substituents are present, one can assume that the inductive effect is very small, and therefore, that it is the electron delocalization which is the factor responsible for the change in the value of A. For example, the value of A for methyl benzoate was 2.99 units; the *m*-dimethylamino group had a value for A of 3.27 units giving a ΔA of 0.28. The same substituent in the *para*- position had a value for A of 4.44 units, ΔA was 1.45 and one can assume that the resonance effect is five times greater than the inductive effect.

When a substituent was a halogen in the *para*-position, the ΔA values were greater than when it was *meta*, but there was only a small difference in the two values. This indicates that the resonance effect of the halogen is of less importance than for the other substituents.[12]

The A values when the substituent is a methyl, are, respectively 3.22 for *meta* and 3.89 for *para*. In the latter, one can assume it is due to inductive and hyperconjugative effects acting in the same direction. Finally, the *meta*- and *para*-nitro have similar A values which were 0.11 units smaller than the values of the original compound, indicating that the inductive effect in the *meta*- position is as the inductive and resonance effects operating in *para*.

In the *m*- and *p*-hydroxybenzoates, two bands were present in the carbonyl region, which overlap in the falling branch of lower frequency. They can be resolved as follows: if the branch of the band

(12) This is in agreement with NMR data since halobenzenes have δ values of nearly zero. P. L. Corio and B. P. Dailey, *J. Am. Chem. Soc.*, **78**, 3043 (1957).

where no overlapping is present is projected on the other side, a symmetric band is obtained. The log I_0/I differences of the overlapped band and the symmetric band can be taken at each point, and the second band can be built with these values.

The addition of the two bands will give the true integrated absorption area. The origin of the second band at lower frequencies in the hydroxy compounds is due to the association between the hydroxy and the carbonyl groups. This association was shown to be intermolecular, since the intensity ratio of the two bands changed with concentration and the percentage of association increased regularly with increasing molarity of the solution (Table IV).

TABLE IV

INTENSITY VALUES OF METHYL *p*-HYDROXYBENZOATE[a]

Concn. Mole L.$^{-1}$ $\times 10^3$	A_1	A_2	$A_1 + A_2$	% Association $\frac{A_2}{A_1 + A_2}$
2.925	3.45	0.37	3.82	9.69
8.280	3.17	0.62	3.79	16.36
9.460	3.19	0.74	3.93	18.83
13.730	2.78	1.16	3.95	29.37

[a] A_1 = Area at higher frequency; A_2 = Area at lower frequency.

This second band disappeared when the hydroxy compounds were measured in carbon tetrachloride with 10% pyridine, as would normally be expected, since pyridine is a stronger base than the carbonyl and the association takes place with the solvent.

TABLE V

INTENSITY VALUES OF METHYL *m*-HYDROXY BENZOATE[a]

Concn. Mole L.$^{-1}$ $\times 10^3$	A_1	A_2	$A_1 + A_2$	% Association, $\frac{A_2}{A_1 + A_2}$
9.885	2.23	1.04	3.27	31.8
12.100	2.16	1.11	3.27	34.0
19.251	1.76	1.32	3.08	42.8
22.950	1.69	1.46	3.15	46.4

[a] Area at higher frequency (nonassociated carbonyl); A_2 = Area at lower frequency (associated carbonyl).

If the values of concentration are plotted against the values of A_1 from Table IV, a straight line is obtained, and by extrapolation to zero concentration, the theoretical value for A_t mon can be obtained. This value was found to be 3.665.

Mills and Thompson[13] found that the concentration is directly related to the integrated absorption area. Therefore, it is possible to calculate the amount of monomer present at each concentration by means of the formula.

(13) I. M. Mills and H. W. Thompson, *Proc. Roy. Soc.*, 228A, 287 (1955).

$$\frac{A_i}{A \text{ mon}} C_i = C_i \text{ mon}$$

where A_t is the integrated absorption value of the monomer at a concentration C_i.

The equilibrium constant of the reaction

$$n(\text{ester}) \rightleftharpoons (\text{ester})n$$

can be calculated with the formula:

$$K = \frac{(\text{ester})n}{(\text{ester})^n} = \frac{C_i - C_i \text{ mon}}{\frac{n}{(C_i \text{ mon})^n}}$$

If this formula is written in a logarithmic form: Log $(C_t - C_i \text{ mon}) = n \log C_i \text{ mon} + \log nK$ it is possible to plot log $(C_t - C_t \text{ mon})$ against log C_t mon, whereby a straight line is obtained, in which the slope is the number of associated molecules n and the intercept, log nK.

Doing these calculations by the minimum square method, the values for n and K were 2.09 and 17.2, respectively. The value of 2.09 for n suggest that there is a cyclic dimer, in which each carbonyl is associated with the hydroxy groups of the other molecule, while the benzene rings are parallel to each other (Fig. 1).

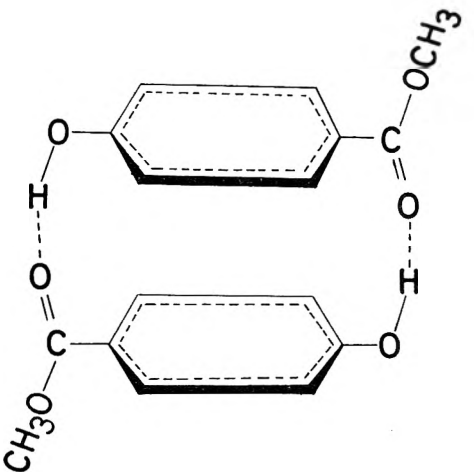


Figure 1

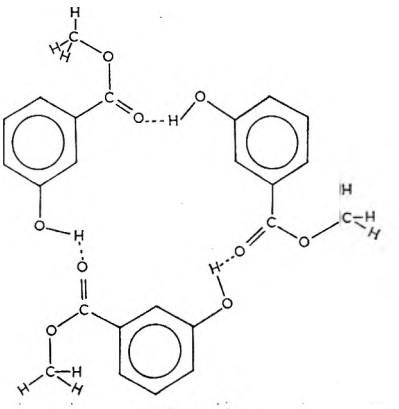


Figure 2

It would be very improbable to have a linear structure, because in that case the number of associated molecules should be greater than two.

The same kind of calculations was carried out with the data of the *m*-hydroxybenzoic ester, and a value for A_i mon was found to be 2.68. $n = 3.08$ and $K = 1.62 \times 10^5$.

The value of n suggests, therefore, that three molecules form a cyclic compound. By building the model it agrees with this suggestion (Fig. 2).

The free energy of association for the *p*-hydroxy ester is -1.56 kcal. and -6.58 kcal. for the *m*-ester.

The ΔF difference between the *m*- and *p*-esters may be explained as follows: when the *p*-hydroxy ester is arranged in a cyclic dimer, the carbonyl group is not in the same plane as the benzene ring, and some resonance energy is lost. In the *m*-hydroxy ester, three molecules can be arranged in such a way that the three benzene rings and the three carbonyls are in the same plane and, therefore, the resonance energy of the system does not decrease.

Acknowledgment. The authors are grateful to the Instituto Nacional de la Investigacion Cientifica for financial support.

MEXICO 20, D. F.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, ILLINOIS INSTITUTE OF TECHNOLOGY]

The Kinetics of Alkaline Hydrolysis and *n*-Butylaminolysis of Ethyl *p*-Nitrobenzoate and Ethyl *p*-Nitrothiolbenzoate[1a]

KENNETH A. CONNORS[1b,c] AND MYRON L. BENDER[1c]

Received November 10, 1960

The kinetics of alkaline hydrolysis of ethyl *p*-nitrobenzoate and ethyl *p*-nitrothiolbenzoate were studied by spectrophotometric analysis at 300 mμ. The rate of alkaline hydrolysis is first order in hydroxide ion concentration in the *p*H range 8 to 12 for the ester and from *p*H 9 to 12 for the thiol ester. The concurrent alkaline hydrolysis and *n*-butylaminolysis of these esters was interpreted in terms of the rate equation $v = k_1[E][OH^-] + k_2[E][RNH_2] + k_3[E][RNH_2]^2 + k_4[E][RNH_2][OH^-] + k_5[E][RNH_2][RNH_3^+] + k_6[E][RNH_3^+]$, where [E] represents the ester or thiol ester concentration. At 25.6° and ionic strength 0.50, in aqueous solution containing 1.7% v/v acetonitrile, ethyl *p*-nitrobenzoate did not undergo any detectable aminolysis; for this ester $k_1 = 0.63$ l./mole sec. Under the same conditions the thiol ester reacted differently, forming principally *N*-*n*-butyl-*p*-nitrobenzamide. The values of the rate constants of its reaction are $k_1 = 0.52$ l./mole sec., $k_2 = 0.015$ l./mole sec., $k_3 = 0.27$ l.²/mole² sec., $k_4 = 13.6$ l.²/mole² sec., $k_5 = k_6 = 0$. General base catalysis of thiol ester aminolysis, indicated by the k_3 and k_4 terms, probably proceeds *via* proton abstraction by a base from the tetrahedral addition intermediate.

The effects of variations in thiol ester structure upon rates of hydrolysis have been reported for many thiol acetates. Schaefgen[2a] studied the acid and alkaline hydrolysis of ethyl thiolacetate in acetone-water mixtures, and the same solvent was subsequently used by several other authors. Rylander and Tarbell[2b] compared the rates of acid and alkaline hydrolysis, and the respective energies of activation, of methyl, ethyl, isopropyl, isobutyl, and *t*-butyl thiolacetates with those of the corresponding acetates. Allyl, benzyl, and triphenylmethyl thiolacetates and acetates were similarly compared by Morse and Tarbell.[3] The kinetics of hydrolysis of many thiolacetates were investigated in fully aqueous solution by Noda, Kuby, and Lardy.[4] From these and other studies[5] a few generalizations can be made concerning the hydrolytic reactions of thiolesters: (1) The rates of alkaline hydrolysis of the compounds CH_3COSR are fairly sensitive to the nature of the R group. The ratios of the rate constants to the corresponding acid hydrolysis constants can be correlated with the Taft substituent constants.[6] The energies of activation in such a series are variable and tend to increase with increase in electron-donating ability of the R group. The rates of alkaline hydrolysis of the corresponding oxygen esters can be either less or greater than those of the thiol esters, though the difference is seldom large (usually within a factor of two). For the oxygen compounds neither the rate constants nor the activation energies are very sensitive to the structure of the R group. (2) The rates of acid hydrolysis of thiol esters appear to be less sensitive to structure than do the rates of al-

(1) (a) This research was supported by Grant H-2416 of the National Institutes of Health; (b) National Institutes of Health Postdoctoral Research Fellow; (c) Present address, Department of Chemistry, Northwestern University.

(2) (a) J. R. Schaefgen, *J. Am. Chem. Soc.*, **70**, 1308 (1948); (b) P. N. Rylander and D. S. Tarbell, *J. Am. Chem. Soc.*, **72**, 3021 (1950).

(3) B. K. Morse and D. S. Tarbell, *J. Am. Chem. Soc.*, **74**, 416 (1952).

(4) L. H. Noda, S. A. Kuby, and H. A. Lardy, *J. Am. Chem. Soc.*, **75**, 913 (1953).

(5) (a) H. Bohme and H. Schran, *Ber.*, **82**, 453 (1949); (b) J. T. G. Overbeek and V. V. Koningsberger, *Koninkl. Ned. Akad. Wetenschap., Proc.*, **57B**, 81, 311 (1954); (c) E. Heilbronn, *Acta Chem. Scand.*, **12**, 1481, 1492 (1958); *Acta Chem. Scand.*, **13**, 1044 (1959).

(6) R. W. Taft, Jr., in *Steric Effects in Organic Chemistry*, M. S. Newman, ed., John Wiley & Sons, Inc., New York, N. Y., 1956.

kaline hydrolysis. Apparently in all cases the rate for the oxygen ester is greater than that for the thiol ester; thus for the ethyl acetate–ethyl thiolacetate pair the factor is about 30-fold.[2a] The energies of activation for the thiol esters are larger than for ordinary esters.

Although explanations have been offered for many of these observations, the comparative kinetics of ester and thiol ester reactions are not well understood. In particular, the similar rates of alkaline hydrolysis for an ester-thiol ester pair are not expected, since the RS^- group, being a weaker base than the RO^- group by several orders of magnitude, should be a superior leaving group.

The above observations apply to those reactions which occur with acyl-sulfur fission, which has been demonstrated in the hydrolysis of many thiol esters.[2b,3,5c] In certain compounds alkyl-sulfur cleavage can occur, and this hydrolytic route has been observed in the acid hydrolysis of triphenylmethyl thiolacetate[3] and triphenylmethyl thiolbenzoate.[7]

Most of the investigations of thiol esters have followed the discovery that acylated coenzyme A, an intermediate in many biochemical reactions, is a thiol ester.[8] In some of these studies the reaction between amines and simple thiol esters has been taken as a possible model for certain coenzyme A systems.[9] Thus Tarbell and his co-workers[10] have measured the rates of *n*-butylaminolysis of $CH_3COSC_2H_5$, $CH_3COSCH_2CH_2NHCOCH_3$, and several related thiol esters; these compounds are simple models for acetyl coenzyme A. The modification of the ethyl thiolacetate structure with β- or γ-amido groups caused no important variations in rates of aminolysis. Overbeek and Koningsberger[5b,11] studied the reaction of glycine with ethyl thiolacetate. The aminolysis of the corresponding oxygen esters was not reported in these papers. The reactions of thiol esters with several other nucleophiles have been briefly studied. Hydroxylamine reacts to give the corresponding hydroxamic acid.[4] Other reagents which react with thiol esters are semicarbazide, hydrazine, and substituted hydrazines.[4] Imidazole catalyzes the hydrolysis of ethyl thiolacetate[12] and acetylthiocholine.[13]

The object of the present work was to compare the relative susceptibility of an oxygen ester-thiol ester pair to some simple nucleophiles in order to obtain a better understanding of thiolester reactivity. Ethyl *p*-nitrobenzoate and ethyl *p*-nitrothiolbenzoate were chosen because their reactions can be easily followed spectrophotometrically without interference from the product ethanethiol, which undergoes subsequent oxidation. The kinetics of alkaline hydrolysis and of the reaction with *n*-butylamine are presented in this paper.

EXPERIMENTAL

Materials. Ethyl *p*-nitrobenzoate (Eastman Kodak white label) was recrystallized from 95% ethanol; m.p. 56.5–57°. Ethyl *p*-nitrothiolbenzoate was prepared by warming *p*-nitrobenzoyl chloride and ethanethiol in pyridine solution; the mixture was poured into ice water and the light yellow precipitate was removed by filtration, washed with sodium bicarbonate solution and then with water, and recrystallized from acidified aqueous ethanol; m.p. 69.5–70° (lit.[14] m.p. 67–68°). *p*-Nitrobenzoic acid (Fisher reagent grade) was recrystallized from benzene; m.p. 243.5–244.5°. *N*-*n*-Butyl-*p*-nitrobenzamide was prepared by adding *n*-butylamine to a benzene solution of *p*-nitrobenzoyl chloride, refluxing for 15 min., and washing successively with sodium carbonate solution, dilute hydrochloric acid, and water. The solution was evaporated to dryness and the residue recrystallized from petroleum ether (b.p. 60–80°) and then from xylene; m.p. 104-104.5° (lit.,[15] m.p. 102.5–103°). *n*-Butylamine (Eastman Kodak white label) was distilled at atmospheric pressure (b.p. 77.2–77.4°), and its purity checked by titration with perchloric acid in acetic acid solution, using *p*-naphtholbenzein as a visual indicator. It was sealed under nitrogen in Pyrex ampoules and stored in a refrigerator. Acetonitrile (Eastman Kodak "spectro" grade) was used directly.

Phosphate, carbonate, and borate buffers were prepared from reagent grade materials according to standard formulas.[16] Standard sodium hydroxide solutions were made from a saturated solution of sodium hydroxide and carbonate-free water and were standardized against potassium biphthalate. Hydrochloric acid solution was standardized against borax. Buffers of *n*-butylamine were prepared from accurately weighed samples of *n*-butylamine and known volumes of standard hydrochloric acid solution. The ionic strength of all solutions was brought to a desired value by the addition of reagent grade potassium chloride, when necessary.

Kinetics of alkaline hydrolysis. The rates of alkaline hydrolysis of ethyl *p*-nitrobenzoate and of ethyl *p*-nitrothiolbenzoate were measured in borate, carbonate, and phosphate buffers and in sodium hydroxide solutions at an ionic strength of 0.05*M*. A stock solution of the sample compound in acetonitrile was added to the thermostatted solvent and the rate was followed by measuring the change in absorbance at 300 mμ for both esters. The acetonitrile concentration was 2% v/v; variation in acetonitrile concentration from 1.7 to 3.3% caused no significant variations in the observed rates. The initial concentration of the thiolester was about $1 \times 10^{-4}M$ and of the oxygen ester about $2 \times 10^{-4}M$. For solutions of *p*H less than 10.5,

(7) Y. Iskander, *Nature*, **155**, 141 (1945).

(8) F. Lynen and E. Reichert, *Angew. Chem.*, **63**, 47, 474 (1951).

(9) R. Schwyzer, *Helv. Chim. Acta*, **36**, 414 (1953).

(10) (a) P. J. Hawkins and D. S. Tarbell, *J. Am. Chem. Soc.*, **75**, 2982 (1953); (b) D. S. Tarbell and D. P. Cameron, *J. Am. Chem. Soc.*, **78**, 2731 (1956).

(11) (a) J. T. G. Overbeek and V. V. Koningsberger, *Koninkl. Ned. Akad. Wetenschap., Proc.*, **57B**, 464 (1954); (b) V. V. Koningsberger and J. T. G. Overbeek, *Koninkl. Ned. Akad. Wetenschap., Proc.*, **58B**, 49 (1955); (c) J. T. G. Overbeek and V. V. Koningsberger, *Koninkl. Ned. Akad. Wetenschap., Proc.*, **58B**, 266 (1955).

(12) M. L. Bender and B. W. Turnquest, *J. Am. Chem. Soc.*, **79**, 1656 (1957).

(13) E. Heilbronn, *Acta Chem. Scand.*, **13**, 1547 (1959).

(14) H. L. Hansen and L. S. Fosdick, *J. Am. Chem. Soc.*, **55**, 2872 (1933).

(15) G. H. Coleman and H. P. Howells, *J. Am. Chem. Soc.*, **45**, 3084 (1923).

(16) I. M. Kolthoff, *Acid-Base Indicators*, Macmillan Co., New York, N. Y., 1937, Chap. VIII; R. G. Bates and V. E. Bower, *Anal. Chem.*, **28**, 1322 (1956).

aliquots were withdrawn at appropriate intervals and the absorbance measured on a Beckman DU spectrophotometer; the temperature of the solutions was 24.7°. Reactions in solutions of higher *p*H were followed by continuous recording of the absorbance with a Beckman DK-2 spectrophotometer fitted with a water-jacketed cell compartment; the temperature in the cell compartment varied from 24.8° to 25.4°. Reactions were usually followed until 75–85% completed and a final (infinity time) reading was taken. *p*H measurements were made with a Radiometer model 3i *p*H meter equipped with a high-alkaline range glass electrode. The estimated uncertainty in *p*H values is ±0.02 unit. For calculations with these results pK_W = 14.00 was used.

Decomposition of the thiol ester was observed to be accelerated by oxygen. Thus at *p*H 10.10, the second-order rate constant was 0.535 l./mole sec. in a nitrogen atmosphere, 0.594 l./mole sec. in air, and 0.744 l./mole sec. in an oxygen atmosphere. At very high *p*H, where the hydrolysis is extremely rapid, this effect is not important. At lower *p*H values solvents were flushed with nitrogen before addition of the sample. For reactions followed with the Beckman DU, aliquots were sealed under nitrogen in Pyrex ampoules, which were immersed in the water bath and removed at intervals for spectral analysis.[17]

The effect of ionic strength upon the rates of hydrolysis was studied in sodium hydroxide solutions containing potassium chloride to give the desired ionic strength. The reactions were followed with the DK-2 spectrophotometer, the cell compartment temperature being 25.6 ± 0.1°. In these solutions the acetonitrile concentration was 1.7%.

Kinetics of aminolysis. The aminolysis of ethyl *p*-nitrobenzoate and ethyl *p*-nitrothiolbenzoate was studied in buffer solutions of *n*-butylamine and *n*-butylammonium chloride at a constant ionic strength of 0.50. All reactions were followed by absorbance measurements at 300 mμ with the Beckman DK-2 spectrophotometer. The temperature was 25.6 ± 0.1° during these measurements and the acetonitrile concentration was 1.7%. Duplicate determinations were performed in most of the kinetic runs; the maximum deviation of any measurement from the mean was 1.7%. *p*H measurements were made with a Radiometer model 4b meter standardized against 0.01*M* trisodium phosphate[18]; the estimated uncertainty is ±0.02 unit.

The compositions of the amine buffers are given in Table IV. Concentrations of free amine, $[RNH_2]$, were found by subtracting the concentration of protonated amine, $[RNH_3^+]$, from the total amine concentration, and $[RNH_3^+]$ was calculated with the relation $[RNH_3^+] = [Cl^-]_{HCl} + [OH^-]$, which represents the principle of electroneutrality in these basic solutions; the quantity $[Cl^-]_{HCl}$ is the concentration of chloride ion added in the form of hydrochloric acid.

In all calculations with data at 25.6° which require the quantity pK_W the value 13.98 was employed.[19] This is probably not the correct value in all solutions, because the measured *p*H will not correspond precisely to hydrogen ion activity and the response of the glass electrode may vary with the salt composition of the sample solutions. Another factor which can affect the experimental *p*H values (and the true value of pK_W) is the modification of the solvent by acetonitrile (1.7%) and free *n*-butylamine (up to 4.5%). Because of these uncertainties the quantity $[OH^-]$ derived from the *p*H measurements may not have any absolute significance, but the values are assumed to be approximately internally consistent.

(17) Overbeek and Koningsberger (Ref. 5b) have reported that ethyl thiolacetate undergoes decomposition in the presence of oxygen.

(18) R. G. Bates, G. D. Pinching, and E. R. Smith, *J. Research Natl. Bur. Standards*, **45**, 418 (1950).

(19) H. S. Harned and W. J. Hamer, *J. Am. Chem. Soc.*, **55**, 2194 (1933).

Analysis of products. Ethyl *p*-nitrobenzoate and ethyl *p*-nitrothiolbenzoate both hydrolyze in alkaline solution to yield *p*-nitrobenzoate anion, and the absorption spectra of completely hydrolyzed solutions were quantitatively accounted for on this basis (except for absorption by ethanethiol, in the thiol ester hydrolysis, at lower wave lengths). The product of ethyl *p*-nitrobenzoate reaction in the presence of *n*-butylamine also was determined to be *p*-nitrobenzoate anion.

The absorption spectrum of completely reacted ethyl *p*-nitrothiolbenzoate in *n*-butylamine buffer solutions resembled that of *N*-*n*-butyl-*p*-nitrobenzamide. A quantitative determination was made of the proportion of amine product by the reaction. Several solutions (similar to those used for the kinetic runs) were prepared with known concentrations of free and protonated amine, and known *p*H; sufficient potassium chloride was added to bring the ionic strength to 0.50. Samples of ethyl *p*-nitrothiolbenzoate in acetonitrile solution were added. After the reactions were complete the amine concentrations of the solutions were brought to a common value and an excess of hydrochloric acid was added. Accurately prepared solutions of *p*-nitrobenzoic acid and *N*-*n*-butyl-*p*-nitrobenzamide, in solvent of the same final amine and hydrochloric acid composition, were also made up, and the absorbances of all solutions at 290 mμ were measured with a Beckman DU spectrophotometer. The molar absorptivities[20] of the standard solutions were: *p*-nitrobenzoic acid, 4.67×10^3; and *N*-*n*-butyl-*p*-nitrobenzamide, 7.96×10^3. From these data and the concentration of thiol ester added the percentage yield of amide was calculated (Table I). The major product is seen to be the amide under these conditions. (For explanation of the last column in Table I see *Results* section.)

TABLE I

PER CENT YIELD OF AMIDE IN THE *n*-BUTYLAMINOLYSIS OF ETHYL *p*-NITROTHIOLBENZOATE

Total Amine Concentration[a]	$[RNH_2]$[a]	*p*H	% Amide Produced	% Amide Calculated
0.1046	0.0524	10.87	79	84
0.4185	0.3033	11.29	95	97
0.1046	0.0324	10.52	73	79

[a] In moles/liter.

To determine whether subsequent hydrolysis of the amide would occur during the kinetic observations a sample of *N*-*n*-butyl-*p*-nitrobenzamide was added to an *n*-butylamine buffer solution (total amine concentration 0.1*M*, *p*H 10.6) and the solution was equilibrated at 24.7°. The absorbance at 270 mμ and at 300 mμ was periodically measured with a Beckman DU, and no change in absorbance was noted in 24 hr. Under the conditions of the kinetic experiments reported here, therefore, no hydrolysis of the product amide occurs before the thiol ester reaction is completed.

RESULTS

Alkaline hydrolysis. The concentration of hydroxide ion was maintained essentially constant in kinetic runs by means of buffers or excess sodium hydroxide, and the observed kinetics were first order with respect to the carboxylic acid derivative; examples of the first order plots are shown in Fig. 1. The observed rate constant calculated from the

(20) H. K. Hughes *et al.*, *Anal. Chem.*, **24**, 1349 (1952).

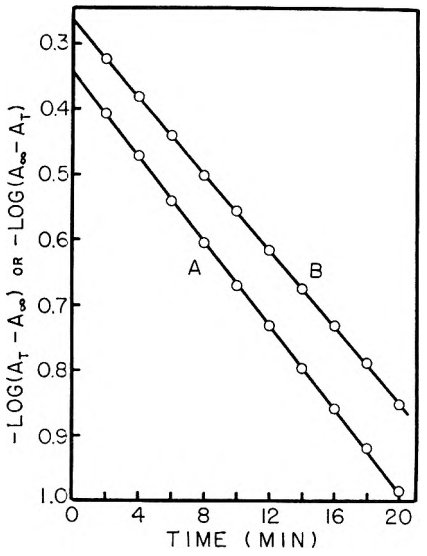


Fig. 1. Alkaline hydrolysis in *p*H 11.38 phosphate buffer. A. Ethyl *p*-nitrobenzoate. B. Ethyl *p*-nitrothiolbenzoate

slopes of plots of log $(A_\infty - A_t)$ [for ethyl *p*-nitrobenzoate] or log$(A_t - A_\infty)$ [for ethyl *p*-nitrothiolbenzoate] *vs.* time, are listed in Table II with the measured *p*H. The calculated second order constants are seen to be constant over the *p*H range 8 to 12 for the ester and 9 to 12 for the thiol ester. The deviations from constancy at lower *p*H values have not been thoroughly studied since this *p*H region did not figure in subsequent work.

TABLE II

KINETICS OF ALKALINE HYDROLYSIS OF ETHYL *p*-NITROBENZOATE AND OF ETHYL *p*-NITROTHIOLBENZOATE

*p*H	No. Detns.	k_{obs}, Sec.$^{-1}$[a]	k_{OH}, L./Mole Sec.
	ETHYL *p*-NITROBENZOATE		
12.00	4	$5.38 \pm 0.04 \times 10^{-3}$	0.538
11.38	4	$1.28 \pm 0.03 \times 10^{-3}$	0.531
10.09	2	$6.64 \pm 0.05 \times 10^{-5}$	0.540
9.09	2	$6.64 \pm 0.05 \times 10^{-6}$	0.540
7.99	1	5.33×10^{-7}	0.546
7.14	1	2.56×10^{-7}	1.86
	ETHYL *p*-NITROTHIOLBENZOATE		
12.00	8	$4.48 \pm 0.20 \times 10^{-3}$	0.448
11.38	5	$1.15 \pm 0.05 \times 10^{-3}$	0.478
10.70	2	$2.43 \pm 0.04 \times 10^{-4}$	0.473
10.10	2	$6.75 \pm 0.38 \times 10^{-5}$	0.535
9.09	3	$5.77 \pm 0.21 \times 10^{-6}$	0.469
8.31	1	1.45×10^{-6}	0.711

[a] Precision expressed as mean deviation, where m.d. $= \frac{\Sigma|x_i - \bar{x}|}{n-1}$.

The second order constants for alkaline hydrolysis increase with ionic strength, as shown in Table III. The change is not large and is similar in magnitude for both compounds.

TABLE III

EFFECT OF IONIC STRENGTH ON RATES OF ALKALINE HYDROLYSIS

Ionic Strength	k_{OH}, l./mole sec.
ETHYL *p*-NITROBENZOATE	
0.006	0.53
0.20	0.64
0.36	0.59
0.49	0.63
0.60	0.65
ETHYL *p*-NITROTHIOLBENZOATE	
0.006	0.45
0.20	0.53
0.36	0.48
0.49	0.51
0.60	0.53

Concurrent hydrolysis and aminolysis. The design of the aminolysis experiments was based upon rate Equation 1.[21]

$$-d[E]/dt = k_1[E][OH^-] + k_2[E][RNH_2] + k_3[E][RNH_2]^2 + k_4[E][RNH_2][OH^-] + k_5[E][RNH_2][RNH_3^+] + k_6[E][RNH_3^+] \quad (1)$$

[E] represents the ester or thiol ester concentration, $[RNH_2]$ is the concentration of free *n*-butylamine, and $[RNH_3^+]$ is the concentration of protonated amine. The experimental rate was observed to be first order with respect to [E] in buffers containing excess amine; that is,

$$-d[E]/dt = k_{obs}[E] \quad (2)$$

The dissociation constant of the protonated amine is written $K_a = [H^+][RNH_2]/[RNH_3^+]$; this expression can be combined with Equations (1) and (2) to give (4),

$$\frac{(k_{obs} - k_1[OH^-])}{[RNH_2]} = (k_3 + k_5[H^+]/K_a)[RNH_2] + (k_2 + k_4[OH^-] + k_6[H^+]/K_a) \quad (4)$$

which indicates that, if the *p*H is maintained constant and the amine concentration is varied, a plot of $(k_{obs} - k_1[OH^-])/[RNH_2]$ *vs.* $[RNH_2]$ should yield a straight line. From such plots at several values of *p*H the constants k_3 and k_5 may be evaluated from the variation of the slope with $[H^+]$. The intercept is a quadratic function of $[H^+]$, but simplifies if either k_4 or k_6 is equal to zero; if both k_4 and k_6 are greater than zero a simple linear extrapolation cannot be made, though the constants can be found analytically.

The rate of reaction of ethyl *p*-nitrobenzoate did not appear to be affected by *n*-butylamine. The kinetics were studied in *n*-butylamine buffers (total

(21) Similar rate equations have previously been suggested to account for aminolysis of esters and thiol esters, though in no single system have all six terms been required to explain the data. (a) J. F. Bunnett and G. T. Davis, *J. Am. Chem. Soc.*, 82, 665 (1960); W. P. Jencks and J. Carriuolo, *J. Am. Chem. Soc.*, 82, 675 (1960); Ref. 10, 11.

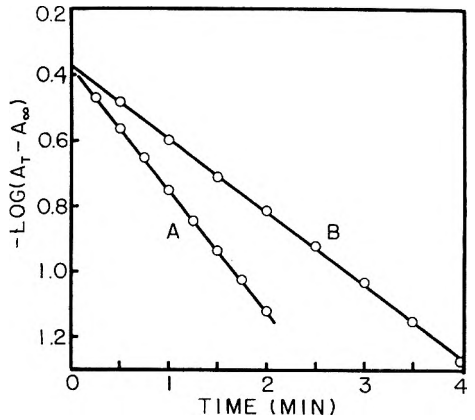


Fig. 2. Typical kinetic runs in the *n*-butylaminolysis of ethyl *p*-nitrothiolbenzoate. A. $(RNH_2]$ = 0.1483, $[RNH_3^+]$ = 0.0595 mole/l.; *p*H = 11.27. B. $[RNH_2]$ = 0.1521, $[RNH_3^+]$ = 0.3703 mole/l.; *p*H = 10.44

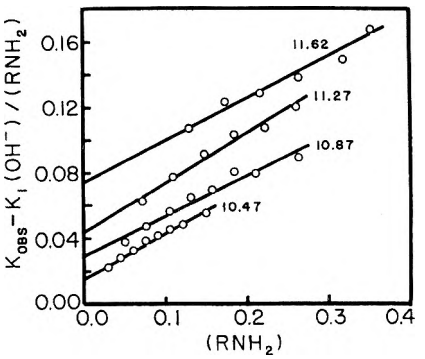


Fig. 3. Plot of Equation (4) for the *n*-butylaminolysis of ethyl *p*-nitrothiolbenzoate. Numbers denote *p*H

amine 0.1–0.5*M*) at three *p*H values. The quantity $(k_{obs} - k_1[OH^-])/[RHN_2]$ was a positive or negative number of the order 10^{-4}; in the calculation of this quantity k_1 was taken as 0.63 l./mole sec. It is concluded that the constants k_2, k_3, k_4, k_5, and k_6 are not significantly different from zero under the conditions of the experiments.

The reaction rate of ethyl *p*-nitrothiolbenzoate was significantly accelerated by *n*-butylamine. Typical first order plots are shown in Fig. 2. The data are listed in Table IV and the plots of $(k_{obs} - k_1[OH^-])/[RNH_2]$ *vs.* $[RNH_2]$ are given in Fig. 3. The lines are reasonably straight, though a slight curvature may be present in some of them. Variations in *p*H may be responsible for some of the deviations. It may be significant that curvature seems to occur at lower values of $[RNH_2]$ when the *p*H is lowered; that is, curvature may be associated with high concentrations of amine salt. This slight trend of points away from linearity was neglected in the construction of lines, which was done by the least-squares method. The equations of the lines are given in Table V.

The slopes of the lines do not appear to vary with *p*H, hence k_5 is taken equal to zero. The mean of the slopes is 0.269 ± 0.025 l.^{2}/mole^2 sec. A plot of the intercepts against $[H^+]$ produces a curve, while the plot of intercept *vs.* $[OH^-]$ yields a reasonably straight line (Fig. 4). The least-squares equation of this line is

$$\text{Intercept} = 13.6[OH^-] + 0.015.$$

TABLE IV

KINETIC DATA FOR ETHYL *p*-NITROTHIOLBENZOATE IN *n*-BUTYLAMINE BUFFERS

Total Amine Concentration[a]	$[RNH_2]$[a]	$k_{obs} \times 10^2$, sec.$^{-1}$	$(k_{obs} - k_1[OH^-])/[RNH_2]$[b]
	*p*H = 10.47 ± 0.02		
0.1045	0.0302	0.0826	0.0217
0.1567	0.0454	0.137	0.0267
0.2089	0.0606	0.212	0.0322
0.2612	0.0759	0.306	0.0381
0.3134	0.0911	0.388	0.0408
0.3657	0.1064	0.493	0.0448
0.4179	0.1216	0.596	0.0477
0.5224	0.1521	0.852	0.0550
	*p*H = 10.87 ± 0.01		
0.1046	0.0524	0.236	0.0370
0.1569	0.0780	0.408	0.0471
0.2092	0.1056	0.634	0.0563
0.2614	0.1321	0.883	0.0637
0.3139	0.1587	1.14	0.0693
0.3660	0.1853	1.53	0.0804
0.4183	0.2120	1.73	0.0794
0.5229	0.2651	2.41	0.0894
	*p*H = 11.27 ± 0.01		
0.1039	0.0733	0.550	0.0621
0.1558	0.1107	0.949	0.0766
0.2078	0.1483	1.45	0.0910
0.2597	0.1857	2.03	0.103
0.3116	0.2234	2.49	0.107
0.3636	0.2609	3.24	0.120
0.4155	0.2986	3.50	0.114[c]
0.5194	0.3735	4.90	0.129[c]
	*p*H = 11.62 ± 0.02		
0.1042	0.0863	0.966	0.0907[d]
0.1563	0.1303	1.61	0.107
0.2085	0.1756	2.37	0.123
0.2606	0.2182	3.03	0.128
0.3127	0.2652	3.89	0.138
0.3648	0.3098	4.86	0.149
0.4169	0.3548	6.20	0.168
0.2512	0.4448	7.28	0.159[c]

[a] In mole/liter. [b] k_1 = 0.52 l./mole sec. [c] Rejected. [d] Rejected because *p*H (11.53) differed widely from the mean.

TABLE V

EQUATIONS OF LINES ACCORDING TO EQUATION (4) FOR THE *n*-BUTYLAMINOLYSIS OF ETHYL *p*-NITROTHIOLBENZOATE

*p*H	$[OH^-]$, Mole/l.	Equation[a]
10.47	3.09×10^{-4}	$y = 0.273x + 0.015$
10.87	7.76×10^{-4}	$y = 0.244x + 0.029$
11.27	1.95×10^{-3}	$y = 0.302x + 0.043$
11.62	$4.37 + 10^{-3}$	$y = 0.257x + 0.074$

[a] $y = (k_{obs} - k_1[OH^-])/[RNH_2]$; $x = [RNH_2]$.

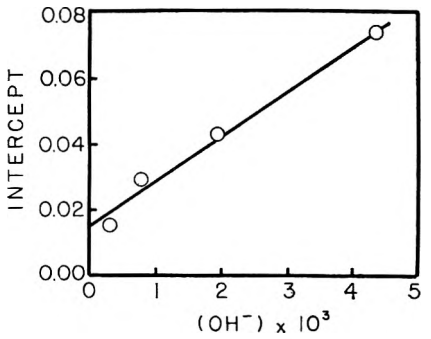


Fig. 4. Plot of the intercepts from Fig. 3 *versus* hydroxide ion concentration

The rate constants for the aminolysis are therefore $k_2 = 0.015$ l./mole sec., $k_3 = 0.27$ l.²/mole² sec., $k_4 = 13.6$ l.²/mole² sec., and $k_5 = k_6 = 0$.

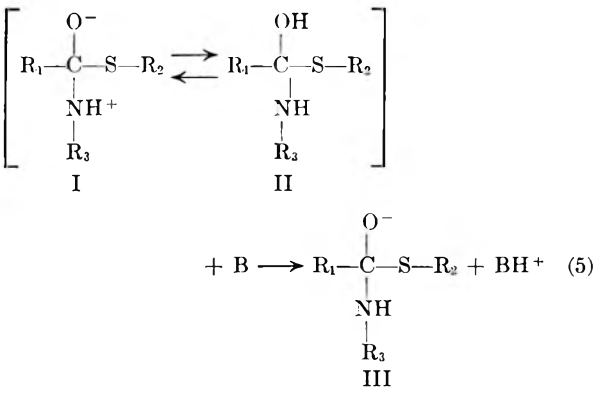
These constants can be used to calculate the expected first order rate constant at any amine concentration and *p*H; the observed values can be reproduced to better than 10%. In a similar calculation the percentage yields of amide to be expected under the conditions given in Table I are listed in the last column of that table. The agreement with experiment is satisfactory.

From the data of Table IV the apparent dissociation constant of *n*-butylammonium ion can be calculated. (Actually the experimental *p*H values, rather than the average values given in the table, were used.) The results show no consistent trend with amine concentration. pK'_a is 10.87 ± 0.01 at ionic strength 0.50 and total amine concentration 0.1–0.5*M*. (The thermodynamic pK_a is 10.597 at 25°.)[22]

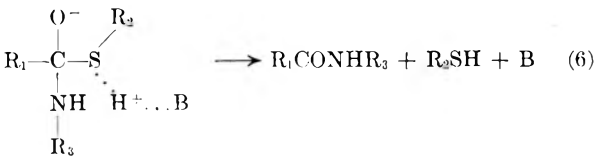
DISCUSSION

Ethyl *p*-nitrothiolbenzoate is considerably more reactive toward hydroxide ion than are most thiolacetates.[2b,4,23] Ethyl *p*-nitrobenzoate is also quite reactive, its second order alkaline hydrolysis rate constant being about one half that of phenyl acetate.[21b] However, while the susceptibility of the thiol ester to aminolysis is consistent with the behavior observed with other thiol esters[10,11a] and with phenyl acetate,[21b] the absence of detectable aminolysis of ethyl *p*-nitrobenzoate is unexpected. That is, $CH_3CH_2S^-$ and $CH_3CH_2O^-$ appear to be equally good leaving groups with respect to hydroxide ion, but $CH_3CH_2S^-$ is a relatively far better leaving group than $CH_3CH_2O^-$ with respect to *n*-butylamine. The similar reactivities of ethyl *p*-nitrobenzoate and ethyl *p*-nitrothiolbenzoate (and of nearly all ester-thiol ester pairs) toward hydroxide ion may perhaps be the result of a difference in solvent participation for the two compounds. The precise nature and extent of such involvement are unknown for either type of compound. Schaefgen[2a] suggested that attack by hydroxide ion on the carbonyl of an ester may be aided by hydrogen-bonding of a water molecule to the ether oxygen, while this interaction would be absent or of less importance for the thiolester.

Several mechanisms have been proposed to account for the observation of general basic catalysis of aminolysis of esters and thiol esters.[10a,21a,b] One of these involves removal of a proton from the attacking amine by a general base during the transition state of the formation of the tetrahedral addition intermediate. This mechanism is similar to another (Equation 5) in which a proton is removed from the tetrahedral addition intermediate (I or II), and there may be no clear distinction between the two descriptions. The proton abstraction is followed by decomposition of III to



the amide and the thiol anion. The mechanism shown by reaction (6) involves general acid catalyzed breakdown of III as the slow step; in this



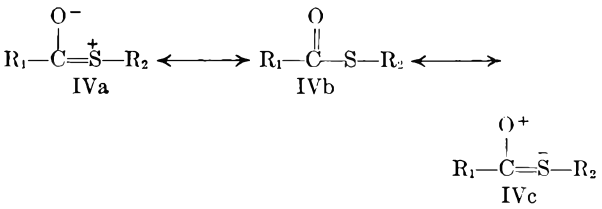
scheme the formation of III from I or II is regarded as a fast reversible reaction.[21a] This mechanism leads to observed general base catalysis if the base B which is responsible for proton removal from I or II is the conjugate base of the general acid BH^+ involved in reaction (6); this may not generally be the case. Bunnett and Davis[21a] have pointed out that the better the leaving group the less is the likelihood that mechanism (6) will be important. In fact, in the *p*H range employed in the present work the product thiol was largely ionized (the

(22) A. G. Evans and S. D. Hamann, *Trans. Faraday Soc.*, **47**, 34 (1951).

(23) Preliminary studies of the alkaline hydrolysis of phenyl thiolbenzoate have shown that this too is a fairly reactive thiol ester, with $k_{OH} = 0.4$ l./mole sec. The reaction was studied at 25° in *p*H 10 carbonate buffer and in sodium hydroxide solutions, the decrease in thiol ester concentration being followed by absorbance measurements at 240 mμ.

pK_a of ethanethiol is about 10.5)[24] and it seems that general acid assistance would be unlikely. The mechanism according to Equation (5) seems more probable, where B is H_2O, RNH_2, or OH^-, giving rise to terms in k_2, k_3, and k_4, respectively. The rate constant k_2 then would include the concentration of water.

Pertinent to the problem of thiol ester reactivity is the recent infrared study of Baker and Harris,[25] who suggested that the thiol ester structure includes the resonance form IVc, in which the sulfur *d*-orbital is utilized. Oxygen esters, on the other hand,



are generally represented by the structures Va and Vb. As a result the carbonyl group of a thiol ester may be considerable less basic than that of

the corresponding ester.[25] Proton attack at the carbonyl oxygen should be more important with the ester than with the thiol ester, therefore, and this is consistent with the greater rate of acid hydrolysis always observed for esters. The mode of attack of hydroxide ion upon a structure like IV is not known. Three mechanisms have been proposed for attack by a nucleophile on a carboxylic acid derivative.[26] One of these involves an approach from the rear with respect to the leaving group, another represents the attack as rearward approach with respect to the carbonyl oxygen, and the third pictures the approach as an attack perpendicular to the plane of the carbonyl group. This last approach permits maximum overlap of the π-orbital of the carboxyl group with the orbital of the incoming nucleophile. In a structure such as IV the carbonyl electron distribution is sufficiently altered by hybridization with the sulfur *d*-orbitals so that the approach of the nucleophile may not be controlled simply by the carbonyl group alone, and predictions about rates of alkaline hydrolysis based upon structure IV cannot be made.

The similarity of alkaline hydrolysis rates for an oxygen ester–thiol ester pair may be explicable in terms of the partition ratio k_2/k_3, where k_2 is the rate constant for return to reactants from the tetrahedral intermediate and k_3 is the rate constant for passage to products.[27] For oxygen esters, values of k_2/k_3 range from essentially zero to about 0.8.[27] It seems reasonable that the constant k_3 for a thiol ester may be considerably larger than that for the corresponding ester, because of the much lower basicity of the thiolate group, and that k_2/k_3 may therefore be even smaller for the thiol ester than for the ester. Because the hydrolytic rate constant may be expressed as $k_h = k_1/(k_2/k_3 + 1)$, where k_1 is the rate constant for the formation of the intermediate, the magnitude of k_h is determined by that of k_1, since k_2/k_3 seems usually to be smaller than one. Thus if the k_1 constants for a thiol ester–ester pair are similar in magnitude it is not surprising that the alkaline hydrolytic constants also are similar. A study of the kinetics of oxygen exchange[27] of ethyl *p*-nitrobenzoate and ethyl *p*-nitrothiolbenzoate has been initiated to obtain evidence bearing on this problem.

The same consideration may be applied to the aminolysis reaction. If the assumption is made that the intermediate corresponding to I and II actually is formed in the oxygen ester–amine system, then the absence of observed reaction may be accounted for by a large value of k_2/k_3 (much greater that one) for this intermediate.

In Table VI reasonable values of k_2/k_3 are shown for the alkaline hydrolysis and aminolysis of both esters. It will be noted that the ratio $(k_2/k_3)_o/(k_2/k_3)_s$ is the same in both systems; this seems to be a reasonable limit to impose upon the possible values of the partition ratio. In the final column of the table are listed the rate constants which would be observed with these assigned ratios. If the values of k_o and k_s (in each system) are comparable, it is seen that the oxygen and thiol esters are of similar reactivity with respect to hydroxide ion, while the thiol ester is much more reactive than the ester with respect to the amine.

TABLE VI

HYPOTHETICAL RATE CONSTANTS FOR HYDROLYSIS AND AMINOLYSIS OF ESTERS AND THIOL ESTERS

	k_1	k_2/k_3	k_{obs}[a]
ALKALINE HYDROLYSIS			
Ester	k_1^o	0.25	$0.8k_1^o$
Thiol ester	k_1^s	0.001	k_1^s
AMINOLYSIS			
Ester	k_1^o	25	$0.038k_1$
Thiol ester	k_1^s	0.1	$0.91k_1^s$

[a] Calculated with the equation $k_{obs} = k_1/(k_2/k_3 + 1)$.

CHICAGO, ILL.

(24) D. L. Yabroff, *Ind. Eng. Chem.*, **32**, 257 (1940); J. P. Danehy and C. J. Noel, *J. Am. Chem. Soc.*, **82**, 2511 (1960).

(25) A. W. Baker and G. H. Harris, *J. Am. Chem. Soc.*, **82**, 1923 (1960).

(26) M. L. Bender, *Chem. Revs.*, **60**, 60 (1960).

(27) M. L. Bender, *J. Am. Chem. Soc.*, **73**, 1626 (1951); M. L. Bender, R. D. Ginger, and J. P. Unik, *J. Am. Chem. Soc.*, **80**, 1044 (1957).

[CONTRIBUTION FROM DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PUERTO RICO AT MAYAGUEZ AND INSTITUTO DE QUÍMICA, UNIVERSIDAD NACIONAL AUTONOMA DE MEXICO]

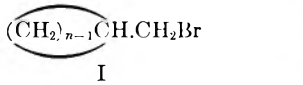
Kinetics of Saponification of Some Cyclic Esters

OWEN H. WHEELER,[1a] O. CHAO,[1b] AND J. R. SÁNCHEZ-CALDAS[1a]

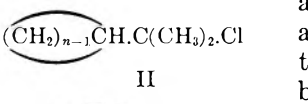
Received October 10, 1960

The alkaline hydrolysis of cycloalkane carbethoxylates (IV. R = C_2H_5, n = 3–6) has been measured at 0° and 25° in 41% aqueous ethanol, and the differences observed are discussed in terms of the steric and electronic effects of the rings.

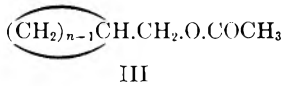
The effect of ring size on the rates of reactions taking place at a ring carbon atom has been well studied[2a] and the observed differences are consistent with the changes in ring strain occurring during the reaction.[2b] However very few data are available concerning the effects of ring size on a reaction center adjacent to the ring, where any differences in rate would be expected to be due to the steric and electronic effects of the ring and not directly to ring strain effects. Royals and Neal[3a] measured the rates of bimolecular displacement of cyclopentyl, cyclohexyl, and cycloheptyl methyl bromides (I, n = 5–7) with thiophenoxide ion finding a relative order of 1.00:1.46:2.95 at 35°, and Skinner and Florentine[3b] reported the rates of unimolecular solvolysis of cyclopentyl and cyclohexyl dimethylcarbinyl chlorides (II, n = 5,6) as having relative rates of 1.00:0.52 in 78% ethanol at 30°. Both of these reactions involve a carbon atom once removed from the ring. The rates of



I



II



III

IV

saponification of cycloalkanyl carbinyl acetates (III. n = 3–6) have been measured by Sarel, Tsai, and Newman,[4] who found values of k_2 ($\times 10^3$ in l. mole^{-1} sec.$^{-1}$ in 70% dioxane-water at 20°) of 31, 23, 16, and 10 for the 3 to 6 ring compounds. The reaction, however, involves a displacement at the carbonyl-carbon atom which is three atoms removed from the ring. In the present work the rates of saponification of cycloalkane carbethoxylates (IV. R = C_2H_5, n = 3–6) have been measured in 41% ethanol-water at 25° and 0° (Table I). The rates showed an order of ring size of 4>>5>3~6 with relative differences of up to 11-fold, which is much greater than those found in the hydrolysis of the cyclic acetates (III). The reaction involves a displacement on the carbonyl-carbon atom which is only once removed from the ring, and an explanation for these relatively large differences must be sorted in the steric and electronic effects produced by the rings.

The mechanism of bimolecular basic hydrolysis ($B_{AC}2$) of simple esters involves a slow rate determining attack of base on the carbonyl-carbon atom followed by a rapid elimination of alkoxide ion (ethoxide in this case) to form the acid anion. Electronic effects which decrease the charge on the carbonyl-carbon atom will accelerate the rate of nucleophilic attack of hydroxyl ion, whereas the steric hindrance of bulky neighboring substituents will decrease the ease of approach of a base. Cyclopropyl and cyclobutyl carboxylic acids have about the same acid strengths and are both stronger acids than cyclopentyl or cyclohexyl carboxylic acids (Table I).[5] This has been attributed[5a] to the increased s-character of the carbon-hydrogen bonds attached to the rings, resulting in a general electron-attracting (−I) effect. This effect is also reflected in the higher carbonyl stretching frequency of cyclopropyl carbethoxylate (Table II), and accounts for the high rate of saponification of the cyclobutyl ester (IV. R = C_2H_5, n = 4). However the much slower rate of hydrolysis of the cyclopropyl ester (IV. R = C_2H_5, n = 3) is not consistent with a purely electronic effect of the ring. In this case it is probable that the hydrogen atoms which are bunched together above and below the ring due to the increased s-character of the carbon-hydrogen bonds (the angle between sp^2-hybrids in 120°),[6] exert a steric hindrance to attack of base. The cyclobutane ring is, however, more open and the carbethoxy group will be less crowded.

There is little or no angle-strain present in a cyclopentane[7] or cyclohexane[2b] ring and their

(1) (a) University of Puerto Rico at Mayaguez; (b) Universidad Nacional Autonoma de Mexico. Contribution No. 124 from the Instituto de Química.

(2) (a) H. C. Brown, *J. Chem. Soc.*, 1248 (1956); (b) H. C. Brown, J. H. Brewster and H. Shechter, *J. Am. Chem. Soc.*, **76**, 467 (1954).

(3) (a) E. E. Royals and A. H. Neal, *J. Org. Chem.*, **21**, 1448 (1956); (b) G. S. Skinner and F. P. Florentine, *J. Am. Chem. Soc.*, **76**, 3200 (1954).

(4) S. Sarel, L. Tsai, and M. S. Newman, *J. Am. Chem. Soc.*, **78**, 5420 (1956).

(5) (a) J. D. Roberts and V. C. Chambers, *J. Am. Chem. Soc.*, **73**, 5030 (1951); (b) M. Kilpatrick and J. G. Morse, *J. Am. Chem. Soc.*, **75**, 1854 (1953).

(6) The H—C—H angle in cyclopropane is 118–120°. O. Bastiansen and O. Hassel, *Tidsskr. Kjemi, Bergvesen Met.*, **6**, 71 (1946); P. W. Allen and L. E. Sutton, *Acta Cryst.*, **3**, 46 (1950).

(7) F. V. Brutcher, Jr., T. Roberts, S. J. Barr, and N. Pearson, *J. Am. Chem. Soc.*, **81**, 4915 (1959).

TABLE I

RATES OF SAPONIFICATION OF ESTERS[a]

Ester	pK_a Acid[a]	$k_2 \times 10^4$ L. Mole^{-1} Sec.$^{-1}$ 25°	$k_2 \times 10^4$ L. Mole^{-1} Sec.$^{-1}$ 0°	Eact. Kcal.	Log PZ	Rel. Rate[b]
$(CH_3)_2CHCO_2C_2H_5$	—	43.7 ± 2.1	5.23 ± 0.14	13.8	7.8	2.5
IV. R = C_2H_5, n = 3	6.15	24.0 ± 0.8	3.09 ± 0.07	13.3	7.2	1.4
IV. R = C_2H_5, n = 4	6.15	187 ± 1	30.6 ± 0.5	11.8	6.9	11
IV. R = C_2H_5, n = 5	6.30	40.9 ± 1.3	7.39 ± 0.27	11.1	5.8	2.4
IV. R = C_2H_5, n = 6	6.35	17.2 ± 0.2	3.23 ± 0.16	10.9	5.2	1.0

[a] In 47% ethanol-water; pK_a's at 25°. [b] Relative rates at 25° to rate of cyclohexyl ester = 1.0.

TABLE II

PHYSICAL CONSTANTS OF ESTERS

Ester	B.P.	n_D^{25}	$\nu_{C=O}$[a]
$(CH_3)_2CHCO_2C_2H_5$	52°/80 mm.	1.3878	—
IV. R = C_2H_5, n = 3	70°/80 mm.	1.4403	1690
IV. R = C_2H_5, n = 4	85°/85 mm.	1.4245	1700
IV. R = C_2H_5, n = 5	75°/28 mm.	1.4340	1705
IV. R = C_2H_5, n = 6	95°/30 mm.	1.4380	1705

[a] Carbonyl stretching for carbon tetrachloride solutions in cm.$^{-1}$

carboxylic acids are thus weaker than the corresponding cyclopropane and cyclobutane acids. Moreover it has recently been suggested[7] that the steric environment of a saturated substituent on a cyclopentane ring (in its "envelope" form) is little different from that on a cyclohexane ring, and in both cases the pair of equatorial hydrogen atoms on the α-carbon atoms are placed near to the equatorial substituent. Since the electronic and steric nature of these two rings are very similar the cyclopentyl and cyclohexyl esters (IV. R = C_2H_5, n = 5,6) hydrolyzed at similar rates, and at a rate little different from that of ethyl isobutyrate.[8] This similarity should be contrasted with the large difference (51-fold) in the rates of saponification of ethyl isobutyrate and ethyl 3-ethylbutyrate (diethylacetate),[9] the open-chain analogue of the ring esters and this is no doubt due to the rigid forms of the ring which hold the carbon chains back from the carbethoxyl group.

The small difference between the rates of saponification of the cyclopentyl and cyclohexyl esters (IV. R = C_2H_5, $n = 5 > n = 6$) are of the same magnitude as that found in the reaction of the cycloalkyl methyl bromides with phenoxide ion (I. $n = 5 < n = 6$)[3a] and the solvolysis of the cycloalkyl dimethylcarbinyl chlorides (II. $n = 5 > n = 6$),[3b] although the absolute orders are different.

The values of the energies of activation and the log PZ factor (Table I) were of the same order as those found for other saturated esters.[10] These values generally increased with increasing ring size but the order of the energies of activation was 3~*i*-Pr > 4 > 5~6, whereas that for the log PZ factors was *i*-Pr > 3 > 4 ~ 5 > 6. The higher energies of activation for the cyclopropane and cyclobutane carboxylic esters (IV. R = C_2H_5, n = 3, 4) reflect the higher dissociation constants of the corresponding acids although no linear relationship existed between the logarithms of the rates of saponification and the pK_a's, illustrating the fact that electronic and steric effects are not readily separable for aliphatic compounds.

EXPERIMENTAL

Acids. Cyclohexane, cyclopropane, and cyclobutane carboxylic acids were commercial samples (Eastman-Kodak Company and Aldrich Chemical Company). Cyclopentane carboxylic acid was prepared by the hydrogenation of cyclopentene carboxylic acid[11] in acetic acid using platinum oxide or by the oxidation of cyclohexanone with hydrogen peroxide in *t*-butyl alcohol in the presence of selenium dioxide.[12]

Esters. The acids (10–15 g.) were esterified by refluxing 3–5 hr. with anhydrous ethanol (25 ml.) and benzene (75 ml.) using concd. sulfuric acid (0.2 ml.) as catalyst, and removing the water continuously with a Dean-Stark separator. The esters were thoroughly washed with 10% sodium carbonate solution before distillation. The physical constants were in good agreement with literature values, and are given in Table II. The infrared spectra were determined with a Baird K-2 instrument using sodium chloride optics and carbon tetrachloride as solvent.

Hydrolyses. 95% Ethanol was purified by refluxing with zinc dust and sodium hydroxide and diluted with freshly boiled distilled water to give an aqueous ethanol of d_{25}^{25} 0.9316 or 41.2% ethanol. Ester (0.2–0.3 g.) was dissolved in about 85 ml. aqueous ethanol, placed in a constant temperature bath for at least 0.5 hr., 0.18*N* sodium hydroxide (10 ml.) in the same solvent at the same temperature added, and the solution rapidly made up to 100 ml. Aliquots (10 ml.) were withdrawn at intervals, added to an excess of 0.026*N* hydrochloric acid and the excess acid titrated with 0.020*N* sodium hydroxide using phenolphthalein as indicator. The hydrolyses were carried out in triplicate or quadruplicate and the average values with their mean errors are

(8) A slower rate of saponification of ethyl cyclohexane carboxylate as compared to ethyl isobutyrate has also been noted in 85% ethanol at 25° (ratio 2.2:1). H. A. Smith and H. S. Leverson, *J. Am. Chem. Soc.*, **62**, 2733 (1940).

(9) *Cf.* W. Hückel, *Theoretical Principles of Organic Chemistry*, Elsevier, New York, 1958, vol. II, p. 738.

(10) D. R. Thomas and H. B. Watson, *J. Chem. Soc.*, 3958 (1956).

(11) O. H. Wheeler and I. Lerner, *J. Am. Chem. Soc.*, **78**, 63 (1956).

(12) G. B. Payne and C. W. Smith, *J. Org. Chem.*, **22**, 1680 (1957).

given in Table I. The energies of activation and the log PZ values were determined from the Arrhenius equation. The values of E act. are considered to be accurate to ±0.2 kcal. and the log PZ factors to ±0.2.

Dissociation constants. These were determined by potentiometric titration using the same sample of aqueous ethanol as used in the hydrolyses. The values reported in Table I are the mean of duplicate determination which differed by 0.05 unit.

MAYAGUEZ, PUERTO RICO
MEXICO 20, D. F.

[COMMUNICATION NO. 2104 FROM THE KODAK RESEARCH LABORATORIES]

Formation and Properties of Isocyanates Derived from Amino Ester Hydrochlorides

W. J. HUMPHLETT AND C. V. WILSON

Received July 27, 1960

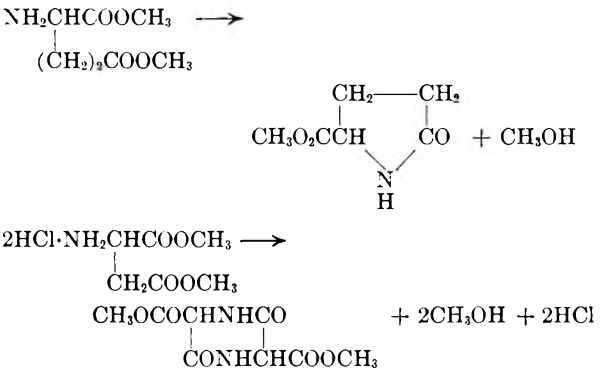
The usual methods for preparing isocyanates from amino ester hydrochlorides fail in many cases. A new, rapid procedure, uncomplicated by secondary reactions, is described for forming isocyanates derived from 2-, 3-, 6-, and 11-amino ester hydrochlorides. It was found that 2-isocyanato esters are activated towards reaction with active hydrogen compounds.

Although hundreds of isocyanates were known previous to the last twenty years, they were of only little technological interest. More recently, as a result of industrial applications, these substances have become the object of intensive research.[1] One method has dominated their synthesis, *i.e.*, the reaction of phosgene with amine hydrochlorides.

$$COCl_2 + RNH_2 \cdot HCl \longrightarrow RNHCOCl + 2HCl$$

$$RNHCOCl \longrightarrow RNCO + HCl$$

Usually by this procedure, the amine salt is suspended in a refluxing diluent into which phosgene is passed. After allowing a reaction time of several hours, the product is isolated by distillation. However, hydrochlorides of certain amino esters undergo secondary reactions under these conditions. Isocyanates cannot be prepared efficiently, for example, from hydrochlorides of esters of glutamic or aspartic acid by this procedure unless the quantities are small, *i.e.*, less than 0.4 mole. Although isocyanates derived from these and other α-amino esters have been reported in 85–97% yields, they were produced in only 10–20 g. quantities.[2] Reaction of phosgene with 0.25, 0.5, and 2 moles of dimethyl glutamate hydrochloride gives 80, 60, and 30% yields, respectively. Phosgenation of three moles of diethyl aspartate hydrochloride yields no isocyanate. These results are attributed partly to the competing reaction of cyclization. We have isolated the corresponding pyrrolidone in high yield and small amounts of the diketopiperazine in these two cases, respectively. Indeed, 5-carbethoxy-2-pyrrolidone is reported to be obtained in 80% yield by heating the base, diethyl glutamate, for twenty minutes.[3]



Following the method of Siefken,[4] ethyl isocyanatoacetate can be prepared from twenty moles of glycine ethyl ester hydrochloride in 85% yield by phosgenation in toluene. Similarly, the isocyanate derived from three moles of methionine ethyl ester hydrochloride is obtained in 84% yield. However, reaction of phosgene with one mole of glycine isopropyl or isobutyl ester hydrochloride gives only a 5–10% yield of the isocyanate.

We have found that isocyanates can be prepared smoothly from hydrochlorides of amino esters in unlimited amounts by a general, *continuous* procedure. By this method, a solution of the salt is passed down a packed, heated column countercurrent to a stream of phosgene. The reaction temperature is the reflux temperature of the solvent, 1,2,3-trichloropropane (b.p. 155°). The reaction time within the apparatus is less than one minute. This method is somewhat similar to that described for other continuous reactions.[5]

Methyl, ethyl, isopropyl, *n*-butyl, and isobutyl α-isocyanato esters have been prepared in this way

(1) A. C. Farthing, *Proc. Chem. Soc.* (*London*), 301 (1957).

(2) S. Goldschmidt and M. Wick, *Ann.*, **575**, 217 (1952).

(3) H. M. Chiles and W. A. Noyes, *J. Am. Chem. Soc.*, **44**, 1805 (1922).

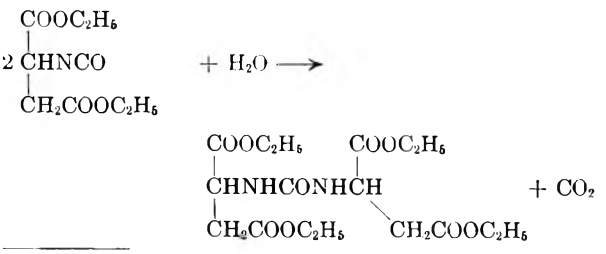
(4) W. Siefken, *Ann.*, **562**, 105 (1949).

(5) C. F. H. Allen, J. R. Byers, Jr., W. J. Humphlett, and D. D. Reynolds, *J. Chem. Educ.*, **32**, 394 (1955). C. F. H. Allen, T. J. Davis, W. J. Humphlett, and D. W. Stewart, *J. Org. Chem.*, **22**, 1291 (1957). C. F. H. Allen and W. J. Humphlett, *Org. Syntheses*, **37**, 2 (1957).

from α-amino mono- or dicarboxylic ester hydrochlorides in good yield. The method proceeds as well with the 3-, 6-, and 11-amino acid derivatives. Glycylglycine methyl ester hydrochloride cleaves under these conditions to form methyl isocyanatoacetate. Cleavage of acylamino compounds by phosgene has been noted previously.[6]

Since suspensions of amine hydrochlorides react slowly with phosgene, solvents for this reaction have been sought.[7] 1,2,3-Trichloropropane dissolves most amino ester hydrochlorides, allowing a high rate of continuous reaction. With this solvent, a three-liter countercurrent apparatus has a capacity of 605 g. of diethyl α-isocyanatoglutarate prepared per hour. Solubility of the hydrochlorides varies with the ester used. While glycine methyl and ethyl ester hydrochlorides are insoluble in 1,2,3-trichloropropane at 25°, the isopropyl and butyl derivatives are soluble. Dimethyl aspartate hydrochloride dissolves at 90°; the ethyl derivative is soluble at 25°. All other hydrochlorides studied are readily soluble in this solvent. The required ester hydrochlorides were obtained by reaction of the amino acid with thionyl chloride in the appropriate alcohol.[8] This esterification results in practically quantitative yields and crystalline products. The base, dimethyl glutamate,[9] in contrast to its hydrochloride, is soluble in most organic solvents. This form gives the isocyanate in 72% yield in continuous synthesis. However, the base is unstable and must be kept at −20° until used. In the preferred procedure, the hydrochloride is employed.

Aliphatic isocyanates are known to be less reactive towards active hydrogen compounds than are aromatic isocyanates.[1] Octadecyl isocyanate emulsified in water is reported to be stable for a day.[7] The reactivity of aromatic isocyanates is increased by *o*- or *p*-substitution of electron-withdrawing groups.[10] We find that the reactivity of aliphatic isocyanates derived from α-amino esters is increased by the carbonyl group of the ester. Thus, diethyl isocyanatosuccinate reacts completely in a dioxane solution containing 25% water in one hour, forming the urea.



Under similar conditions, the yields of urea formed by isocyanates derived from esters of glutamic acid, glycine, and the branched leucine are 90, 80, and 45–50%, respectively. Reaction with water was stopped after one hour by addition of the much more reactive benzylamine forming a benzyl urea. Activation of the isocyanate group disappears when the carbonyl is separated by more than one methylene group. Isocyanates derived from esters of β-alanine, 6-aminocaproic acid, and 11-aminoundecanoic acid are inert in aqueous dioxane solution under similar conditions. The extent of reaction with water was determined by infrared-spectra analysis based on pure symmetrical and benzyl urea samples.

Other data characteristic of the isocyanates and related compounds are summarized in Table I.

EXPERIMENTAL

Apparatus. A small apparatus suitable for preparing isocyanates in 25–200-g. quantities is made from standard laboratory glassware. For this purpose, a 3-ft. column of $^3/_4$-inch internal diameter is packed with $^1/_4$-inch glass helices and clamped vertically to a ringstand in a hood. A flask is attached to the bottom of the column to receive the product. A dropping funnel and a reflux condenser are connected to the top of the column. A side-arm located near the bottom allows introduction of phosgene. The column is heated by two lengths of $^1/_2$-inch by 6-ft., 288-watt, heating tape connected to variable transformers. A somewhat similar apparatus for countercurrent circulation has been diagrammed.[11] A larger apparatus was used more often and is described in detail in the next paragraph. However, the $^3/_4$-inch column can be operated in the same way on a smaller scale.

A 5-ft. column of 2-inch internal diameter (volume equal to 3.1 l.), packed with $^1/_4$-inch Berl saddles, is useful for preparing 100–5,000-g. quantities of isocyanates. A 3-l. flask is connected to the bottom of the column through a 75/50 ball-and-socket joint. The flask is provided with a stopcock at the bottom for withdrawing the product. A stoppered, second neck on the flask is of advantage. A side-arm tube, $^3/_8$ in. in internal diameter, located 24 inches from the bottom of the column, allows introduction of phosgene. Phosgene is metered through a calibrated flowmeter.[12] (Bubbling phosgene through sulfuric acid contained in a suitable bottle is an alternative method.) Provision for the release of abnormal pressure is made by a safety valve located between the phosgene tank and the column. Attached to the top of the column through a 75/50 ball-and-socket joint is a head with two openings at its top. Removal of the head allows the column to be packed. One opening at the top of the head serves as an inlet for the solution of amino ester hydrochloride. The solution is, preferably, metered by a calibrated proportionating pump[13] made of inert materials connected through 19/8 ball-and-socket joints by $^1/_4$-inch, heavy-walled, glass tubing to the column head. (Use of a dropping funnel connected at the top of the column can be a substitute method of addition. A constant-rate dropping funnel is more satisfactory.[14] Attached to the other opening of the head through a 29/42 standard tapered joint is a 14-inch reflux condenser of 1-inch internal diameter, packed

(6) H. Krzikalla, U. S. Patent 2,666,787 (Jan. 19, 1954); *Chem. Abstr.*, 48, 3995 (1954).

(7) J. H. Saunders and R. J. Slocombe, *Chem. Revs.*, **43**, 203 (1948).

(8) M. Brenner and W. Huber, *Helv. Chim. Acta*, **36**, 1109 (1953).

(9) V. G. Hillmann, *Z. Naturforschung*, 1, 682 (1946).

(10) R. G. Arnold, J. A. Nelson, and J. J. Verbanc, *Chem. Revs.*, **57**, 47 (1957).

(11) C. F. H. Allen, J. R. Byers, Jr., and W. J. Humphlett, *Org. Syntheses*, **37**, 66 (1957).

(12) A Fischer and Porter Co. Precision Bore Flowrator Tube No. 2F 1/4-20-5/35 was used.

(13) Pumps used were Lapp Insulator Co. Lapp Microflo Pulsafeeders, Models LS and LS-20, with Teflon heads.

TABLE I

ISOCYANATES FROM AMINO ESTER HYDROCHLORIDES AND THEIR UREA DERIVATIVES

		Ethyl Ester Hydrochlorides						Isocyanates				Sym. Ureas					
		Calcd.			Found			B.P.,[a]		Yield,[j]		Calcd.			Found		
Acids	M.P.[a]	C	H	N	C	H	N	mm.	n_D^{25}[i]	%	M.P.	C	H	N	C	H	N
DL-Aspartic acid	96[b]	42.6	7.2	6.2	42.2	7.0	6.1	87/0.5	1.4357	91	80[k]	50.5	7.0	6.9	50.8	6.9	6.5
								132/8									
L-(+)-Glutamic acid	115[c]							116/2	1.4390	94	96[l]	52.8	7.5	6.5	52.5	7.4	6.7
DL-Methionine	76[d]	39.3	7.6	6.6	39.4	7.6	6.9	98/1	1.4735	82	90[l]	47.6	6.9	7.4	47.8	7.2	7.2
β-Alanine	58[e]							77/8	1.4272	92	116[m]	50.8	7.7	10.8	50.9	8.0	10.9
L-(−)-Leucine	135[f]	49.1	9.3	7.2	49.2	9.5	7.5	93/8	1.4273	81	113[l]	59.3	9.4	8.1	59.6	9.5	7.8
11-Aminoundecanoic acid	143[b]	58.7	10.6	5.3	58.8	10.6	4.9	149/2	1.4450	80	100[m]	66.9	10.8	5.8	66.9	11.0	5.7
Methyl Ester Hydrochlorides																	
DL-Aspartic acid	116[f]	36.5	6.1	7.1	36.8	6.0	6.9	97/1	1.4445	70	135[m]	44.8	5.7	8.0	45.0	5.7	7.8
L-(+)-Glutamic acid	95[g]	39.7	6.7	6.6	39.4	6.3	6.3	103/1.5	1.4442	95	118[m]	47.8	6.4	7.5	47.9	6.3	7.3
β-Alanine	106[f]	34.4	7.2	10.0	34.7	7.1	10.0	61/6	1.4312	86	88[m]	46.5	6.9	12.1	46.1	7.3	12.1
6-Aminocaproic acid	125[f]	46.0	8.8	7.7	46.1	8.8	8.0	68/0.1	1.4378	74	95[m]	56.9	8.9	8.9	56.7	8.5	8.8
								123/15									
n-Butyl Ester Hydrochloride																	
Glycine	72[h]							79/6	1.4301	97	49.5[k,n]						
Isopropyl Ester Hydrochloride																	
Glycine	112[f]	39.1	7.9	9.1	39.0	7.8	9.2	64/6	1.4188	59	115[l]	50.8	7.7	10.7	50.4	7.4	11.0
Isobutyl Ester Hydrochloride																	
Glycine	94[g]	43.0	8.4	8.4	43.4	8.8	8.6	76/6	1.4229	95	86[o]	54.1	8.4	9.7	54.3	8.2	9.8

[a] Melting points are corrected; boiling points are uncorrected. [b] Recrystallized from ethyl acetate. [c] Reported m.p. 113–114°, R. B. Angier *et al.*, *J. Am. Chem. Soc.*, **72**, 74 (1950). [d] Recrystallized from xylene. [e] Reported m.p. 58°, S. K. Mitra, *J. Indian Chem. Soc.*, **15**, 455 (1938). [f] Recrystallized from methyl alcohol–ethyl acetate. [g] ethyl acetate–ether. [h] Reported m.p. 69–71°, W. T. J. Morgan, *J. Chem. Soc.*, 79 (1926). [i] Refractive indices were taken of mid-cuts of redistilled isocyanates. [j] Yields include preparation of ester-hydrochlorides. [k] Recrystallized from ether-ligroin (b.p. 35–60°). [l] Methyl alcohol–water. [m] Methyl alcohol. [n] The corresponding carboxylic acid melts at 203°, recrystallized from water. *Anal.* Calcd. for $C_5H_8N_2O_5$: C, 34.1; H, 4.6; N, 15.9. Found: C, 34.1; H, 4.9; N, 15.6. [o] Recrystallized from benzene-ligroin (b.p. 35–60°).

with 1/4-inch Berl saddles for efficient condensation of solvent. Waste gases pass from the top of the condenser to a 6-ft. gas trap[15] of 1-inch internal diameter, packed with 1/2-inch Berl saddles. The trap is more effective when ammonia is added in addition to water. Under these conditions, no phosgene can be detected at the bottom of the trap. The column is heated by two 2-inch by 10-ft., 1000-watt and one 1/2-inch by 6-ft., 288-watt heating tapes. The small tape is wound around the upper part of the column. The heating tapes are wrapped with 2-inch asbestos tape. The entire apparatus is set up in a hood.

Reagents. 11-Aminoundecanoic acid was obtained from Organic Research Chemicals Ltd., Bucks, England, and 6-aminocaproic acid from Columbia Organic Chemicals Co., Inc. Other amino acids, 1,2,3-trichloropropane, and thionyl chloride were Eastman White Label products. Ethyl isocyanatoacetate (carbethoxymethyl isocyanate) was a redistilled Eastman product, b.p. 67°/11 mm., n_D^{25} 1.4195.

General procedure. Amino ester hydrochlorides. These were prepared by modifications of the method of Brenner and Huber.[8] In a typical synthesis of diethyl glutamate hydrochloride, commercial absolute ethyl alcohol (8 l., 137 moles) was placed in a 12-l. round flask equipped with a mechanical stirrer. Thionyl chloride (2 l., 27.8 moles) was added from a dropping funnel during 1 hr., with stirring, the temperature of the mixture being kept below 25° by a Dry Ice–acetone bath. When the addition was complete, L-(+)-glutamic acid (1471 g., 10 moles) was added. The mixture was stirred at 50° for 3 hr., forming a yellow solution. (Alternatively, the mixture could be stirred overnight at room temperature.) The volatile components were removed *in vacuo* by a water pump. When crystallization began, 1,2,3-trichloropropane (4 l.) was added and the remainder of the thionyl chloride and alcohol removed. Heat was applied to aid the removal, but the temperature of the solution was not allowed to rise above 40°. (Excessive heating at this point caused the solution to darken, resulting in lower yields of isocyanate, with tar formation.) The solution was diluted to 8 l. with 1,2,3-trichloropropane and used for the isocyanate synthesis. Hydrochlorides of glycine isopropyl ester or leucine ethyl ester were diluted to one half of this concentration and warmed to 45° to maintain a solution. Preparation of glycine isopropyl, isobutyl, or *n*-butyl ester hydrochloride required 10 moles of alcohol and 2.7 moles of thionyl chloride per mole of glycine. Reaction time was 1–3 days at 45° or until solution occurred. (These ester derivatives were also prepared, in 65–80% yield after 3-hr. reaction time, in 2.75 moles of alcohol per mole of glycine catalyzed by anhydrous hydrogen chloride. The unchanged glycine hydrochloride was separated by fractional crystallization.) All other amino ester hydrochlorides were obtained by the procedure described for ethyl glutamate hydrochloride.

Samples of the hydrochlorides were isolated by diluting their 1,2,3-trichloropropane solutions with ether and collecting the precipitate. Since certain previously reported melting points have been lower or sirups noted, melting points and recrystallization data are given in Table I.

Isocyanates. In a typical continuous preparation, the column was heated with variable transformer settings to the top, middle, and bottom heating tapes at 85, 100, and 100 volts, respectively. 1,2,3-Trichloropropane was added slowly to wet the column. After 30 min., when the solvent began to reflux, phosgene was added at a rate to provide a phosgene/amine molar ratio of about 2 (Flowrator reading of 3.5). The solution of diethyl glutamate hydrochloride in 1,2,3-trichloropropane was added at a rate of 490 ml./hr. (*i.e.*, 147 g. of diethyl glutamate hydrochloride/hr.). A brown solution of the isocyanate collected in the flask at the bottom of the column. When the addition was complete, the column was rinsed with 300 ml. of solvent. The collected effluent was distilled *in vacuo* to remove the solvent, b.p. 39–44°/7 mm. The distilled solvent, which was dry and contained some phosgene, was used repeatedly with little loss. The isocyanate was distilled from the residue. The apparatus was used in continuous preparations of 130–5500 g. of isocyanate from 0.5–21 l. of diethyl glutamate hydrochloride solution. At addition rates of solution of 500–1920 ml./hr., yields were 91–94%. Addition of 2400 ml./hr., or preparation of 605 g. of isocyanate/hr. in 88% yield, is about the capacity of the column. Higher rates gave increased amounts of 5-carbethoxy-2-pyrrolidone, m.p. 55°,[3] recrystallized from ether. The same procedure was used to prepare the other isocyanates of Table I.

Ureas. Symmetrical ureas were prepared from the corresponding isocyanates by standing 24 hr. in an acetone-water solution. They were precipitated by dilution with water. Ethyl isocyanatoacetate gave a urea, m.p. 147°, recrystallized from ether.

Anal. Calcd. for $C_9H_{16}N_2O_5$: N, 12.1. Found: N, 12.1.

Benzyl ureas were prepared in a few minutes in an acetone-benzylamine solution. 1-Benzyl-3-carbethoxymethylurea was recrystallized from methyl alcohol–water, m.p. 96°.

Anal. Calcd. for $C_{12}H_{16}N_2O$: N, 11.8. Found: N, 12.0.

1-Benzyl-3-(1,2-dicarbethoxyethyl)urea was recrystallized from ether-ligroin (b.p. 35–60°), m.p. 82°.

Anal. Calcd. for $C_{16}H_{22}N_2O_5$: N, 8.7. Found: N, 8.5.

1-Benzyl-3-(1,3-dicarbethoxypropyl)urea, recrystallized from ether, melted at 91°.

Anal. Calcd. for $C_{17}H_{24}N_2O_5$: N, 8.3. Found: N, 8.1.

1-Benzyl-3-(2-carbethoxyethyl)urea was recrystallized from methyl alcohol, m.p. 83°.

Anal. Calcd. for $C_{13}H_{18}N_2O_3$: N, 11.2. Found: N, 10.9.

1-Benzyl-3-(1-carbethoxyisovaleryl)urea was recrystallized from ligroin (b.p. 66–75°), m.p. 49°.

Anal. Calcd. for $C_{16}H_{24}N_2O_3$: N, 9.6. Found: N, 9.6.

1-Benzyl-3-(10-carbethoxydecyl)urea, recrystallized from ethyl alcohol, melted at 97°.

Anal. Calcd. for $C_{21}H_{34}N_2O_3$: N, 7.7. Found: N, 7.7.

1-Benzyl-3-(5-carbomethoxyamyl)urea, recrystallized from ethyl alcohol, melted at 90°.

Anal. Calcd. for $C_{15}H_{22}N_2O_3$: N, 10.0. Found: N, 9.8.

Reactivity of isocyanates. Comparison of the rates of reaction of redistilled isocyanates with water was made by dissolving 0.05 mole of the isocyanate in 100 ml. of 1,4-dioxane and adding 35 ml. of water. (The undecanoate required 150 ml. of dioxane.) After 1 hr. at 25°, benzylamine (6 ml., 0.055 mole) was added to stop the reaction with water. After standing for 10 min., the solvent was removed *in vacuo*, and the residue dried for 4 hr. at 1 mm. and 100°. The contents of symmetrical and benzyl ureas in the mixture were found by infrared-spectra analysis based on 14.3 μ peak of the out-of-plane deformation of the C—H bonds of the phenyl group. Ureas derived from isocyanates of the ethyl esters of aspartic, glutamic, and 11-undecanoic acids; β-alanine; and the methyl ester of 6-aminocaproic acid were examined in dioxane. The leucine derivative was assayed in carbon disulfide, and the glycine derivative in a pressing.

Acknowledgment. The authors are grateful to the following colleagues: Dr. C. F. H. Allen, for many helpful suggestions; Mr. W. Blum and Miss T. Davis, for infrared spectra analyses; and Messrs. D. T. Culley, D. C. Gini, D. E. Janssen, and A. A. Lopa, for assistance in synthesis.

ROCHESTER 4, N. Y.

(14) W. J. Humphlett, *Org. Chem. Bulletin*, Vol. 27, No. 3 (1955), published by the Research Laboratories of the Eastman Kodak Co.

(15) C. F. H. Allen, *Org. Syntheses*, Coll. Vol. II, 3 (1943).

[COMMUNICATION NO. 2105 FROM THE KODAK RESEARCH LABORATORIES, EASTMAN KODAK CO.]

Solubilization of Certain Organic Compounds by Use of Isocyanato Esters

W. J. HUMPHLETT AND C. V. WILSON

Received July 27, 1960

A new procedure for the solubilization of many types of organic molecules carrying one or more hydroxy, carboxy, or amino groups is described. Besides simple long-chain alcohols and acids which lead to surfactants, such substances as the sterols, vitamins, dyes, optical bleaches, etc., have been made water-soluble. The method consists, essentially, in treating isocyanato esters with molecules containing one or more of the above-named functional groups, and selectively hydrolyzing the ester group to the alkali salt of the corresponding acid.

Broadly speaking, organic compounds may be classified as water-soluble or water-insoluble. The soluble compounds frequently are salts derived by neutralization of acidic (sulfo, sulfato, carboxy, hydroxy) or basic (amino) groups in the molecule. These are, of course, supplemented by the nonionic, exemplified by the polyhydroxy compounds (glycerin, sugars) and, more recently, the polyoxyethyl derivatives of a great variety of alcohols, amines, acids, and phenols. While sulfonation or sulfation imparts the greatest solubility, these groups may often be undesirable for various reasons. The use of the carboxy group is often of considerable value but direct carboxylation is not a generally convenient reaction and such acids are usually built up stepwise.

An indirect method for introducing carboxy groups has recently been devised in these Laboratories. Briefly, it consists in treating an alcohol, phenol, amine, or carboxy acid under anhydrous conditions with any one of the isocyanato esters derived from the amino acids, as already described.[1] The product (urethane-, urea-, or amide-ester) is then selectively hydrolyzed to yield the mono-, di- or polycarboxylic acid, usually as the sodium or potassium salt. The urethane, urea or amide linkage established by the isocyanato group is much more resistant to hydrolysis. By this procedure many substances having low solubility in water can be converted to water-soluble products. The reactions may be illustrated by the following general equations:

$$\mathrm{ROH} + \mathrm{OCNCHR'COOR''} \longrightarrow \mathrm{ROCONHCHR'COOR''} \longrightarrow \mathrm{ROCONHCHR'COONa} \quad \text{(A)}$$

$$\mathrm{RNH_2} + \mathrm{OCNCHR'COOR''} \longrightarrow \mathrm{RNHCONHCHR'COOR''} \longrightarrow \mathrm{RNHCONHCHR'COONa} \quad \text{(B)}$$

$$\mathrm{RCOOH} + \mathrm{OCNCHR'COOR''} \longrightarrow \mathrm{RCONHCHR'COOR''} \longrightarrow \mathrm{RCONHCHR'COONa} \quad \text{(C)}$$

Solubilization by such a procedure may have valuable application in many fields. Long-chain alcohols, amines or acids, for example, yield water-soluble compounds with excellent surface-active properties. The product (I) derived from lauryl alcohol and ethyl isocyanatoacetate, followed by selective hydrolysis, is more soluble than lauric

$$\mathrm{C_{12}H_{25}OCONHCH_2COONa}$$
I

$$\mathrm{C_{12}H_{25}OCONHCHCOONa}$$
$$\mathrm{CH_2CH_2COONa}$$
II

acid. A still more soluble compound (II) results if dimethyl isocyanatoglutarate is substituted for the isocyanatoacetate. Many nonionic materials, such as *p-t*-octylphenoxytetraethoxyethanol[2] can be converted to anionic materials by this reaction. Soluble urea derivatives such as III, derived from laurylmethylamine and diethyl isocyanatosuccinate, are easily obtained. The solubilization of long-chain acids proceeds easily. For example, lauric acid yields the product IV, obtained with difficulty by the usual Schotten-Baumann procedure or by a recent method described by Jungermann *et al.*[3]

$$n\text{-}\mathrm{C_{12}H_{25}N(CH_3)CONHCHCOOH}$$
$$\mathrm{CH_2COOH}$$
III

$$n\text{-}\mathrm{C_{11}H_{23}CONHCHCOOH}$$
$$\mathrm{(CH_2)_2COOH}$$
IV

Many more complex materials, such as the rosin acids, rosin amine,[4] rosin alcohol[4] and the low-molecular-weight polyethylene glycol derivatives of these substances, can be solubilized by this procedure. Abitol,[4] which is described as a mixture

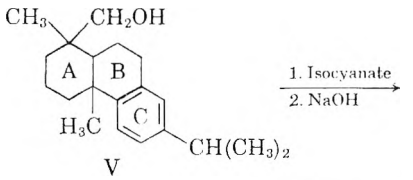
(1) W. J. Humphlett and C. V. Wilson, *J. Org. Chem.*, 26, 2507 (1961).

(2) Rohm and Haas product, Triton X-45.

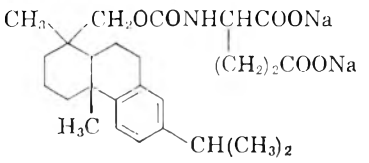
(3) E. Jungermann, J. F. Gerecht, and I. J. Krems, *J. Am. Chem. Soc.*, 78, 172 (1956).

(4) Obtainable from Hercules Powder Co., Wilmington, Del.

of three closely related alcohols, one of which has the structure V (the others have ring C reduced, and one double bond in ring B, respectively), can be converted to a water-soluble product by treatment with dimethyl isocyanatoglutarate, followed by selective hydrolysis. Structure VI represents



V



VI

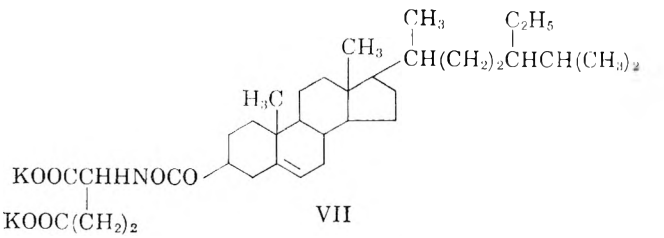
that part of the solubilized material derived from V. Commercial rosin can be solubilized by a similar reaction; the products contain an intermediate amide linkage (see Equation B) rather than the urethane linkage resulting from the alcohols. Since rosin is often used as one of the ingredients of soaps,[5] some of these more soluble derivatives may be of use in the modern detergents.

Since both primary and secondary alcohols react with the isocyanates, the sterol group as a class was investigated. Soluble products were obtained from cholesterol, stigmasterol, β-sitosterol, campesterol, etc.[6] It is of interest that the potassium salts of these substances are usually much more soluble than the sodium or ammonium salts. As an example, the structure of the product obtained from β-sitosterol and dimethyl isocyanatoglutarate is shown in VII. The mixture of soluble soy sterols obtained by this procedure is of considerable interest for use in hypercholesterolemia.[7]

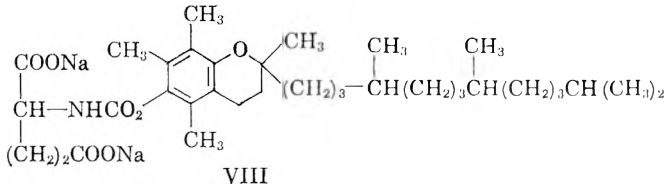
Other substances having physiological activity which contain alcoholic or phenolic functions that can be solubilized by this procedure include Vitamin D_2 (Calciferol), phytol, Vitamin A, and Vitamin E (α-tocopherol).[8] The product (VIII) obtained from Vitamin E and dimethyl isocyanatoglutarate, followed by selective hydrolysis, is a free-flowing powder which is readily soluble in water.

The generality of this reaction may be open to question but it has been established that phenol itself reacts with diethyl isocyanatosuccinate under the same conditions used in the preparation of VIII. Isocyanates derived from α-amino acids are, of course, activated by the carbonyl group of the ester, as discussed previously. The reactivity with phenols would probably be increased further by the use of catalysts such as tertiary amines. Details on the reaction with phenol are included in the experimental section.

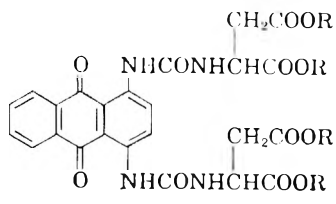
Dyes of many types carrying reactive OH or NH_2 groups could be modified by this procedure to yield either the so-called disperse dyes or their water-soluble analogs. Such a pair of dyes (IXa and IXb) was prepared from 1,4-diaminoanthraquinone and dimethyl isocyanatosuccinate. Optical bleaches in which water-solubility is bestowed upon the molecule by introduction of the aspartic or glutamic acid residue, rather than by the usual sulfonation, can also be obtained. Such a substance is 3,7-bis(1,3-dicarboxypropylureylene)dibenzothiophene dioxide (sodium salt) (X). Similar substances are available from 4,4″-diamino-*p*-terphenyl and 3-(4-aminophenyl)coumarin.



VII



VIII



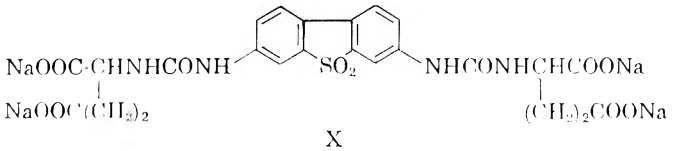
IXa. R = CH_3
IXb. R = Na

(5) Surface Active Agents, Schwartz and Perry, Interscience, New York (1949), Vol. I, p. 28.

(6) W. J. Humphlett and C. V. Wilson, U. S. Patent 2,875,214 (1959).

(7) D. C. Herting and P. L. Harris, *Federation Proc.*, 19, 18 (1960).

(8) W. J. Humphlett and C. V. Wilson, U. S. Patent 2,875,195 (1959).



X

The ease and completeness with which the isocyanato esters react with compounds having an active hydrogen, particularly as OH or NH_2 groups, make them attractive solubilizing agents. In the medical or pharmaceutical fields, they might be used advantageously, for the amino acids, essential or nonessential, produced by hydrolysis, would have no ill effects upon the human system.

EXPERIMENTAL

Sodium carbolauroxyglycinate (I). *Ethyl carbolauroxyglycinate.* A mixture of 18.6 g. (0.1 mole) of lauryl alcohol and 12.9 g. (0.1 mole) of ethyl isocyanatoacetate (protected from moisture) was allowed to stand overnight and then heated for 3 hr. at 80°. After cooling, 75 ml. of petroleum ether (b.p. 35–60°) was added and the resulting solution was chilled in Dry Ice–acetone. The solid that separated was collected on a chilled funnel and dried in the air; yield, 29 g. (92%). A sample, recrystallized from petroleum ether, melted at 36°.

Anal. Calcd. for $C_{17}H_{33}O_4N$: C, 64.8; H, 10.5; N, 4.4. Found: C, 64.4; H, 10.2; N, 4.6.

Hydrolysis was effected by dissolving 21.5 g. of the ester in 50 ml. of absolute alcohol at 60° and adding thereto 2.8 g. of sodium hydroxide in 3 ml. of water and an additional 25 ml. of alcohol. The sodium salt began to separate almost at once. The mixture was heated on the steam bath for 15 min., cooled to 10° and filtered. The resulting solid was washed with ether and dried; yield, 19 g. (90%). The free acid, carbolauroxyglycine, was obtained in 94% yield by acidification of an aqueous solution of the sodium salt. The crude acid was recrystallized from ether, m.p. 96°.

Anal. Calcd. for $C_{15}H_{29}O_4N$: C, 62.7; H, 10.1; N, 4.9. Found: C, 62.6; H, 10.5; N, 4.6.

Dimethyl carbolauroxyglutamate, the disodium salt (II) and the free acid therefrom were obtained by similar procedures.

Anal. Calcd. for the ester (m.p. 44°, from petroleum ether): $C_{20}H_{37}O_6N$: C, 62.0; H, 9.5; N, 3.6. Found: C, 62.2; H, 9.1; N, 3.8.

Anal. Calcd. for the free acid (m.p. 76°, from ether–petroleum ether): $C_{18}H_{33}O_6N$: C, 60.2; H, 9.2; N, 3.9. Found: C, 60.0; H, 9.1; N, 3.8.

Sodium 1-lauryl-1-methylureidosuccinate (III). *Diethyl 1-lauryl-1-methylureidosuccinate.* To 10.35 g. (0.16 mole) of diethyl isocyanatosuccinate was added, with stirring and cooling, 33.4 g. (0.16 mole) of *N*-methyllaurylamine. The addition was carried out at such a rate that the temperature did not rise above 70°. The mixture was heated at 70–75° for 0.5 hr. after the addition was complete. The mixture solidified on cooling. A small sample recrystallized from hexane melted at 35°.

Anal. Calcd. for $C_{22}H_{42}O_5N_2$: C, 63.7; H, 10.1; N, 6.7. Found: C, 64.0; H, 10.5; N, 6.5.

The ester was converted to the sodium salt by treating it in 100 ml. of water and 50 ml. of ethyl alcohol with 12 g. of sodium hydroxide. The salt (III) was isolated by removal of the solvent. Acidification of a solution of the sodium salt gave the free acid, m.p. 70–72°.

Anal. Calcd. for $C_{18}H_{34}O_5N_2$: C, 60.3; H, 9.5; N, 7.8. Found: C, 60.0; H, 9.4; N, 8.1.

Solubilization of Abitol.[4] To 62 g. of Abitol was added 45 g. of diethyl isocyanatoglutarate. The mixture was warmed slightly. Two layers formed. On further warming and mixing, an exothermic reaction set in, the temperature rising to 165°. After standing for several hours, the product was dissolved in 100 ml. of alcohol and treated with 19 g. of sodium hydroxide dissolved in 19 ml. of water and 400 ml. of alcohol. A solid began to separate at once. The mixture was heated for 1 hr. at 65–70°, cooled to 20° and the solid collected on a filter, washed with alcohol, and dried; yield, 105 g. The product is quite soluble in water and has a high calcium tolerance.

Solubilization of sterols. Potassium carbositosterylcxyglutamate (VII). A solution of 1.5 g. (0.0036 mole) of β-sitosterol (m.p. 134–136°) and 0.66 g. (0.0033 mole) of dimethyl α-isocyanatoglutarate in 25 ml. of xylene was refluxed for 5 hr. and the solvent removed under reduced pressure. The ester was saponified with 0.5 g. of potassium hydroxide in 100 ml. of 45% alcohol. The product, a white, free-flowing powder, amounted to 1.8 g. (80%).

For purification, the potassium salt was dissolved in water and acidified with hydrochloric acid. The free acid, recrystallized twice from ethyl ether, melted at 193°. The pure potassium salt was obtained from the acid by redissolving the latter in alcohol and adding an alcoholic solution of potassium hydroxide (5% excess) thereto. This salt is quite soluble in water, e.g., 1.6 g. dissolved easily in 6 ml. of water. The corresponding sodium salt is only slightly soluble in water.

Several other sterols were solubilized by a similar procedure. Melting points, yields and analyses of various derivatives are collected in Table I.

Solubilization of Vitamin E (VIII). A solution of 40.6 g. (0.09 mole) of α-tocopherol (93.7% α-tocopherol. 95.5% total tocopherols), 16.1 g. (0.08 mole) of dimethyl α-isocyanatoglutarate and 200 ml. of anhydrous xylene was refluxed for 48 hr. After removal of the solvent under reduced pressure, the residual ester was obtained as an orange oil. The ester was saponified by warming with a solution of 7 g. of sodium hydroxide in 200 ml. of 90% alcohol for 45 min. The solid product was collected and washed with acetone; yield, 35.8 g. (69.5%) of a tan powder.

For further purification, the salt was dissolved in 150 ml. of water and the solution extracted with ether. The aqueous phase was separated, warmed with powdered charcoal and filtered. To this solution was added an excess of dilute hydrochloric acid and the precipitated solid acid product was collected and dried. The acid was dissolved in alcohol and the solution warmed with charcoal and filtered. To this solution was added a 5% excess of sodium hydroxide dissolved in alcohol. The precipitated product amounted to 22.1 g. (62% recovery), E(1%, 1 cm.) (283 mμ) = 24.2, m.p. 292.° This and other ultraviolet analyses employed ethanol as a solvent.

To demonstrate the solubility of this product, 1 g. of the salt was dissolved readily in 2 ml. of water.

A solution of the salt gave the corresponding acid upon acidification with hydrochloric acid, E(1%, 1 cm.) (283 mμ) = 35.6, m.p. 107°.

Anal. Calcd. for $C_{36}H_{57}O_7N$: C, 69.7; H, 9.4; N, 2.3. Found: C, 70.2; H, 9.2; N, 2.3.

Analyses in the infrared of both the salt and the acid gave curves having characteristics of the Vitamin E molecule.

By a method identical to that in the foregoing example, 48.8 g. (0.11 mole) of α-tocopherol and 18.7 g. (0.10 mole) of dimethyl α-isocyanatosuccinate were caused to react and subsequently saponified with 8.3 g. of sodium hydroxide; yield, 41.3 g. (66%) of a water-soluble product, m.p. 234°.

The corresponding acid was prepared from the salt, E(1%, 1 cm.) (283 mμ) = 32.7.

Anal. Calcd. for $C_{34}H_{55}O_7N$: C, 69.3; H, 9.4; N, 2.4. Found: C, 69.4; H, 9.4; N, 2.4.

TABLE I

URETHANES DERIVED FROM VARIOUS STEROLS

R—OCONHCHCOOM
|
$(CH_2)_nCOOM$

R	n	M	Formula	M.P.	Yield, %	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
		CH_3		120[a]							
β-Sitosteryl	2	K		286	80						
		H	$C_{35}H_{57}O_6N$	192–193[b]		71.5	9.7	2.4	71.7	9.4	2.7
		CH_3		121–122[c]							
Campesteryl	2	K		281	84						
		H	$C_{34}H_{55}O_6N$	197–198[b]		71.2	9.6	2.4	71.3	9.3	2.8
		CH_3	$C_{37}H_{59}O_6N$	124–126[d]		72.3	9.7	2.3	72.0	9.5	2.2
Stigmasteryl	2	K		282	100						
		H	$C_{35}H_{55}O_6N$	203[b]		71.8	9.5	2.4	71.9	9.9	2.5
Cholesteryl	2	CH_3	$C_{35}H_{57}O_6N$	133[d]	99	71.5	9.7	2.4	70.8	9.6	2.5
		Na			97						
		H	$C_{33}H_{53}O_6N$	190–192[e]		70.7	9.5	2.5	70.3	9.7	2.9
		CH_3	$C_{36}H_{57}O_6N$	125[a]		72.1	9.6	2.3	72.3	9.9	2.4
Stigmasteryl	1	K		255	87						

[a] Recrystallized from ethanol. [b] Recrystallized from ether. [c] Recrystallized from methanol. [d] Recrystallized from aqueous ethanol. [e] Recrystallized from acetone/toluene.

Phenyl 1,2-dicarboxyethylcarbamate. A solution of 23.5 g. (0.25 mole) of redistilled phenol and 53.8 g. (0.25 mole) of diethyl isocyanatosuccinate in 300 ml. of anhydrous xylene was refluxed under anhydrous conditions (calcium chloride tube) for 48 hr. The xylene was removed *in vacuo* and the residual product crystallized from aqueous acetone. This crude product (75 g.) was recrystallized twice from ether to give 32 g. of white crystals, m.p. 73°. The urea derived from the above isocyanate has m.p. 80° and gives a marked depression in melting point on admixture with the carbamate.

Anal. Calcd. for $C_{15}H_{19}NO_6$: C, 58.2; H, 6.2; N, 4.5. Found: C, 58.5; H, 6.4; N, 4.6.

Solubilization of Vitamin A. A solution was prepared of 3.33 g. (0.012 mole) of crystalline Vitamin A alcohol (m.p. 63–64°) E(1%, 1 cm.) (325 mμ) = 1820, 2.09 g. (0.01 mole) of dimethyl isocyanatoglutarate, 1.8 ml. of anhydrous pyridine and 23 ml. of anhydrous benzene in a 50-ml. amber flask. The solution was refluxed for 1 hr. 35 min., protected from atmospheric moisture by a calcium chloride tube. After removal of the solvent *in vacuo*, the corresponding urethane-ester was obtained as a viscous oil, E(1%, 1 cm.) (325 mμ) = 990 and having a characteristic carotenoid spectrum in the infrared. To a solution of the ester in 95% ethyl alcohol was added 0.9 g. of sodium hydroxide pellets dissolved in 20 ml. of alcohol and the reaction mixture swirled at room temperature for 30 min. The resulting sodium salt was collected and washed with ethyl alcohol and then ethyl ether, yielding 4.17 g. (83%) of a yellow, free-flowing powder, E(1%, 1 cm.) (325 mμ) = 885, m.p. 360° and having a characteristic carotenoid infrared spectrum.

The solubility of this product was demonstrated by dissolving 2.0 g. of the sodium salt in 5.0 ml. of water, giving a yellow, homogeneous, clear solution.

A solution of the salt yielded the corresponding acid upon addition of dilute hydrochloric acid, E(1%, 1 cm.) (325 mμ) = 765, m.p. 80°.

Anal. Calcd. for $C_{26}H_{37}O_6N$: C, 67.9; H, 8.1; N, 3.0. Found: C, 67.7; H, 8.3; N, 2.9.

By a method identical to that just described, employment of dimethyl α-isocyanatosuccinate (b.p. 65° at 0.5 mm. n_D^{25} 1.4445) in a reaction with crystalline Vitamin A also yielded a water-soluble product, E(1%, 1 cm.) (325 mμ) = 815, m.p. 310°. The water-soluble derivatives of Vitamin A are unstable in solution, losing about one-half of their specific extinction in 4 hr.

Solubilization of Vitamin D_2 (Calciferol). A solution of 5.0 g. (0.013 mole) of Vitamin D_2 [m.p. 114°, E(1%, 1 cm.) (263 mμ) = 467], 2.3 g. (0.011 mole) of dimethyl α-isocyanatoglutarate, 5 ml. of pyridine and 30 ml. of benzene was refluxed for 2 hr. and the solvent removed under reduced pressure. The urethane-ester, obtained as a viscous oil, was dissolved in a solution of 1.58 g. of potassium hydroxide in 95% ethyl alcohol and refluxed for 45 min. The potassium salt, precipitated from the cooled solution, was collected and rinsed with acetone and then with ethyl ether, yielding 6.2 g. (84%) of a white, free-flowing powder, m.p. 240°, E(1%, 1 cm.) (265 mμ) = 208 in water solution. This product is readily soluble in water.

A water solution of the potassium salt was acidified with hydrochloric acid, giving the corresponding acid, m.p. 83°, E(1%, 1 cm.) (263 mμ) = 289.

Anal. Calcd. for $C_{34}H_{51}O_6N$: N, 2.5. Found: N, 2.4.

The sodium salt was prepared by dissolving the corresponding acid in an ethyl alcohol solution containing a slight excess of sodium hydroxide. This product, m.p. 318°, is soluble in water.

The ammonium salt was prepared by dissolving the corresponding acid in ethyl alcohol and adding an excess of concentrated ammonium hydroxide solution. Evaporation under reduced pressure left the solid ammonium derivative, m.p. 180°, E(1%, 1 cm.) (268 mμ) = 210 in water solution. This product is readily soluble in water.

Solubilization of diaminoanthraquinone (IXb). A mixture of 12 g. of 1,4-diaminoanthraquinone and 20 g. of dimethyl isocyanatosuccinate in 75 ml. of chlorobenzene was heated to the boiling point of the solvent under reflux for 1 hr. and allowed to cool. The solid that separated was collected on a filter, washed with alcohol, and dried; yield, 24 g. (75%).

An analytical sample was prepared by recrystallization from alcohol.

Anal. Calcd. for the ester (IXa) $C_{28}H_{28}O_{12}N_4$: C, 54.9; H, 4.6; N, 9.2. Found: C, 55; H, 4.7; N, 9.4.

A solution of 5 g. of the ester in 75 ml. of ethanol was heated to 60–70° and treated with 1.5 g. (about 4 molar equivalents) of sodium hydroxide in 30 ml. of water. The mixture was heated for 15 min. and then poured into alcohol. The aqueous alcohol was decanted from the precipitated oil. The oil was slurried with fresh absolute alcohol, the liquid decanted and the washing repeated until the oil became a granular solid. This sodium salt has high solubility in water. A sample was converted to the free acid by acidification of its aqueous solution with hydrochloric acid. The acid was collected on a filter, taken up in acetone and crystallized therefrom by concentration and cooling.

Anal. Calcd. for $C_{24}H_{20}O_{12}N_4$: C, 51.8; H, 3.6; N, 10.1. Found: C, 51.4; H, 3.4; N, 10.3.

Solubilization of 4,4″-diamino-p-terphenyl. To a solution of 10 g. of 4,4″-diamino-*p*-terphenyl in 300 ml. of boiling chlorobenzene was added 15.5 g. (2 molar equivalents) of dimethyl isocyanatoglutarate. The heating was continued, and within 0.5 hr. the mixture had set to a crystalline mass. After heating for 15 min. more, the mixture was diluted with acetone, slurried, and filtered.The semisolid product was removed from the filter, slurried again in acetone, and again filtered. This was repeated with ether as the diluent. The dry product (15.5 g.) is pure 4,4″-bis(1,3-dicarbomethoxypropylureylene)-*p*-terphenyl, m.p. about 225°.

Anal. Calcd. for $C_{34}H_{38}N_4O_{10}$: C, 61.3; H, 5.7; N, 8.4. Found: C, 61.8; H, 5.9; N, 8.3.

This ester could be hydrolyzed with sodium hydroxide in dimethylformamide-methanol to give a crystalline water-soluble product. However, it was not found possible to prepare an analytically pure sodium salt or the free acid therefrom.

Solubilization of 3,7-diaminodibenzothiophenedioxide (X). To 5 g. (0.02 mole) of 3,7-diaminodibenzothiophenedioxide and 8 g. (0.04 mole) of dimethyl isocyanatoglutarate in a small flask was added 6 ml. of dimethyl sulfoxide. The flask was fitted with a drying tube containing calcium chloride and heated at 70° for 2 hr. The resulting syrup was dissolved in ethanol and treated with 4 g. (0.1 mole) of sodium hydroxide in 6 ml. of water. A taffylike product formed. After warming for 1 hr. at 60° and adding 100 ml. more ethanol, the product became solid. It was ground to a powder under alcohol, collected on a filter, washed with water, and dried; yield, 13 g. This material, which is essentially the tetrasodium salt of 3,7-bis(1,3-dicarboxypropylureylene)dibenzothiophenedioxide is highly soluble in water.

A solution of 3 g. of the sodium salt in water was acidified, warmed, and treated with ethanol until the solid which formed on acidification dissolved. On cooling, the free acid crystallized. Recrystallization from a mixture of ethylacetate and methanol gave a product melting at 175–178° dec.

Anal. Calcd. for $C_{24}H_{24}O_{12}N_4S$: C, 48.6; H, 4.1; N, 9.5; S, 5.4. Found: C, 48.3, 48.6; H, 4.4, 4.7; N, 9.1; S, 5.2.

ROCHESTER 4, N. Y.

[CONTRIBUTION FROM THE GENERAL ELECTRIC RESEARCH LABORATORY]

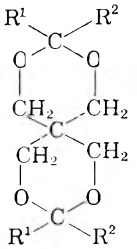
Preparation of Methyl Esters Containing the 1,3-Dioxane or 2,4,8,10-Tetroxaspiro[5.5]undecane Structure by Ketal Exchange

ROBERT M. LUKES[1]

Received September 6, 1960

Methyl diesters containing the 2,4,8,10-tetroxaspiro[5.5]undecane structure have been prepared from methyl keto esters and pentaerythritol by ketal exchange between the keto esters and the diacetone ketal of pentaerythritol. The method has been extended to the preparation of methyl hydroxy esters containing the 1,3-dioxane structure by ketal exchange between keto esters and the acetone ketal of 1,1,1-trishydroxymethylethane. Polyesters have been prepared from both types of esters, by transesterification with ethylene glycol in the case of the diesters or self-transesterification in the case of the hydroxy esters.

The coupling of aldehyde esters or keto esters through the nonester carbonyl function provides a route to the preparation of high molecular weight diesters suitable for conversion into linear polyesters by alcohol interchange with glycols. Böeseken and Felix,[2] as part of their intensive study of the structure and reactions of pentaerythritol, prepared a series of just such compounds (I–V) by condensing the appropriate ethyl esters with pentaerythritol.



I. $R^1 = CH_3$, $R^2 = CO_2C_2H_5$
II. $R^1 = CH_3$, $R^2 = CH_2CO_2C_2H_5$
III. $R^1 = CH_3$, $R^2 = CH_2CH_2CO_2C_2H_5$
IV. $R^1 = H$, $R^2 = m\text{-}C_6H_4SO_3H$
V. $R^1 = H$, $R^2 = m\text{-}C_6H_4CO_2H$

The ethyl diester III prepared according to their directions has been found to condense with ethylene glycol under alkaline catalysis to form an insoluble gel, obviously cross-linked.[3]

It was decided to prepare the methyl diester corresponding to III, since past experience had shown that this would be more likely to be a crystalline solid than would the ethyl ester, and hence would be more easily purified. However, to prepare the methyl diester from the crude ethyl diester *via* saponification and re-esterification seemed unnecessarily tedious, and to use the direct condensation of the methyl keto ester with pentaerythritol, distilling the byproduct water as an azeotrope[4] was impractical because of the likelihood of a supervening transesterification and distillation of methanol.

(1) Present address: Locomotive and Car Equipment Dept., General Electric Co., Erie, Pa.

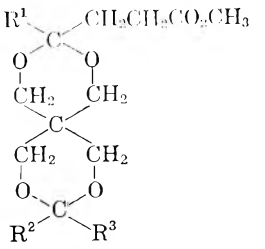
(2) J. Böeseken and B. B. C. Felix, *Ber.*, 61B, 787 (1928).

(3) The cause of the cross linking was no mystery, since III was a liquid purified only by distillation and undoubtedly contained as a contaminant the dihydroxy ester VI, the monoketal of pentaerythritol. This compound was indeed isolated by Böeseken and Felix in their work.

(4) *Cf.* E. J. Salmi, *Ber.*, 71, 1803 (1938); M. S. Newman and R. J. Harper, Jr., *J. Am. Chem. Soc.*, 80, 6350 (1958); R. I. Meltzer *et al.*, *J. Org. Chem.*, 25, 712 (1960).

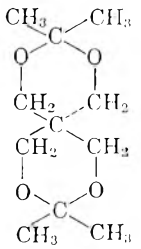
TABLE I

ESTERS CONTAINING THE 2,4,8,10-TETROXASPIRO[5.5]UNDECANE STRUCTURE



Compound	R^1	R^2	R^3	M.P.	Empirical Formula	Calcd. C	Calcd. H	Found C	Found H	Saponification Equivalent, G. Calcd.	Saponification Equivalent, G. Found
IX	CH_3	CH_3	$CH_2CH_2CO_2CH_3$	59–60	$C_{17}H_{28}O_8$	56.65	7.83	56.51	8.05	180	181
X	C_6H_5	C_6H_5	$CH_2CH_2CO_2CH_3$	127–128	$C_{27}H_{32}O_8$	66.92	6.66	67.12	6.80	242	240
XIII	C_6H_5	CH_3	CH_3	110	$C_{19}H_{26}O_6$	65.12	7.48	65.30	7.71	350	310

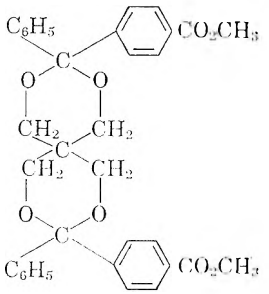
The preparation of the desired methyl diester by a ketal exchange technique appeared to be an attractive method. Accordingly, when an acidified methanol solution containing methyl levulinate and the acetone diketal of pentaerythritol[5] (3,3,9,9-tetramethyl-2,4,8,10-tetraxaspiro[5.5]undecane, VIII) was distilled slowly, the distillate consisted



VIII

largely of the methanol-acetone azeotrope, and the residual solution yielded the desired diester IX, a crystalline solid melting at 59–60°. By the same method, the crystalline diester X (m. p. 127–128°) was prepared from VIII and methyl β-benzoylpropionate. Both IX and X, when heated with ethylene glycol[6] in the presence of an alkaline catalyst, yielded soluble polyesters having molecular weights of the order of 100,000, as measured by light scattering in 1,2-dimethoxyethane.

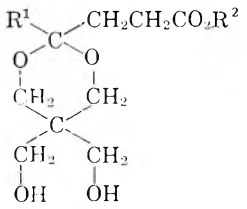
There is some evidence[7] that a 1,3-dioxane ring having two aryl substituents in the 2-position is less susceptible to acid catalyzed hydrolysis than is such a ring having one or two alkyl substituents in that position. In order to see if this held true for 1,3-dioxane rings part of a spiro structure, the preparation of the diester XI from methyl *p*-benzoylbenzoate and VIII by the same ketal exchange technique used for IX and X was attempted. After several fruitless trials in which only starting ma-

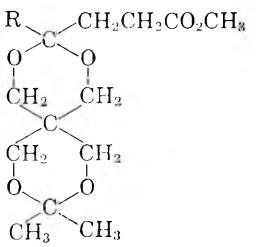


XI

terial was recovered the synthesis was abandoned. Apparently the ketone carbonyl group was too inactive to show an appreciable rate of ketal formation. This is consistent with the reluctance of benzophenone to form cyclic ketals, a phenomenon which has been observed by others.[8]

The purification of crude IX and X involved chromatography over alkaline alumina, and this operation led to the isolation of two side product, the expected monoketal XII and the unexpected mixed diketal XIII respectively. In no case, over several repeats of the preparations of IX and X, were the respective alternate compounds XIV and VII isolated.





VI. $R^1 = CH_3$, $R^2 = C_2H_5$
VII. $R^1 = C_6H_5$, $R^2 = CH_3$
XII. $R^1 = CH_3$, $R^2 = CH_3$
XIII. $R = C_6H_5$
XIV. $R = CH_3$

The ketal exchange method was found to be applicable to the preparation of the hydroxy esters XVI–XX from 1,1,1-trishydroxymethyl-

(5) L. Orthner, *Ber.*, 61B, 116 (1928).

(6) *Cf.* W. H. Carothers and J. A. Ruin, *J. Am. Chem. Soc.*, 51, 2560 (1929).

(7) O. Ceder, *Arkiv Kemi*, 6, 523 (1954). See also M. Skrabal and M. Zlatewa, *Z. physik. Chem.*, 119, 305 (1926).

(8) M. Sulzbacher, E. Bergmann, and E. R. Pariser, *J. Am. Chem. Soc.*, 70, 2827 (1948).

TABLE II

2,2,5,5-SUBSTITUTED 1,3-DIOXANES

Compd.	R^1	R^2	R^3	B.P.	Mm.	Empirical Formula	Calcd. C	Calcd. H	Found C	Found H	Saponification Equiv., g. Calcd.	Saponification Equiv., g. Found
XII	CH_3	$CH_2CH_2CO_2CH_3$	CH_2OH	96–97[a]		$C_{11}H_{20}O_6$	53.21	8.12	53.20	8.00	248	247
XV	CH_3	CH_3	CH_3	95	4.5	$C_8H_{16}O_3$	59.98	10.07	60.01	10.30		
XVI	CH_3	$CH_2CH_2CO_2C_6H_5$	CH_3	136–138	0.6	$C_{12}H_{22}O_6$	58.51	9.00	58.25	8.90	246	249
XVII	CH_3	$CH_2CH_2CO_2CH_3$	CH_3	163–165	1.0	$C_{11}H_{20}O_6$	56.88	8.68	56.71	8.80	232	232
XVIII	C_6H_5	$CH_2CH_2CO_2C_2H_5$	CH_3	163–170	0.1	$C_{17}H_{24}O_5$	66.21	7.85	66.30	7.90	308	295
XIX	C_6H_5	$CH_2CH_2CO_2CH_3$	CH_3	175–178	0.4	$C_{16}H_{22}O_6$	65.29	7.50	65.50	7.70	294	291
XX	$CH_2CH_2CO_2CH_3$	$CH_2CH_2CO_2CH_3$	CH_3	186–188	0.1	$C_{14}H_{24}O_7$	55.25	7.95	55.47	8.00	152	151

[a] Melting point.

ethane and the appropriate keto esters. The acetone ketal of 1,1,1-trishydroxymethylethane (XV), a viscous liquid, was prepared in the way as was the acetone diketal of pentaerythritol, and the exchanges with the keto esters were carried out as before. All the hydroxy esters prepared were very viscous liquids, and none had crystallized after standing at room temperature for a year.

When XVI was heated *in vacuo* in the presence of sodium methoxide, the product was an amorphous solid soluble in chloroform. The molecular weight (ebullioscopic) in chloroform was measured initially as about 2000, but continued boiling gave successively lower values. The other hydroxy esters (XVII–XX) in the series behaved similarly.

EXPERIMENTAL[9]

The diketal of pentaerythritol and acetone (VIII) was prepared by the method of Orthner.[5] The same general method was used to prepare the ketal (XV) of acetone and 1,1,1-trishydroxymethylethane.

2,2,5-Trimethyl-5-hydroxymethyl-1,3-dioxane (XV). A mixture of 1400 ml. of acetone, 100 g. of anhydrous cupric sulfate, and 100 g. (0.83 mole) of 1,1,1-trishydroxymethylethane was shaken vigorously for 48 hr., then filtered and evaporated to 200-ml. volume on the steam bath. The viscous residue was diluted with 500 ml. of ether, filtered, evaporated on the steam bath, and then distilled under vacuum to give 75 g. (56%) of 2,2,5-trimethyl-5-hydroxymethyl-1,3-dioxane (XV), b.p. 95° (4.5 mm.), n_D^{25} 1.4520.

Anal. Calcd. for $C_8H_{16}O_3$: C, 59.98; H, 10.07. Found: C, 60.01; H, 10.30.

The following is an example of the procedure used to prepare the products IX and X, and to isolate the side products XII and XIII.

3,9-Diphenyl-3,9-bis(2-carbomethoxyethyl)-2,4,8,10-tetroxaspiro[5.5]undecane (X). A solution of 200 g. (1.04 moles) of methyl β-benzoylpropionate,[10] 60 g. (0.28 mole) of the diketal VIII, 300 ml. of anhydrous methanol and 0.2 ml. of 96% sulfuric acid was distilled slowly through a ¾ × 12″ fractionating column packed with glass helices; after 6 hr. 105 ml. of distillate, b.p. 56–64° had been collected (the acetone-methanol azeotrope boils at 55.7°). The residue was poured into 1 l. of saturated sodium bicarbonate solution, and this mixture was extracted with two 1-l. portions of ethylene dichloride. The combined extracts were washed with water, dried over anhydrous sodium sulfate, filtered, and evaporated under nitrogen on the steam bath. The residue (about 250 g.) was transferred to a Claisen flask and distilled under vacuum until all the unreacted methyl β-benzoylpropionate had been collected (134 g., b.p. 102–110°). A 1.65-g. portion of the still residue was dissolved in 5 ml. of benzene, and this solution was poured into a 25-mm. chromatographic column which had been packed with 40 g. of alkaline alumina (Merck). Elution of the column with 300 ml. of a 3:2 ether–hexane mixture gave 200 mg. of 3,3-dimethyl-9-phenyl-9-(2-carbomethoxyethyl)-2,4,8,10-tetraxaspiro[5.5]undecane (XIII), m.p. 110° after crystallization from ether-hexane.

Anal. Calcd. for $C_{19}H_{26}O_6$: C, 65.12; H, 7.48. Found: C, 65.30; H, 7.71. Calcd. for saponification equivalent: 350 g. Found: 310 g.

Further elution of the chromatographic column with a 4:1 ether-hexane mixture gave 400 mg. of 3,9-diphenyl-3,9-

(9) Melting points are corrected, boiling points are uncorrected.

(10) L. F. Somerville, and C. F. H. Allen, *Org. Syntheses*, Coll. Vol. II, 81 (1943).

bis(2 - carbomethoxyethyl) - 2,4,8,10 - tetroxaspiro-[5.5]undecane (X), m.p. 127–128° after crystallization from ether-hexane.

Anal. Calcd. for $C_{27}H_{32}O_8$: C, 66.92; H, 6.66. Found: C, 67.12; H, 6.80. Calcd. for saponification equivalent: 242 g. Found: 240 g.

The gross residue from the distillation was dissolved in ether, and from this solution 16 g. (12%) of X was obtained by crystallization.

The preparation of XVI, XVII, XVIII, XIX, and XX is illustrated by the following example.

5-Hydroxymethyl-5-methyl-2,2-bis(2-carbomethoxyethyl)-1,3-dioxane (XX). A solution of 120 g. (0.75 gole) of the ketal XV, 200 g. (1.0 mole) of dimethyl γ-ketopimelate,[11] 300 ml. of anhydrous methanol, and 0.2 ml. of 96% sulfuric acid was distilled slowly through the fractionating column used in the preparation of X until 200 ml. of distillate, b.p. 55–65°, had been collected. The residue was cooled to room temperature, and to it was added 10 ml. of saturated aqueous sodium bicarbonate solution, 500 ml. of water, and 200 ml. of saturated aqueous sodium sulfate solution in that order. This mixture was extracted with three 300-ml. portions of ether, and the combined extracts were filtered through anhydrous sodium sulfate and then evaporated on the steam bath under nitrogen, leaving a residue of about 300-ml. volume. This residue, when distilled under vacuum, yielded 120 g. (53%) of 5-hydroxymethyl-5-methyl-2,2-bis(2-carbomethoxyethyl)-1,3-dioxane (XX), b.p. 186–188° (0.1 mm).

Anal. Calcd. for $C_{14}H_{24}O_7$: C, 55.25; H, 7.95. Found: 55.47; H, 8.00. Calcd. for saponification equivalent: 152 g. Found: 151 g.

Polyesters. The following example illustrates the method of preparing polyesters from IX and X.

A mixture of 10 g. of the diester IX, 20 ml. of ethylene glycol, and 5.0 mg. of sodium methoxide was heated at 150° for 2 hr., all the while bubbling a fine stream of dry nitrogen through the mixture *via* a capillary tube. The mixture was then heated under vacuum according to this schedule: 1 hr. at 150° (0.1 mm.); 1 hr. at 190° (0.01 mm.); 1 hr. at 240° (0.1 mm.). The residue (10 g.), upon cooling, was a glassy solid slowly soluble in dioxane and chloroform.

The procedure for polymerizing the hydroxy esters XVI–XX was the same except that no ethylene glycol was added to the reaction mixture.

Acknowledgment. The author wishes to thank Dr. E. M. Balis and associates of this laboratory for the microanalyses reported.

SCHENECTADY, N. Y.

(11) For a method of preparation see R. M. Lukes, G. I. Poos, and L. H. Sarett, *J. Am. Chem. Soc.*, 74, 1401 (1952).

[CONTRIBUTION FROM RESEARCH CENTER, KOPPERS CO., INC.]

Polymers from Bisphenols. Steric Inhibition of Condensation Polymerization[1]

SAMUEL C. TEMIN

Received December 15, 1960

A series of substituted bisphenols were utilized in the attempted preparation of polyesters with adipic and sebacic acids Both *p,p'*- and *o,o'*-bisphenols, with alkylene or sulfide bridging groups, were examined. It was observed that, although all of the bisphenols readily formed diacetates with acetic anhydride, the diacetates of some of the bisphenols did not undergo the trans-acidolysis reaction which is necessary for polymerization to occur. The failure to polymerize can be related to steric hindrance and is explained in terms of transition states.

Polyesters derived from a diphenolic material and a dicarboxylic acid were first investigated by Bischoff.[2] Later, polyesters were prepared by reaction of hydroquinone diacetate with dicarboxylic acids.[3] This technique was used by Levine and Temin[4] to prepare bisphenol polyesters. Conix[5] and Eareckson[6] synthesized polyesters from acid chlorides and diphenates by interfacial polycondensation. Korshak and co-workers,[7] and others,[8] also prepared polyphenyl esters using acid chlorides. In addition, a large number of bisphenols have been used in preparing polycarbonates.[9] In this previous work it appeared that substitution in the benzene rings of a bisphenol lowered the softening point of the corresponding polyesters.

In the present work a variety of bisphenol alkanes and bisphenol sulfides were studied in an effort to prepare liquid polyesters. It was hoped that the introduction of sufficient bulky groups, particularly in the *o,o'*-bisphenols, would yield liquid polymers. This objective was not attained but it was noted that certain of the bisphenols

(1) Presented at 138th National Meeting of the American Chemical Society, New York, September, 1960.

(2) C. A. Bischoff and A. von Hedenstrom, *Ber.*, 35, 3455 (1902).

(3) J. G. N. Drewitt and J. Lincoln, British Pat. 621,102 (1947); *Brit. Abstr.*, 1949, BII, 1114; E. R. Wallsgrove and F. Reeder, British Pat. 636,429 (1950); *Chem. Abstr.*, 44, 7878d (1950).

(4) M. Levine and S. C. Temin, *J. Polymer Sci.*, 28, 179 (1958).

(5) A. Conix, *Ind. chim. belge*, 22, 1457 (1957); *Ind. Eng. Chem.*, 5, 147 (1949).

(6) W. M. Eareckson, *J. Polymer Sci.*, 40, 399 (1959).

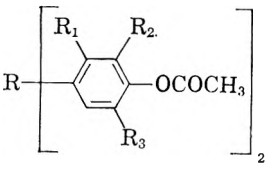
(7) V. V. Korshak and S. V. Vinogradova, *Doklady Akad. Nauk S.S.S.R.*, 123, 849 (1958); *Chem. Abstr.*, 53, 8700c (1959); *Vysokomolekulyarnye Soedineniya*, 1, 1482 (1959).

(8) N. I. Volynkin and G. I. Braginskii, U.S.S.R. Pat. 121,556 (1959); *Chem. Abstr.*, 54, 7357d (1960).

(9) H. Schnell, *Angew. Chem.*, 68, 633 (1956); *Ind. Eng. Chem.*, 51, 157 (1959).

TABLE I

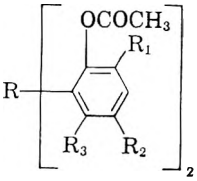
p,p'-BISPHENOL DIACETATES



No.	R	R_1	R_2	R_3	M.P.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
1	S	CH_3	H	$-C(CH_3)_3$	88	70.5	70.6	7.7	7.8
2	$CHCH_3$	CH_3	H	$-CH(CH_3)_2$	99–100	76.1	76.3	8.3	8.3
3	$C(CH_3)_2$	H	CH_3	CH_3	59–60	75.0	75.2	7.7	7.6
4	—	H	$C(CH_3)_3$	$C(CH_3)_3$	215–216	77.7	77.8	9.4	9.4
5	S	H	$C(CH_3)_3$	$C(CH_3)_3$	88–89	70.5	70.4	7.7	7.7

TABLE II

o,o'-BISPHENOL DIACETATES



No.	R	R_1	R_2	R_3	M.P.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
6	—	H	H	H	94–95	[a]			
7	CH_2	H	CH_3	H	59–60	73.1	73.2	6.5	6.5
8	CH_2	Cl	Cl	Cl	175–177	41.5	41.7	2.1	2.2
9	CH_2	Cl	$C(CH_3)_3$	H	92.3	64.5	64.3	6.5	6.5
10	S	$C(CH_3)_3$	CH_3	H	116	70.5	70.9	7.7	7.8
11	CH_3	$C(CH_3)_3$	CH_3	H	None	76.4	76.1	8.6	8.7
12	$CHCH_3$	$C(CH_3)_3$	H	CH_3	150	77.0	76.6	8.8	8.8
13	$C(CH_3)_3$	$C(CH_3)_3$	CH_3	H	163–164	77.0	77.2	8.9	9.0

[a] G. Kraemer and R. Weissgerber, *Ber.*, **34**, 1667 (1901).

could not be made to polymerize under the conditions used.

The polymerization reaction employed was the acidolysis of the bisphenol diacetate, with either adipic or sebacic acid, using magnesium metal as catalyst. The diacetates were prepared in essentially quantitative yields by reaction of the bisphenol with excess acetic anhydride in the presence of sulfuric acid.[4] The bisphenols and diacetates, mostly new compounds, are listed in Tables I and II.

A discussion of the phenomenon observed here involves the question of steric hindrance in phenols. Completely sterically hindered phenols were first observed by Stillson and co-workers.[10] They reported that hindrance of the phenolic function seemed to reach its maximum effect with an *o-t*-butyl group after examination of the chemical properties of several hindered bisphenols. They also reported that these hindered phenols did not readily yield acyl derivatives. They succeeded in preparing acetates only by elaborate techniques involving liquid ammonia or sodium-potassium alloy.

Coggeshall,[11] using spectroscopic means, classified phenols as unhindered, partially hindered, or hindered. The classification was based on the wave length shift, at approximately 2.7 μ, in going from a dilute solution to the crystalline state. Later, Sears and Kitchen[12] refined these measurements and described a "hydrogen bonding index" which was based on the infrared shift in going from a dilute solution to the liquid state. Coggeshall[11] considered a 2,6-dimethylphenol as "unhindered," a 2-methyl-6-*t*-butylphenol as "partially hindered," and a 2,6-di-*t*-butylphenol as "hindered." Sears and Kitchen[12] confirmed these generalizations but found also that the "*t,t*-octyl" group offered more hindrance than the *t*-butyl group. Recently, Puttnam,[13] basing his results on a

(10) G. H. Stillson, D. W. Sawyer, and C. K. Hunt, *J. Am. Chem. Soc.*, **67**, 303 (1945).

(11) N. D. Coggeshall, *J. Am. Chem. Soc.*, **69**, 1620 (1947).

(12) W. C. Sears and L. J. Kitchen, *J. Am. Chem. Soc.*, **71**, 4110 (1949).

(13) N. A. Puttnam, *J. Chem. Soc.*, 486 (1960).

spectroscopic measure of hydrogen bonding, concluded that alkyl groups, other than *t*-butyl in *ortho*-substituted phenols have only a slight effect on hydrogen bonding. Further, he reported that one *o*-*t*-butyl produces the same effect as an *o*-methyl coupled with a methyl, isopropyl, or *sec*-butyl group in the other *ortho* position.

The results obtained in the present work, based essentially on chemical reactivity, are in good agreement with the results of spectroscopic measurements. In general, one *o*-*t*-butyl group is insufficient to prevent polymerization, but if coupled with any other adjacent alkyl group, provides enough steric hindrance to inhibit the reaction. The results with one bisphenol (No. 3) indicate that two adjacent methyl groups are insufficient to prevent polymerization, a degree of hindrance in agreement with Puttnam.[13] Further, a chlorine group is shown to exert about the same steric effect as a methyl group on bisphenol reactivity. In summary, hindrance due to substitution, that leads to a spectroscopic classification of "hindered," is sufficient to inhibit the polymerization reaction.

Table III also illustrates that where hindrance is sufficient completely to prevent alkali solubility of a bisphenol, it is generally sufficient to inhibit the acidolysis reaction of its diacetate.

TABLE III

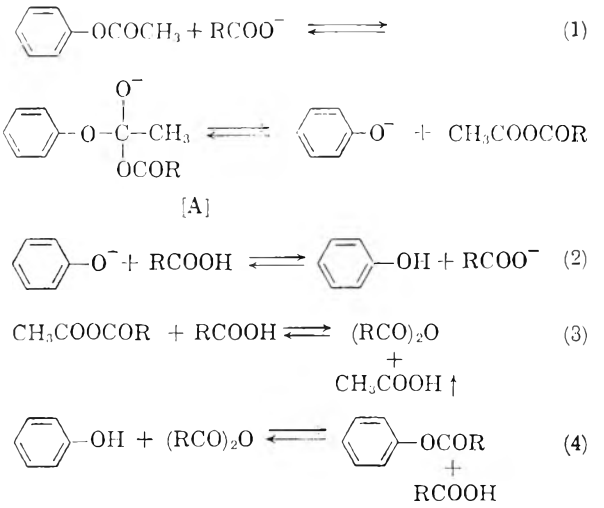
BISPHENOL POLYESTERS

Bisphenol No.	Bisphenol Alkali Soluble	Acid	Sb_2O_3, %[a]	Polymer, $n_{sp/c}$
1	P[b]	S[c]	0.05	0.094
2	P	S	0.17	0.098
3	P	S	0.05	0.064
4	No	S	0.17	None
5	No	S	0.17	None
6	Yes	S	0.17	0.22
7	Yes	A[d]	0	0.092
8	Yes	A	0	0.090
9	Yes	S	0	0.056
10	No	S	0.17[e]	None
11	No	A	0	None
12	No	A	0.05	None
13	No	S	0.05	None

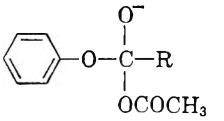
[a] All experiments included ~0.8% Mg ribbon as well. [b] Partially soluble. [c] Sebacic acid. [d] Adipic acid. [e] Same results obtained with no Sb_2O_3 present.

Nevertheless, all of the bisphenols readily yielded diacetates in essentially quantitative yield. It is somewhat puzzling that hindered bisphenols would readily undergo acylation but, as diacetates, not undergo acidolysis which is part of the polyesterification reaction. Reflection, however, indicates that different mechanisms must operate for the two reactions. Inhibition of polymerization in this case is an effect based on the difference in energy levels of initial and transition states. The importance of transition states in predicting steric hindrance to reactivity is well known.

Unfortunately, the mechanism of acidolysis reactions involving phenols seems to have been neglected in the literature although much attention has been given to the similar reactions of esterification, hydrolysis, and alcoholysis.[14] A scheme has been postulated for the acidolysis, Equations 1 to 4, which involves mixed anhydride formation and then interchange to liberate the more volatile acid. It is illustrated for a simple phenol acetate below:

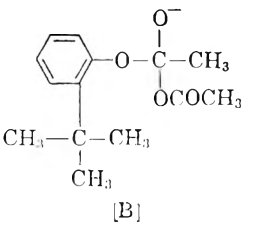


It is possible that, as Equation 1 is an equilibrium reaction, the phenoxide ion and mixed anhydride may also form the intermediate [A′], shown below. In this case an alternate route to the product, involving decomposition of [A′] to yield product and acetate ion, can be visualized.



[A′]

It is possible that the role of the catalyst is to furnish the positive cation not shown in Equations 1 and 2. Thus the initial attack may be by a catalyst cation rather than by carboxyl anion. In either case the transition state intermediate, [A], must involve a considerable amount of compressional energy as shown, for example, [B], with one *o*-*t*-

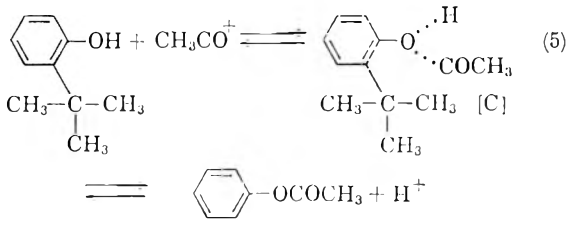


[B]

(14) See, for example, (a) J. Hine, *Physical Organic Chemistry*, McGraw-Hill, New York, N. Y., 1956, chap. 12; (b) P. H. Hermans, *Introduction to Theoretical Organic Chemistry*, Elsevier, New York, 1954, Chap. 19; (c) C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, Cornell University Press, New York, 1953, pp. 752 *ff*.

butyl group. Inspection of models[15] shows that the carbon of the acetate carbonyl is extremely hindered in 2,6-di-*t*-butylphenol acetate. The carbonyl group is forced out of coplanarity[16] with the ring and the transition state cannot be constructed. Kadesch[1] has discussed the relation of coplanarity to steric hindrance.

In contrast, the acetylation reaction must proceed by attack of an acetylium ion,[17] as sulfuric acid is used as a catalyst, on the phenolic oxygen. The reaction is shown, Equation 5, for an *o-t*-



(5)

butylphenol. Inspection of models[5] shows that [C] is sterically possible even in the case of a 2,6-di-*t*-butylphenol. Although the —OH of the phenol is forced out of the plane of the ring, it is considerably more accessible than the carbonyl carbon of the phenol acetate. This is of some theoretical interest since the latter is one atom further removed from the ring than the phenolic oxygen.

Although the work reported here dealt only with bifunctional reagents, and consequently with a polymerization reaction, the application of this reaction to monofunctional reagents might be a useful tool in determining the steric effect of groups in positions adjacent to the functional group. It would also be of interest, in connection with mechanisms, to study the reaction of hindered phenols or bisphenols with acid chlorides and to investigate the hydrolysis of the hindered phenol acetates. Such a program is beyond the scope of the present investigation.

EXPERIMENTAL

All of the bisphenols were commercial samples or available in the Koppers laboratory.

The adipic and sebacic acid were pure commercial samples.

The bisphenol diacetates, Tables I and II, were obtained in essentially quantitative yields as previously described.[4] Frequently, the addition of sulfuric acid to the slurry of bisphenol in acetic anhydride caused a rise in temperature and immediate solution. Bisphenol No. 11, 2,2′-methylene bis-(6-*t*-butyl-4-methylphenol), did not give a crystalline diacetate although distillation gave a glass that could be ground to a powder.

The polymerization technique was similar to that previously described.[4] After about 3 hr. heating (200–230°) at atmospheric pressure (during which time the odor of acetic acid became apparent in the experiments where polymer resulted), the melts were subjected to heating *in vacuo*. The final 30 min., at least, was at 1 mm. pressure or less. The polymers described in Table III were all brittle glasses at room temperature.

In the experiments involving bisphenols No. 3, 4, 5, and 10, where no polymer was formed, an attempt was made to identify the material remaining in the tubes. Quantitative recovery was not attempted because part of the starting materials had distilled or sublimed out of the tube. However, it was possible to isolate, and identify, both starting materials in good yields. As an example, the manipulations, after attempted polymerization of bisphenol No. 5 diacetate and sebacic acid, are described. The solid remaining after heating was dissolved in acetone to remove inorganic matter and the acetone solution taken to dryness. The residue was triturated in the cold with sodium carbonate solution and the mixture filtered. The solid remaining on the filter was recrystallized from methanol-water to yield a product, m.p. 80–82°. A second recrystallization from petroleum ether gave a material melting at 84°. A mixed melting point with the original diacetate (m.p. 88°) gave 85–88°. The filtrate from the sodium carbonate treatment was acidified with sulfuric acid to precipitate a solid, m.p. 130–132°. A mixed m.p. with authentic sebacic acid gave 130–133°.

CONCLUSIONS

The results of the polymerization attempts are given in Table III. The data clearly demonstrate that in a bisphenol where the hydroxy groups are situated between a *t*-butyl group and one other group, no polymer is formed. Thus all *o,o′*-bisphenols with *t*-butyl groups in the 3-position (Nos. 10, 11, 12, and 13) did not yield polymers. A 3-(or 5-)*t*-butyl alone (No. 1) in a *p-p′*-bisphenol is not sufficient to prevent polymerization.

Where polymers were not obtained, the starting materials could be recovered (see Experimental). These results, therefore, present an instance of steric inhibition of a reaction used to effect condensation polymerization. Numerous examples of steric hindrance to addition polymerization have been reported,[18] but this appears to be the first report of steric inhibition in condensation polymerizations.

Acknowledgment. The author is grateful to Dr. R. D. Hinkel and his staff for analyses and to Dr. A. V. DiGiulio for helpful discussions of the mechanism presented here.

PITTSBURGH, PA.

(15) Fisher-Taylor-Hirschfelder Models.

(16) R. G. Kadesch, *J. Am. Chem. Soc.*, **66**, 1207 (1944).

(17) See C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, Cornell University Press, New York, 1953, p. 295.

(18) P. J. Flory, *Principles of Polymer Chemistry*, Cornell University Press, Ithaca, N. Y., 1953, pp. 246–248; C. Walling, *Free Radicals in Solution*, Wiley, New York, 1957, pp. 127–131.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE OHIO STATE UNIVERSITY]

Dimethylformamide as a Useful Solvent in Preparing Nitriles from Aryl Halides and Cuprous Cyanide; Improved Isolation Techniques[1a]

L. FRIEDMAN[1b] AND H. SHECHTER

Received July 12, 1960

Reaction of aryl bromides and activated aryl chlorides with cuprous cyanide occurs advantageously in dimethylformamide to give the corresponding nitriles. Effective methods have been developed for efficient decomposition of complexes of nitriles and cuprous halides and subsequent isolation of products.

Cuprous cyanide reacts with aryl halides to yield the corresponding nitriles (Equations 1 and 2); the general value of this reaction is demonstrated

$$2\ \mathrm{Ar{-}X} + \mathrm{CuCN} \longrightarrow [\mathrm{Ar{-}CN}]_2\mathrm{CuX} + \mathrm{CuX} \quad (1)$$

$$[\mathrm{Ar{-}CN}]_2\mathrm{CuX} \longrightarrow 2\ \mathrm{Ar{-}CN} + \mathrm{CuX} \quad (2)$$

by the frequency in which it has been used (*vide infra*). The displacement is usually effected in excellent yield (> 85%) by heating a mixture of the aryl halide with cuprous cyanide in the presence of pyridine or quinoline as a promoter or solvent.[2] Aryl chlorides, unless especially activated require more severe reaction conditions (eighteen to twenty-four hours; 190–240°) than do aryl bromides (two to eight hours; 130–200°). The general disadvantages of these reactions are the media (pyridine and quinoline, etc., are expensive and malodorous), the necessary temperatures, and the equipment required for stirring a relatively immobile mixture.

Reactions of cuprous cyanide with aryl bromides have also been effected at 220–300° (sealed tubes; metal baths with stirring) in the absence of basic solvents.[3] Without such solvents these reactions are autocatalytic; small amounts of copper sulfate and nitriles or basic compounds such as pyridine, quinoline or cyclohexylamine have marked accelerative effects and overcome the usual induction periods.[4] It thus appears that the original methods[2] are often superior to some of the subsequent modifications.[3]

The isolation of nitriles from such reaction mixtures is usually difficult and laborious. The methods used involve direct distillation,[3] extraction,[5] or decomposition of the nitrile–copper halide and nitrile–cuprous cyanide complexes with aqueous ammonia and/or aqueous hydrochloric acid.[2] Direct distillation is seldomly used and is only readily applicable when the reaction is effected in the absence of solvents. Extraction has been used but the difficulties involved led to the use of distillation or treatment with ammonia and acid. The most practical method, even though arduous and lengthy, has been the latter.

In the present research it has been found that reactions of aryl bromides and suitably active aryl chlorides with cuprous cyanide proceed rapidly (two to six hours) and efficiently in refluxing dimethylformamide. The reactions are mildly exothermic[6a] and catalysts[6b,c] are usually unnecessary.[6d] As a reaction proceeds, the mixture becomes dark brown. The complex formed from the nitrile and cuprous halide is soluble, and copper, uncomplexed copper halides, and excess cuprous cyanide remain as precipitates. Technical dimethylformamide and cuprous cyanide are satisfactory reagents.

Preparative examples using dimethylformamide are summarized in Table I. There were no substituents found which prevent displacement reactions of aryl bromides and cuprous cyanide from occurring. The yields are comparable if not slightly better than when pyridine is used. Use of dimethylformamide as a reaction medium is superior to that of previous methods with respect to equip-

(1) (a) Abstracted in part from the Ph.D. dissertation of L. Friedman, The Ohio State University, 1959. (b) Present address: Department of Chemistry, Case Institute, Cleveland, Ohio.

(2) (a) For a complete literature survey using this method, see Ref. 1a. (b) Principal references are: Ger. Patent, **271,790** (1914); Ger. Patent, **275,517** (1914); Ger. Patent, **293,094** (1919); H. de Diesbach and E. von der Weid, *Helv. Chim. Acta*, **10**, 886 (1927); M. S. Newman, *J. Am. Chem. Soc.*, **59**, 2472 (1937); W. Braun and K. Koberle, U. S. Patent, **2,195,076** (1940); W. Braun, O.T.S.P.B. Report 626 (1946); R. C. Fuson, J. W. Kneisly, N. Rabjohn and M. L. Ward, *J. Am. Chem. Soc.*, 68, 533 (1946), and D. T. Mowry, M. Renoll, and W. F. Huber, *J. Am. Chem. Soc.*, 68, 1108 (1946).

(3) Principal references[1a] are: J. v. Braun and G. Manz, *Ann.*, **488**, 116 (1931); C. K. Bradsher, *J. Am. Chem. Soc.*, **62**, 486 (1940); M. A. Goldberg, E. P. Ordas, and G. Carsh, *J. Am. Chem. Soc.*, 69, 260 (1947); J. E. Callen, C. A. Dornfeld, and G. H. Coleman, *Org. Syntheses*, Coll. Vol. III, 212 (1955); and R. G. Haber, A. Ebnather, and H. Schmid, *Helv. Chim. Acta*, **39**, 1536 (1956).

(4) C. F. Koelsch and A. G. Whitney, *J. Org. Chem.*, 6, 795(1941).

(5) E. Mosettig and J. van de Kamp, *J. Am. Chem. Soc.*, **54**, 3334 (1932).

(6) (a) In large scale reactions, the mixtures may reflux vigorously as a result of the exotherms. (b) *o*-Bromo-*t*-butylbenzene was unreactive under these conditions unless catalyzed with a little pyridine; L. Friedman and M. E. D. Hillman, private communication. (c) The presence of cupric ion at the beginning of reaction is indicated by the green color the dimethylformamide mixture assumes and by the precipitation of copper. (d) The method does not effect conversion of *o*- and *p*-chlorotoluenes and 1-chloronaphthalene to their corresponding nitriles.

TABLE I

REACTION OF AROMATIC HALIDES AND CUPROUS CYANIDE IN DIMETHYLFORMAMIDE

Halide	Moles	Cuprous Cyanide, Moles	Reaction Time, Hr.	Isolation Method	M.P.[c]	Yield, %
5-Bromoacenaphthene	0.26	0.30	4	B[a]	111–112	91
4-Bromoacetophenone	0.25	0.30	3	A[b]	54–56[d]	88
4-Bromoaniline	0.50	0.50	4	C[a]	85–86	83
m-Bromobenzaldehyde	0.20	0.24	6	A[a]	76–77	92
4-Bromobiphenyl	0.50	0.58	4	A[b]	85–86[e]	92
4-Bromofluoranthene	0.25	0.30	5	C[a]	114–115[f]	75
2-Bromofluorene	0.50	0.58	4	A[b]	88–89[g]	92
1-Bromonaphthalene	1.00	1.15	4	A, B, C[b]	33–34[h]	94
9-Bromophenanthrene	0.50	0.58	4	A[b]	107–108[i]	95
o-Bromotoluene	3.35	3.80	4	A, B, C[b]	—[j]	93
p-Bromotoluene	2.00	3.40	6	A[b]	27–28[k]	91
2-Bromo-*p*-xylene	1.30	1.58	6	A[b]	9–10[l]	88
4-Bromo-*m*-xylene	1.48	1.72	4	B[b]	20–22[m]	91
4-Bromo-*o*-xylene	0.20	0.24	6	A[b]	65–66[n]	87
o-Bromoethylbenzene	0.20	0.24	4	A[b]	—[o]	90
p-Dibromobenzene	1.00	2.30	4	B, C[a]	221–222[p]	100
4,4′-Dibromobiphenyl	0.50	1.16	4	B, C[a]	242–244[p]	100
Methyl 3-bromobenzoate	0.20	0.24	3	A[a]	64–65	95
Methyl 4-chlorobenzoate	0.20	0.24	5	A[a]	61–63	87

[a] The product was purified by distillation. [b] The product was purified by recrystallization. [c] The physical constants of the products compare favorably with those reported previously.[2a] [d] B.p. 110–112° (1 mm.). [e] B.p. 162–163° (10 mm.). [f] Fluoranthene-3-carboxamide, m.p. 277–279°, was also obtained in 10% yield. [g] B.p. 200–205° (1 mm.). [h] B.p. 160–161° (14 mm.) [i] B.p. 170–175° (1 mm.). [j] B.p. 88–89° (14 mm.), $n^{25}D$ 1.5251. [k] B.p. 74–75° (8 mm.). [l] B.p. 62–63° (1 mm.). [m] B.p. 102–103° (10 mm.). [n] B.p. 102–103° (10 mm.). [o] B.p. 100–102° (10 mm.). Hydrolyzed to *o*-ethylbenzoic acid, m.p. 67–68°. [p] The product obtained is the dinitrile.

TABLE II

REACTION OF AROMATIC CHLORIDES AND CUPROUS CYANIDE IN PYRIDINE

Halide	Moles	Cuprous Cyanide, Moles	Reaction Time, Hr.	Temp., °	Isolation Method	Yield, %
1-Chloronaphthalene	1.00	1.15	24	220–250	A[a]	94[b]
o-Chlorotoluene	1.00	1.20	72[c]	190–210	A[a]	85[d]
p-Dichlorobenzene	1.00	2.30	24	210–220	C[e]	93[f]
2,4-Dichlorotoluene	1.52	3.77	24	200–220	B[e]	93[g]

[a] The product was purified by distillation. [b] M.p. 33–34°. [c] Reaction was effected by adding the halide to a stirred melt of cuprous cyanide-pyridine at such a rate that the temperature was maintained above 190°. [d] B.p. 88–89° (14 mm.). [e] The product (dinitrile) was purified by recrystallization. [f] M.p. 221–223°. [g] M.p. 142–144°.

ment, reaction conditions, odor, convenience and expense.[7]

The previous methods for preparing nitriles from aryl halides and cuprous cyanide have been greatly improved in the present study by developing more effective procedures for decomposing the complexes of the nitriles and cuprous halides. Aqueous ferric chloride has been found to be an excellent general reagent for destroying the reaction complexes formed in dimethylformamide (Table I) or in pyridine (Table II)[8] and subsequent isolation of the nitriles (Method A). Ferric chloride rapidly oxidizes the adduct of cuprous halide and a nitrile to cupric ion[9]; the nitrile does not complex with cupric ion and separates from the aqueous solution. Aqueous ethylenediamine is also an effective reagent (Method B) because it complexes efficiently with cupric and cuprous ions and allows efficient isolation of a nitrile.[10] In use of

(7) After the present study was completed it was found in this laboratory (M. S. Newman and D. K. Phillips, *J. Am. Chem. Soc.*, 81, 3667 (1959); H. Boden, Ph.D. dissertation, The Ohio State University, 1960) that *N*-methylpyrrolidone is also a satisfactory solvent for reaction of aryl halides and cuprous cyanide. Cuprous cyanide is soluble in *N*-methylpyrrolidone at temperatures above 90° and reactions in such homogeneous mixtures occur relatively rapidly. The yields of nitriles on using dimethylformamide and *N*-methylpyrrolidone are essentially identical; dimethylformamide is of advantage with respect to expense.

(8) Typical examples are included using pyridine since this solvent is often of advantage for reaction of aryl chlorides with cuprous cyanide.

(9) C. Rabaut, *Bull. Soc. Chim., France*, (3), 19, 785 (1898) reports that complexes of nitriles and cuprous halides are decomposed by air, ferric chloride, aqueous ammonia and hydrogen sulfide, respectively.

(10) The cupric ethylenediamine complex is apparently more stable than that of cuprous ion and ethylenediamine since additional copper is formed in the workup; see H. A. Laitinen, E. I. Onstatt, J. C. Bailar, Jr., and S. Swann, Jr., *J. Am. Chem. Soc.*, 71, 1550 (1949).

this method it is often advantageous to extract the crude nitrile with aqueous sodium cyanide; the sodium cyanide dissolves suspended copper derivatives and removes residual traces of copper ions. Excess aqueous sodium cyanide (Method C) is also a satisfactory reagent in that it rapidly destroys the complexes of cuprous halides by formation of soluble sodium cuprocyanide with liberation of the nitrile.

The isolation methods are often comparable and usually quantitative; there are virtues in their differences however. Method A is recommended for isolation of cyano acids, esters, ketones, and aldehydes, and other relatively non-basic nitriles. Methods B and C are of advantage in isolating basic nitriles such as *p*-aminobenzonitrile and 2-cyanopyridine, etc.[11] The use of dimethylformamide (or pyridine) as a solvent medium[7] and any of the above isolation techniques thus makes the reaction of aryl halides and cuprous cyanide a convenient, efficient, and general synthetic method.

EXPERIMENTAL

General techniques. The reactions of bromoaromatic compounds (1 mole) and cuprous cyanide (1.15 to 1.2 moles; 15–20% excess) to give nitriles are effected in refluxing dimethylformamide (150 ml., 3–6 hr.). In preparations on a large scale the quantity of dimethylformamide was decreased (125 ml./mole). When the reaction is completed, the nitrile can be isolated by one of several routes: (1) isolation of the complex of the aromatic nitrile and cuprous halide by pouring the reaction mixture into water and then decomposing the complex by Methods A, B, or C; or (2) working up the preparative mixture directly by Methods A, B, or C. The properties of the nitrile and scale of operation determine which route is the most desirable. As the techniques vary little from compound to compound, only representative procedures will be described and the remaining experimental data are contained in Table I and II. Pertinent details to the tables appear as footnotes.

1-Naphthonitrile. Method A. A stirred mixture of 1-bromonaphthalene (207 g., 1 mole), cuprous cyanide (103 g., 1.15 moles; 15% excess) and dimethylformamide (150 ml.; DuPont, technical) was refluxed for 4 hr. The reaction was mildly exothermic. The resulting brown mixture was poured (residues are conveniently transferred with hot dimethylformamide) into a solution of hydrated ferric chloride (400 g.) and concd. hydrochloric acid (100 ml.) in water (600 ml.). After the reaction mixture had been maintained at 60–70° for 20 min. to decompose the complex, the layers were separated.

Separation of the layers was difficult since the interface is obscured by dark colors. However, light reflected off the separatory funnel helps, or differences in fluidity of the two layers may be discerned as the liquid leaves the separatory funnel. The hot aqueous layer was extracted with toluene (2 × 250 ml.); the extracts were combined with the organic layer, washed with dilute hydrochloric acid (1:1, 250 ml.), water, and 10% aqueous sodium hydroxide. The organic layer was filtered to remove the dark insoluble matter (copper, etc.), dried and vacuum distilled. After the solvent was separated, colorless 1-naphthonitrile (144 g., 0.94 mole; 94%), b.p. 160–161° (14 mm.), m.p. 33–334°, was collected (pot residue 3–4 g.).

Method B. The hot, dark reaction mixture from 1-bromonaphthalene (1 mole), cuprous cyanide (1.15 moles), and dimethylformamide (150 ml.) was poured into a solution of ethylenediamine (200 ml.) in water (600 ml.) and gave a dark blue aqueous lower layer, a small interface containing copper and the copper chloride complex of 1-naphthonitrile and a light brown organic layer. After vigorous shaking the blue aqueous layer was separated and extracted with benzene; the benzene extract was added to the organic layer and washed with 10% aqueous sodium cyanide (150 ml.) and water and then filtered through sodium sulfate. After removal of solvent, 1-naphthonitrile (142 g.), b.p. 152–153° (8 mm.), m.p. 33–34°, was obtained in 93% yield.

Method C. The hot, dark reaction mixture, obtained as described in Method A, was poured into a warm solution of sodium cyanide (200 g.) in water (600 ml.). After the mixture had been vigorously shaken, the lower aqueous layer was separated, extracted once with benzene (250 ml.) and discarded. The extract was combined with the organic layer and washed with 10% aqueous sodium cyanide (200 ml.) and water, and then dried over sodium sulfate. After removal of solvent, 1-naphthonitrile (143 g.), b.p. 152–155° (8 mm.), m.p. 33–34°, was obtained in 94% yield.

The yields *via* the various work-up methods are similar. Although another step is involved, isolation of the crude nitrile–cuprous bromide complex (pouring the reaction mixture into water and filtering) prior to cleavage is desirable in large scale reactions as large volumes of dimethylformamide can thus be discarded conveniently. This operation does not affect the yield.

2,4-Dimethylbenzonitrile. Method B. 1-Bromo-2,4-dimethylbenzene (274 g., 1.48 moles), cuprous cyanide (154 g., 1.72 moles, 15% excess), and dimethylformamide (225 ml.) were refluxed for 4 hr. while being stirred; the hot reaction mixture was poured, while stirring, into cold water (1:1). The near white-tan precipitate was collected, washed thoroughly with water, and then shaken with a warm (50°) solution of ethylenediamine (300 ml.) in water (700 ml.). Benzene was added, the mixture was shaken thoroughly, and the lower aqueous layer was discarded. The benzene extract was washed with 10% aqueous sodium cyanide (150 ml.), water, and dried over sodium sulfate. After removal of solvent, the residue was rectified *in vacuo*. A 91% yield of 2,4-dimethylbenzonitrile (176 g., 1.34 moles), b.p. 102–103° (10 mm.), n_D^{25} 1.5279–1.5281, was obtained.

Reactions in pyridine. 1-Naphthonitrile. Method A. 1-Chloronaphthalene (163 g., 1 mole), cuprous cyanide (103 g., 1.15 moles; 15% excess) and pyridine (65 ml.) were heated at 220–250° for 24 hr. The resulting brown mixture was poured into a solution of hydrated ferric chloride (400 g.) and hydrochloric acid (150 ml.) in water (650 ml.). The nitrile was isolated using techniques described previously for ferric chloride and hydrochloric acid; 143 g. (0.94 mole, 94%).

4-Methylisophthalonitrile. Method B. 2,4-Dichlorotoluene (245 g., 1.52 moles), cuprous cyanide (337 g., 3.75 moles; 25% excess) and pyridine (250 ml.) were heated at 200–220° for 24 hr. The dark reaction mixture was poured into a warm solution of ethylenediamine (500 ml.) in water (1500 ml.) and heated to break up the complex and precipitate 4-methylisophthalonitrile. The finely-divided solid was collected and washed successively with aqueous ethylenediamine (25%, 300 ml.), water, warm aqueous sodium cyanide (10%, 200 ml.) and water. 4-Methylisophthalonitrile was obtained as a buff-colored powder, 200 g. (1.41 moles, 93%), m.p. 142–144°, lit.[12] m.p. 144–150°. Hydrolysis with sodium hydroxide-triethylene glycol gave 4-methylisophthalic acid, m.p. 330–332°, lit.[13] m.p. 332°.

COLUMBUS 10, OHIO

(11) Hot strong alkali can be used to decompose the complexes and hydrolyze a nitrile to its carboxylic acid. Though the hydrolysis is quantitative, the difficulty in filtering the copper oxide precipitates from the alkaline solution seriously limits the usefulness of this method.

(12) W. Borsche, *Ann.*, **386**, 308 (1912).

(13) A. Claus, *J. prakt. Chem.*, (2), **42**, 510 (1890).

Notes

A department for short papers of immediate interest.

N-Methylpyrrolidone as Solvent for Reaction of Aryl Halides with Cuprous Cyanide[1]

MELVIN S. NEWMAN AND HERBERT BODEN

Received September 28, 1960

The reaction of aryl chlorides and bromides with cuprous cyanide to yield nitriles is a useful reaction which has been carried out in the presence and absence of solvents.[2] The advantage of using *N*-methylpyrrolidine as a reaction medium because of its ability to dissolve cuprous cyanide has been pointed out.[3] Although we have not studied this method in great detail, we report our findings now because of their possible utility.

As can be seen from the results summarized in Table I, the yields are generally near 90%. One advantage in the use of *N*-methylpyrrolidone is the shorter time needed.[4] Most runs were carried out with about 0.1 mole[5] of halide and an 80% excess of cuprous cyanide in 100 ml. of *N*-methylpyrrolidone at reflux (202°). Other studies[5] showed that the amount of *N*-methylpyrrolidone can be decreased markedly. Lower temperatures than that of refluxing solvent (202°) can be used (see Footnotes *f*, *g*, and *h* in Table I) but this variable has not been much studied. 1-Chloronaphthalene afforded a high yield[6] but insufficient work was done with chloro compounds to generalize.

To our knowledge, the synthesis of cinnamononitrile represents the first conversion of a vinylic halide to a nitrile by this method.

We hope to utilize the fact that cuprous cyanide dissolves in *N*-methylpyrrolidone at about 90° to carry out relative rate measurements on a series of aryl halides.

TABLE I

REACTIONS OF ARYL AND HETEROCYCLIC HALIDES WITH CUPROUS CYANIDE IN *N*-METHYLPYRROLIDONE

Halide[a]	Reaction Time (hr.)	Yield,[b] %
1-Bromonaphthalene	3	89
1-Bromonaphthalene	3	60[c]
1-Chloronaphthalene	24	87
2-Bromonaphthalene	3	90[d]
2-Bromonaphthalene	3	88[e]
2-Bromonaphthalene	3	85[f]
2-Bromonaphthalene	11	84[g]
9-Bromophenanthrene	4.5	92
β-Bromostyrene	2	92
2-Bromothiophene	19	67[h]
2-Chloroquinoline	4.5	42
4-Bromoisoquinoline	2.5	90
1-Bromobenzo[c]-phenanthrene	1.5	83
Methyl 2-chloro-3,5,6-trimethylbenzoate	3	82

[a] All experiments in Table I involved 0.1 mole of halide and 0.18 mole of cuprous cyanide in 100 ml. of distilled *N*-methylpyrrolidone[7] at reflux (202°) unless otherwise noted. [b] Yield represents per cent of material, distilled or recrystallized, agreeing well with the properties described in the literature for the pure substances. All products after sodium fusion gave negative tests for halogen. [c] In refluxing (165°) dimethylacetamide.[8] [d] The yield in a 0.5-mole run (4 hr. heating, 100 ml. of *N*-methylpyrrolidone) was 95%. [e] Only 0.15 mole of cuprous cyanide used. [f] Same as *e* except temperature held at 180°. [g] Same as *e* except temperature held at 155 ± 5°. [h] In a similar run at 180–190° for 34 hours the yield was 55%.

McPHERSON UNIVERSITY LABORATORY
OHIO STATE UNIVERSITY
COLUMBUS 10, OHIO

(1) This work was supported by grant G-9482 from the National Science Foundation.

(2) For a review see L. Friedman and H. Shechter, *J. Org. Chem.*, 26, 2522 (1961). In this paper the advantage of using ferric chloride solution in working up the reaction mixture is pointed out.

(3) M. S. Newman and D. K. Phillips, *J. Am. Chem. Soc.*, 81, 3667 (1959).

(4) For example, M. Newman, *Org. Syntheses*, Coll. Vol. III, 633 (1955) reports a yield of 82–90% of 1-naphthonitrile from 1-bromonaphthalene after fifteen hours of heating.

(5) In every case in which a run considerably larger than 0.1 mole was made, the yield of purified product was over 90%. For example, Dr. M. V. George prepared pure *p*-tolunitrile in 95% yield from *p*-bromotoluene (85.5 g.) in a *N*-methylpyrrolidone (100 ml.) by heating for two hours at reflux.

(6) Only one experiment with 1-chloronaphthalene was made. The long reaction time (twenty-four hours) might be unnecessary.

(7) We acknowledge with thanks a generous gift of *N*-methylpyrrolidone from the Antara Chemical Co.

(8) We acknowledge with thanks a generous gift of *N,N*-dimethylacetamide from the du Pont Company.

A Convenient Synthesis of Water-Soluble Carbodiimides

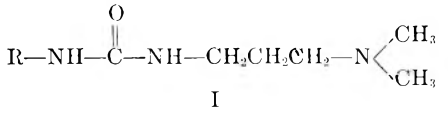
JOHN C. SHEEHAN,[1,2] PHILIP A. CRUICKSHANK,[2] AND GREGORY L. BOSHART[1]

Received October 24, 1960

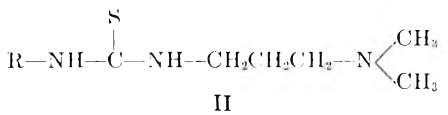
The utility of the carbodiimide procedure for formation of the amide bond has been well established by the synthesis of many complex pep-

tides.[3] Dicyclohexyl- and diisopropylcarbodiimides have been commonly used as the condensing agents; however, the corresponding ureas and acylureas[4] frequently have solubility properties similar to the peptides, rendering separation of the products difficult. An earlier publication from one of these laboratories described the preparation of some acid-soluble and water-soluble carbodiimides.[5] With these reagents the by-product ureas and acylureas were easily removed by washing with dilute acid or water.

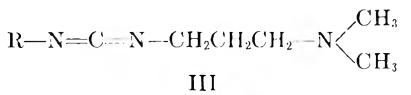
In this note we wish to describe some new acid- and water-soluble carbodiimides prepared from commercially available starting materials. The most generally useful compounds are 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (IIIA) and the corresponding hydrochloride salt. Other compounds prepared and evaluated include 1-cyclohexyl-3-(3-dimethylaminopropyl)carbodiimide (IIIC), the hydrochloride salt, and several quaternized derivatives (VI). Derivatives of 1-isopropyl-3-(3-dimethylaminopropyl)carbodiimide (IIIB) are too hygroscopic to be of practical value.



I



II



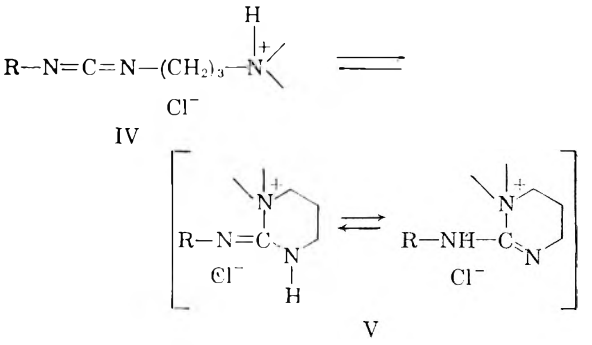
III

A. R = C_2H_5—
B. R = $(CH_3)_2CH$—
C. R = C_6H_{11}—

The basic carbodiimides (III) were prepared either by dehydration of the corresponding urea (I) or by removal of the elements of hydrogen sulfide from the corresponding thiourea (II). The desulfurization procedure[6] is not recommended, however, in that large quantities of mercuric oxide and long reaction times are required, and the product is likely to be contaminated with sulfur-containing impurities.

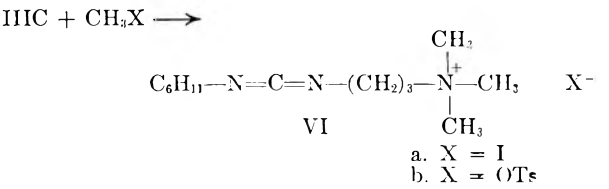
Dehydration of the basic ureas was effected with *p*-toluenesulfonyl chloride and triethylamine in methylene chloride solution. This is a modification of the procedure of Amiard and Heymes[7] for the dehydration of 1,3-dicyclohexylurea in which a large volume of pyridine was used both as base and as solvent.

Hydrochloride salts of the basic carbodiimides were prepared by metathesis with pyridine hydrochloride in methylene chloride solution; addition of ether precipitated the products. The hydrochlorides of 1-alkyl-3-(3-dimethylaminopropyl)-carbodiimides (III) appear to be capable of existence in two structurally isomeric forms. An infrared absorption spectrum in chloroform solution has the 2130 cm.$^{-1}$ band characteristic of the —N=C=N— chromophore. The infrared absorption of the crystalline solid (Nujol or potassium bromide dispersion), however, has ν_{max} at 3250 cm.$^{-1}$ and at 1700 cm.$^{-1}$, characteristic of —NH— and C=N— respectively. We would therefore like to suggest a ring-chain tautomerism IV ⇄ V for these compounds.



IV V

Quaternized salts of the basic carbodiimides were prepared in ether solution from which the products (VI) separated spontaneously.



VI

a. X = I
b. X = OTs

The basic ureas (I) and thioureas (II) were prepared by reaction of the appropriate isocyanate or isothiocyanate, respectively, with *N*,*N*-dimethyl 1,3-propanediamine. An improved procedure for preparation of cyclohexyl isocyanate from cyclohexylamine and phosgene was developed; this isocyanate could be utilized without isolation for the preparation of 1-cyclohexyl-3-(3-dimethylaminopropyl)urea (IC).

Peptides have been synthesized in high yields and in very pure form with the carbodiimides described in this note. The reagents have also been utilized to form amide bonds in proteins.

(1) Department of Chemistry, Massachusetts Institute of Technology, Cambridge 39, Mass.

(2) Research Institute for Medicine and Chemistry, Cambridge 42, Mass.

(3) For a recent review see M. Goodman and G. W. Kenner, *Advances in Protein Chemistry*, **12**, 488 (1957).

(4) H. G. Khorana, *Chem. and Ind.*, 1087 (1955); J. C. Sheehan, M. Goodman, and G. P. Hess, *J. Am. Chem. Soc.*, **78**, 1367 (1956).

(5) J. C. Sheehan and J. J. Hlavka, *J. Org. Chem.*, **21**, 439 (1956).

(6) H. G. Khorana, *Chem. Revs.*, **53**, 145 (1953).

(7) G. Amiard and R. Heymes, *Bull. Soc. Chim. France*, 1360 (1956).

EXPERIMENTAL[8]

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (IIIA). *Desulfurization of thiourea* IIA. To a cooled solution of 17.43 g. (0.2 mole) of ethyl isothiocyanate in 50 ml. of ether was added dropwise a solution of 20.44 g. (0.2 mole) of *N,N*-dimethyl-1,3-propanediamine in 50 ml. of ether. After 5 hr. at room temperature the ether was evaporated under reduced pressure; the residual oil was used without purification for subsequent experiments.

The crude thiourea IIA derived from 0.2 mole of ethyl isothiocyanate was dissolved in 150 ml. of dry methylene chloride. To this solution was added 108.5 g. (0.5 mole) of yellow mercuric oxide and the mixture was shaken mechanically for 20 hr. Another 21.2 g. (0.1 mole) portion of the mercuric oxide was then added and the shaking was continued for an additional 5 hr. At this time a probe test[9] for unchanged thiourea was negative. The mixture was filtred under dry nitrogen pressure, and the methylene chloride removed from the filtrate by evaporation under reduced pressure. Distillation of the residue under reduced pressure afforded 22.9 g. (74%) of carbodiimide IIIA, b.p. 47–48° (0.27 mm.), n_D^{25} 1.4582.

Anal. Calcd. for $C_8H_{17}N_3$: C, 61.89; H, 11.04; N, 27.07. Found: C, 61.53; H, 11.11; N, 27.81.

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (IIIA). *Dehydration of urea* IA. To a solution of 20.5 g. (0.288 mole) of "practical" ethyl isocyanate in 200 ml. of anhydrous ether was added slowly 28.9 g. (0.280 mole) of *N,N*-dimethyl-1,3-propanediamine in 100 ml. of ether; the reaction temperature was moderated by means of external cooling. After stirring at room temperature for 2 hr. the ether was removed under reduced pressure leaving a quantitative yield of crude 1-ethyl-3-(3-dimethylaminopropyl)urea as a pale yellow oil. This crude material was used directly for preparation of the carbodiimide (IIIA).

To a solution of 42 g. (0.24 mole) of crude 1-ethyl-3-(3-dimethylaminopropyl)urea (IA) in 750 ml. of methylene chloride and 130 ml. of triethylamine was added a solution of 91.3 g. (0.48 mole) of recrystallized *p*-toluenesulfonyl chloride in 500 ml. of methylene chloride. The temperature of the reaction mixture was maintained at 5° or less during the addition by means of external cooling. After the addition of the *p*-toluenesulfonyl chloride the reaction was allowed to warm to room temperature, and then was heated under reflux for 3 to 4 hr. The reaction mixture was stirred with three 200-ml. portions of 40% aqueous potassium carbonate; the solids and aqueous phase were removed after each treatment and were washed thoroughly with methylene chloride. The combined methylene chloride phases were concentrated and the residual oil extracted with several portions of ether. After evaporating the ether the residue was distilled to give 19.3 g. (51%) of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, b.p. 53–54° (0.60 mm.), n_D^{22} 1.4594.

1-Isopropyl-3-(3-dimethylaminopropyl)carbodiimide (IIIB) via 1-isopropyl-3-(3-dimethylaminopropyl)urea (IB). The urea IB was prepared in the same manner as the ethyl analog IA. An extremely hygroscopic solid, m.p. 62–69°, was obtained upon removal of solvent. A small sample was purified by sublimation, m.p. 66–71°.

Anal. Calcd. for $C_9H_{21}N_3O$: N, 22.44. Found: N, 22.61.

Dehydration of the urea IB by the *p*-toluenesulfonyl chloride-triethylamine procedure as described above for the 1-ethyl homolog afforded 1-isopropyl-3-(3-dimethylaminopropyl)carbodiimide (IIIB), b.p. 57–59° (0.7 mm.), n_D^{25} 1.4545.

Anal. Calcd. for $C_9H_{19}N_3$: C, 63.86; H, 11.31; N, 24.83. Found: C, 64.21; H, 11.39; N, 24.69.

1-Cyclohexyl-3-(3-dimethylaminopropyl)carbodiimide (IIIC). *Desulfurization of thiourea* IIA. Carbon disulfide (20.14 g., 0.26 mole) was added slowly to a stirred solution of 57.47 g. (0.53 mole) of cyclohexylamine in 400 ml. of dry ether at 0°. The colorless solid was collected by filtration, dissolved in 750 ml. of water, and treated with 70 g. (0.26 mole) of mercuric chloride at 90° for a few minutes. Steam distillation removed the cyclohexyl isothiocyanate[10] from the reaction mixture; the crude product, recovered from the distillate by extraction with ether, amounted to 28.0 g. (76%). To a cooled solution of this isothiocyanate in 100 ml. of ether was added 20.2 g. (0.20 mole) of *N,N*-dimethyl-1,3-propanediamine in 100 ml. of ether. The thiourea separated during the reaction; 32 g. (66% based on the crude cyclohexyl isothiocyanate), m.p. 70.4–71.0°.

Anal. Calcd. for $C_{12}H_{25}N_3S$: C, 59.20; H, 10.35; N, 17.26. Found: C, 59.18; H, 10.37; N, 17.52.

A solution of 15 g. (0.062 mole) of 1-cyclohexyl-3-(3-dimethylaminopropyl)thiourea in 90 ml. of methylene chloride was shaken for 20 hr. with 53.55 g. (0.25 mole) of yellow mercuric oxide. Since some thiourea still was present in the reaction mixture[11] an additional 13.4 g. (0.062 mole) of mercuric oxide was added and the shaking continued for 12 hr. The solution was filtered under nitrogen, the solvent removed, and the residue distilled. The yield of carbodiimide was 9.15 g. (71%) b.p. 89.5–91.5 (0.40 mm.), n_D^{25} 1.4844.

Anal. Calcd. for $C_{12}H_{23}N_3$: C, 68.84; H, 11.07; N, 20.07. Found: C, 68.72; H, 10.94 N, 19.98.

1-Cyclohexyl-3-(3-dimethylaminopropyl)carbodiimide (IIIC). *Dehydration of urea* IC. To a solution of 54. 5 g. (0.551 mole) of phosgene in 350 ml. of benzene was added slowly a solution of 13.6 g. (0.137 mole) of cyclohexylamine in 100 ml. of benzene. This slurry was stirred for 16 hr. at 60–75° during which the solids dissolved. The resulting pale yellow solution was refluxed vigorously for 2 hr., after which approximately half the benzene was distilled. The solution of cyclohexyl isocyanate[11] remaining in the flask was cooled with an ice bath, and a solution of 14.0 g. (0.137 mole) of *N,N*-dimethyl-1,3-propanediamine in 200 ml. of ether was added. After stirring at room temperature for 3 hr. the solvents were removed under reduced pressure. Trituration of the residue with ether afforded 28.6 g. (92%) of crude urea, m.p. 79.5–84°. Recrystallization from ether raised the m.p. to 90.4–91.0°.

Anal. Calcd. for $C_{12}H_{25}N_3O$: C, 63.39; H, 11.08; N, 18.49. Found: C, 63.40; H, 11.08; N, 18.35.

To a solution of 1-cyclohexyl-3-(3-dimethylaminopropyl)-urea (46.32 g., 0.204 mole) in 600 ml. of methylene chloride and 100 ml. of triethylamine was added a solution of 58.0 g. (0.306 mole) of *p*-toluenesulfonyl chloride in 400 ml. of methylene chloride; the temperature was kept below 5° by external cooling. After completing the addition the mixture was stirred for 30 min. at room temperature and finally for 2 hr. under gentle reflux. The cooled mixture was extracted with 1.0 l. of 10% aqueous potassium carbonate; the organic phase was dried over magnesium sulfate and the solvents removed under reduced pressure. The residue was freed of triethylamine by dissolving in toluene and again evaporating under reduced pressure. The residue was triturated with several portions of ether to remove the carbodiimide from a resinous byproduct. After evaporating the ether distillation afforded 28.46 g. (67%) of product, b.p. 104° (0.8 mm.).

(8) All melting points are corrected. Analyses were by S. M. Nagy, Massachusetts Institute of Technology, Cambridge, Mass., or by A. Bernhardt, Max Planck Institute, Mulheim, Germany.

(9) This test constitutes addition of 2 drops of 0.25*M* silver nitrate solution and 4 drops of ammonium hydroxide to a small aliquot of the reaction mixture. Appearance of a brown precipitate indicates the presence of thiourea.

(10) A. Skita and H. Rolfer, *Ber.*, **53**, 1242 (1920).

(11) Pure cyclohexyl isocyanate may be obtained by fractional distillation, b.p. 53°/11 mm.; W. Siefken, *Ann.*, **562**, 75 (1949) reports b.p. 54°/11 mm.

The crude carbodiimide obtained from the ether solution could be used without distillation for preparation of quaternized derivatives.

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride. A mixture of 1.71 g. (0.011 mole) of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide and 1.07 g. (0.0092 mole) of pyridine hydrochloride in 10 ml. of methylene chloride was stirred at room temperature for 3 min. Anhydrous ether (100 ml.) was added dropwise and the crystalline product was collected by filtration. Recrystallization from methylene chloride-ether afford 1.76 g. (99.5%), m.p. 113.5–114.5°.

Anal. Calcd. for $C_8H_{18}N_3Cl$: C, 50.11; H, 9.47; N, 21.92. Found C, 49.76; H, 9.61; N, 22.07.

When scaled up 10–20 fold the yield of carbodiimide hydrochloride was 85–90%, m.p. 108–112.5°.

1-Cyclohexyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride. To a solution of 4.20 g. (0.02 mole) of 1-cyclohexyl-3-(3-dimethylaminopropyl)carbodiimide in 30 ml. of methylene chloride was added 2.14 g. (0.019 mole) of recrystallized pyridine hydrochloride. After 5 min. the mixture was homogenous; 300 ml. of ether was added to precipitate 4.29 g. (94%) of product, m.p. 99–104°.

Anal. Calcd. for $C_{12}H_{24}N_3Cl$: C, 58.64; H, 9.84; N, 7.10; Cl, 14.43. Found: C, 59.14; N, 10.01; N, 16.95; Cl, 14.57.

1-Cyclohexyl-3-(3-dimethylaminopropyl)carbodiimide methiodide (VIa). The crude 1-cyclohexyl-3-(3-dimethylaminopropyl)carbodiimide (IIIC) obtained by dehydration of 22.7 g. (0.10 mole) of the corresponding urea IC was treated with 28.4 g. (0.20 mole) of methyl iodide in 500 ml. of anhydrous ether. After stirring at room temperature for 18 hr. 27 g. (77%) of crystalline product was obtained, m.p. 158–159°. Recrystallization from acetone-ether afforded an analytical sample, m.p. 161.5–163°.

Anal. Calcd. for $C_{13}H_{26}N_3I$: C, 44.45; H, 7.46; N, 11.97. Found: C, 44.46; H, 7.38; N, 11.84.

A portion of VIa was converted to the urea by action of acetic acid in methylene chloride; m.p. 194–195.5° after recrystallization from ethanol-ether.

Anal. Calcd. for $C_{13}H_{28}N_3OI$: C, 42.28; H, 7.64; N, 11.38. Found: C, 42.23; N, 7.75; N, 11.09.

1-Cyclohexyl-3-(3-dimethylaminopropyl)carbodiimide metho-p-toluenesulfonate. Methyl *p*-toluenesulfonate (3.9 g., 0.021 mole) and 1-cyclohexyl-3-(3-dimethylaminopropyl)carbodiimide (3.94 g., 0.019 mole) in 40 ml. of ether were allowed to react at room temperature for 20 hr. The yield of quaternary salt was 6.09 g. (82%), m.p. 164.4–165.4°.

Anal. Calcd. for $C_{20}H_{33}N_3O_3S$: C, 60.72; H, 8.41; N, 10.62. Found: C, 60.80; H, 8.40; N, 10.68.

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide methiodide. Quaternization of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (IIIA) was carried out in the manner described above for the preparation of VIA. The solid product was recrystallized from chloroform-ethyl acetate; m.p. 106.5–107.5.°

Anal. Calcd. for $C_9H_{20}N_3I$: C, 36.37; H, 6.78; N, 14.14. Found: C, 36.17; H, 6.88; N, 14.17.

Acknowledgment. Financial assistance for one of us (G. L. B.) from a contract with the Office of Naval Research is gratefully acknowledged. We also wish to thank Mrs. Shirley Wilt[2] and Mrs. Nina Burlingame[2] for technical assistance during part of this work.

Department of Chemistry
Massachusetts Institute of Technology
Cambridge 39, Mass.

Research Institute for Medicine and Chemistry
Cambridge 42, Mass.

Reduction of Phenols to Aromatic Hydrocarbons

W. N. Moulton and C. G. Wade

Received August 11, 1960

The reduction of phenols to aromatic hydrocarbons is one of the most difficult of organic reactions. Zinc dust distillation, treatment with hydrogen iodide and red phosphorus, and various catalytic hydrogenations have been used with limited success. The two best procedures available appear to be the reduction of aryl diethyl phosphates with sodium or lithium in liquid ammonia[1], and the catalytic hydrogenation of aryl *p*-toluenesulfonates over Raney nickel.[2]

In 1883 Guether[3] reported that phenol could be reduced to benzene and cresol (isomer unspecified) to toluene in low yield by heating with phosphorus trisulfide. The reaction equation given was:

$$8C_6H_4OH + P_2S_3 \longrightarrow 2C_6H_6 + 2(C_6H_5O)_3PO + 3H_2S$$

We have reinvestigated the reaction and studied some modifications which make the reaction more useful.

Our preliminary experiments confirmed Guether's report. For example phenol and phosphorus trisulfide were heated together, the temperature being slowly raised. Between 50 and 100° a large amount of hydrogen sulfide was evolved. No other product was obtained until the temperature reached 300°. Between 300 and 400° a liquid distilled from which benzene was isolated in 18% yield. The results of several similar experiments are recorded in Table I. The temperatures at which the products were obtained varied from 250 to 400°. In each case a black intractable residue remained in the flask. None of the desired reduction product was obtained from *p*-chlorophenol, *p*-aminophenol, resorcinol,

TABLE I

Reduction of Individual Compounds

Reactants	Products	% Conversion
Phenol	Benzene	18
2-Naphthol	Naphthalene	20
1-Naphthol	Naphthalene	11
2-Hydroxybiphenyl	Biphenyl	18
1-Octanol	Octane and octene	10 26
Cyclohexanol	Cyclohexene	65

(1) G. W. Kenner and N. R. Williams, *J. Chem. Soc.*, 552 (1955).

(2) G. W. Kenner and M. A. Murray, *J. Chem. Soc.*, S178 (1949).

(3) A. Geuther, *Ann.*, 221, 55 (1883).

or guaiacol. These compounds apparently decomposed as none of the starting materials were recoverable. As shown in Table I aliphatic alcohols largely underwent dehydration, but *n*-octyl alcohol was reduced to octane in 10% yield.

On the basis of the Guether equation only one fourth of phenol would be expected to be reduced, and the yields obtained bore this out. This suggested that if the reaction was carried out on a mixture, one phenol might be selectively reduced. The results of several experiments using mixtures of phenol and a second phenolic compound are given in Table II. The results suggest that the reaction might be useful in the synthesis of polycyclic hydrocarbons using phenol as a coreactant. In the cases shown the product was distilled from the flask as the reaction proceeded. It may be possible to carry out the reaction in a sealed tube and isolate the hydrocarbon by extraction or chromatography. However, we have used only the distillation technique.

TABLE II

REDUCTION OF MIXTURES OF PHENOLS

Reactants (Mole Ratios)	Products	Yield, %
2-Naphthol:Phenol		
1:1	Naphthalene	33
1:3	Naphthalene	67
1:7	Naphthalene	53
	Benzene	14
1-Naphthol:Phenol		
1:1	Naphthalene	18
2-Hydroxybiphenyl:Phenol		
1:3	Benzene	21

The reagent was originally designated phosphorus trisulfide, P_2S_3. However, it has been established that this composition is not a pure compound, but rather a mixture of phosphorus sesquisulfide, P_3S_3, and phosphorus heptasulfide, P_4S_7.[4] The reagent used in our experiments was prepared by igniting a mixture of phosphorus and sulfur in a two to three mole ration in a closed crucible. Neither commercial P_4S_3 or P_4S_7, nor a mixture of the two in the same proportions as P_2S_3, gave satisfactory results. Not all batches of the reagent we prepared were effective in the reaction. In some instances we obtained a material that behaved very similarly to the mixture of commercial phosphorus sulfides with the P_2S_3 composition. There was no visual difference between effective and ineffective reagent. A sample of each new batch was checked using the reduction of 2-naphthol as a test. If the reduction was unsatisfactory, the batch was discarded. The reagent did not deteriorate on standing. The addition of small amounts of free phosphorus or sulfur to inactive reagent had no effect.

No serious effort to isolate any product but the desired hydrocarbon has been made. It would be premature to speculate on the mechanism of the reaction until further studies are made. That the reaction involves a phosphate ester is suggested by the observation that at temperatures from 50–100° a reaction occurs in which hydrogen sulfide is evolved and the phenol reacts to form a high boiling intermediate. No phenol is distilled from the reaction even at temperatures more than a hundred degrees above its boiling point. Walling[5] has recently observed that thiophenol and triethyl phosphite react at 145° in presence of a free radical catalyst to give benzene and triethyl phosphorothionate in 10–15% yield.

EXPERIMENTAL

Phosphorus trisulfide. An intimate mixture of 31 g. of phosphorus and 48 g. of sulfur were ignited in an unglazed crucible buried in a pail of sand. When the reaction was complete and the crucible cold the reagent was removed by breaking up the crucible. The reagent was gummy at first, but completely crystallized in 24 hr. Each batch was tested using the procedure which follows.

Reduction procedure. A mixture of 70 g. of phenol and 60 g. of phosphorus sulfide was placed in a 20-ml. Claisen flask, fitted with a thermometer reaching nearly to the bottom of the flask. A second thermometer was placed in the side arm to measure the vapor temperature of the distillate. As the mixture was slowly heated to 150° hydrogen sulfide was evolved. After holding the temperatures at 150° for 30 min. heating was increased. At pot temperatures above 300° benzene distilled. The reaction was discontinued when the temperature reached 400° at which point the black residue foamed up to nearly fill the flask. The distillate (10.5 g.) was redistilled to give 7.3 g. (12.5%) of benzene, b.p. 80–81°, n_D^{25} 1.4976.

All reductions were carried out by essentially the same procedure. Yields reported in tables are for products after one distillation or crystallization, and are based on total phenol used. In mixed reactions the mole ratio of phosphorus trisulfide to combined phenols was the same as described above.

Acknowledgment. The authors wish to express their appreciation to Drs. W. L. Truett, W. E. Parham, and C. F. Koelsch of the University of Minnesota for many helpful suggestions during the initial stages of this investigation. The financial support of the National Science Foundation Undergraduate Research Participation Program is gratefully acknowledged.

DEPARTMENT OF CHEMISTRY
SOUTHERN ILLINOIS UNIVERSITY
CARBONDALE, ILL.

(4) J. C. Pernert and J. H. Brown, *Chem. Eng. News*, 27, 2143 (1949).

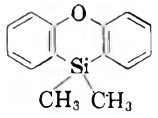
(5) C. Walling, O. H. Basedow, and E. S. Savas, *J. Am. Chem. Soc.*, 82, 2181 (1960).

The Use of Organodilithium Compounds for the Synthesis of 1,1-Dimethylsilacyclopentane and 1,1-Dimethylsilacyclohexane[1]

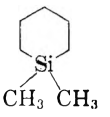
RALPH FESSENDEN AND MARVIN D. COON

Received September 30, 1960

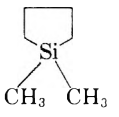
Organodilithium compounds have been successfully employed for the preparation of sila-heterocyclic compounds,[2] such as 10,10-dimethylphenoxasilin (I).[3] However, organodilithium compounds have not been extensively employed for the synthesis of compounds such as II and III. Tamborski and Rosenberg[5] have reported that the



I



II



III

reaction of 1,5-dilithiopentane and dimethyldichlorosilane failed to yield compound II. Wittenberg and Gilman,[4] however, report that 1,1-diphenylsilacyclopentane may be prepared in 46% yield from 1,4-dilithiobutane and diphenyldichlorosilane.

Compounds II and III have been previously prepared utilizing a two-step synthesis.[5] The ring closure reaction was accomplished by reaction of the di-Grignard reagent with silicon tetrachloride. The second step of the synthesis was accomplished by reaction of the resulting dichlorosilacycloalkane with either methyl Grignard reagent[5] or methyllithium.[6]

In this investigation, it has been observed that a modification of the reaction conditions of Tamborski and Rosenberg[6] will allow the direct preparation of II and III from the appropriate dilithioalkane and dimethyldichlorosilane.

In order to obtain the best yield of III, a mixture of 1,4-dibromobutane and dimethyldichlorosilane was added to a chilled mixture of lithium shot[7] using an ether solvent. The reaction was exothermic and a Dry Ice–acetone bath was necessary for cooling. The rate of addition of the mixture did not appear to be of importance if the reaction temperature was kept below 20°. Using this procedure, the yields of III varied from 54 to 76%. Dilution reduced the yield of III to 40%. When the dilithium reagent was prepared prior to the addition of dimethyldichlorosilane, the yield of III was 42%.

Compound II could be obtained in yields of only 27 to 32% using this procedure. In a run when the dilithium reagent was prepared prior to the addition of dimethyldichlorosilane, no silacyclohexane was obtained. This latter observation is in agreement with the report of Tamborski and Rosenberg.[6]

No cyclic silanes were obtained when 1,4-dichlorobutane, 1,4-dichloro-2-butene or 1,3-dibromopropane were used in this reaction.

EXPERIMENTAL[8]

1,1-Dimethylsilacyclopentane (III). In a 1-l. flask, equipped for a nitrogen atmosphere and fitted with a mechanical stirrer dropping funnel, and reflux condenser with a thermometer insert, were placed 300 ml. of dry ether and 11.2 g. (1.60 moles) of lithium shot.[4] The reaction flask was then cooled to 10° with a Dry Ice–acetone bath. To this mixture was then added dropwise (CAUTION) a mixture of 51.6 g. (0.40 mole) of dimethyldichlorosilane and 86.4 g. (0.40 mole) of 1,4-dibromobutane. Throughout the addition period (*ca.* 1 hr.) care was taken to maintain the temperature of the reactants below 20°. After the addition had been completed, the mixture was heated under reflux for 1 hr. then filtered to remove the lithium halide. The filter cake was washed with three 100-ml. portions of ether. The ethereal solution was concentrated to *ca.* 100 ml., then filtered to remove the lithium halide precipitated during the concentration. Distillation resulted in 29.1 g. (65%) of 1,1-dimethylsilacyclopentane (III), b.p. 103–105°, n_D^{22} 1.4340 (lit.[5] b.p. 107°, n_D^{25} 1.4334). Yields varied from 54 to 76%.

In one run when 500 ml. of ether was used with 0.2 mole of reactants, only a 40% yield of dimethylsilacyclopentane was obtained.

In another run when the 1,4-dilithiobutane (0.20 mole) was prepared prior to the reaction with dimethyldichlorosilane, a 42% yield of the dimethylsilacyclopentane was obtained.

When 1,4-dichlorobutane was used in place of 1,4-dibromobutane no precipitation of lithium halide was observed and no dimethylsilacyclopentane was obtained.

1,1-Dimethylsilacyclohexane (II). Using the procedure described for the preparation of the silacyclopentane, 5.6 g. (0.80 mole) of lithium shot,[7] 25.8 g. (0.20 mole) of dimethyldichlorosilane, and 46.0 g. (0.20 mole) of 1,5-dibromopentane yielded 8.5 g. (33%) of 1,1-dimethylsilacyclohexane (II), b.p. 129–131°, n_D^{23} 1.4421 (lit.[5] b.p. 133°, n_D^{25} 1.4380). In another run using the same procedure, the yield of II was 27%.

In another reaction when 0.1 mole of 1,5-dilithiopentane was prepared prior to addition of dimethyldichlorosilane, only nondistillable residue was obtained.

(1) This work was supported by a Frederick Gardner Cottrell grant from Research Corp.

(2) (a) H. Gilman and R. D. Gorsich, *J. Am. Chem. Soc.*, **77**, 6380 (1955); (b) K. Oita and H. Gilman, *J. Org. Chem.*, **22**, 336 (1957); (c) C. H. S. Hitchcock, F. G. Mann, and A. Vanterpool, *J. Chem. Soc.*, 4537 (1957); (d) K. Oita and H. Gilman, *J. Am. Chem. Soc.*, **79**, 339 (1957); (e) H. Gilman and D. Miles, *J. Org. Chem.*, **23**, 1363 (1958); (f) H. Gilman and R. D. Gorsich, *J. Am. Chem. Soc.*, **80**, 1883 (1958).

(3) Ref. 2(c) and 2(d).

(4) D. Wittenberg and H. Gilman, *J. Am. Chem. Soc.*, **80**, 2677 (1958).

(5) R. West, *J. Am. Chem. Soc.*, **76**, 6012 (1954).

(6) C. Tamborski and H. Rosenberg, *J. Org. Chem.*, **25**, 246 (1960).

(7) R. West and E. G. Rochow, *J. Org. Chem.*, **18**, 1739 (1953).

(8) All boiling points are uncorrected. Distillations were accomplished using a 2-meter modified Podbielniak column (*cf.* J. Cason and H. Rapoport, *Laboratory Text in Organic Chemistry*, Prentice-Hall, Inc., New York, 1950, p. 237) and were run at atmospheric pressure.

Reactions with 1,4-dichloro-2-butene (0.10 molar reaction) and with 1,3-dibromopropane (0.20 molar reaction) using the same solvent ratios and procedures as described for compound III, resulted in nondistillable residues.

DEPARTMENT OF CHEMISTRY
SAN JOSE STATE COLLEGE
SAN JOSE, CALIF.

Amine Oxidations with Iodine Pentafluoride. Preparation of Azoisobutane[1]

TRAVIS E. STEVENS

Received November 21, 1960

Several organic amines, and some related organic compounds, have been exposed to the mild fluorinating agent, iodine pentafluoride,[2] in methylene chloride or methylene chloride–pyridine solutions. The results of some of these experiments are summarized in Table I. Although most organic amines were observed to react vigorously when mixed with iodine pentafluoride, a controllable interaction occurred in the presence of the inert solvent. In the experiments reported in the table, hydrolysis of the reaction mixture was carried out before isolation of any products was attempted; hence, some of the materials isolated were formed by hydrolysis of uncharacterized intermediates.

The first five examples in the table illustrate the dehydrogenation of a primary amine containing an α-methylene group. With pyridine present in the reaction mixture it was possible to isolate the corresponding nitrile in 50–90% yield. Since the aldehyde accompanying the nitrile probably arises from hydrolysis of an imine (the product of

$$R{-}CH_2NH_2 \xrightarrow[(2)\,H_2O]{(1)\,IF_5} R{-}CN + RCHO$$

incomplete dehydrogenation), conditions better for this dehydrogenation than those given in the table may exist.[3]

t-Butylamine was oxidized readily to 2,2′-dimethyl-2,2′-azopropane (azoisobutane). This method of preparation of this interesting and useful azo compound appears to be quite superior to that reported.[4] However, vapor phase chromatography of the azoisobutane produced in the iodine pentafluoride oxidation indicated a very small amount of impurity that was not removed readily by washing and distillation. Chromatographic purification of samples might be required to obtain uncontaminated material.

Hydrazobenzene was oxidized readily to azobenzene. There was no sign of further reaction iodine pentafluoride and azobenzene; solutions of azobenzene in pure iodine pentafluoride were warmed to 100°, and the azobenzene was recovered unchanged upon hydrolysis of the iodine pentafluoride.

Although oxidation of dibenzylamine and tribenzylamine proceeded smoothly to produce benzaldehyde, oxidation of other secondary and tertiary amines, of primary amines containing an α-substituent, and of aromatic amines led mostly to uncharacterized, tarry products.

Oximes, when added to a methylene chloride solution of iodine pentafluoride, underwent a Beckmann rearrangement. The last three examples in the table illustrate this. Hydrolysis of unchanged oxime during the processing of the reaction mixture appeared to be the major side reaction, although some of the acetanilide produced in the acetophenone oxime rearrangement underwent aromatic iodination.

EXPERIMENTAL

Melting points and boiling points are uncorrected. Iodine pentafluoride was obtained from the Matheson Co.; it was pumped *in vacuo* from the cylinder, trapped in a Kel-F test tube at −78°, and allowed to melt in a stream of dry nitrogen. The test tube then was detached from the vacuum line and the iodine pentafluoride was withdrawn and measured in a glass pipet.

Reaction of iodine pentafluoride and amines. Not all of the amine reactions mentioned in the table are detailed here, but the methods and results are illustrated amply.

(a) *Benzylamine.* A solution of 3.0 ml. (0.043 mole) of iodine pentafluoride in 120 ml. of methylene chloride was cooled to 3° and 4.3 g. (0.040 mole) of benzylamine in 30 ml. of methylene chloride was added dropwise over 30 min. The solution was stirred at 15° for 2 hr. Ice water then was added and the methylene chloride was separated and washed with dilute hydrochloric acid, water, and dilute sodium thiosulfate solution. Evaporation of the methylene chloride left 1.35 g. of residue. The infrared spectrum of this oil indicated that it was a benzonitrile-benzaldehyde mixture. The sample was chromatographed on Perkin-Elmer vapor phase chromatogram Column A at 150°, utilizing acetophenone as an internal standard. In this way it was determined that the residue consisted of benzaldehyde, 0.84 g. (20%), and benzonitrile, 0.35 g. (9%). The retention time of the benzaldehyde and of the benzonitrile was the same as that of the authentic material used in obtaining the calibration curves.

(1) This research was carried out under Army Ordnance Contract DA-01-021-ORD-5135.

(2) M. C. Sneed, J. L. Maynard, and R. C. Brasted, *Comprehensive Inorganic Chemistry*, Vol. III, *The Halogens*, D. Van Nostrand Co., Inc., New York, N. Y., 1954, pp. 210–13; General Chemical Division, Allied Chemical and Dye Corporation, Technical Bulletin TA-8532-2, "Chlorine Trifluoride and Other Halogen Fluorides."

(3) As a referee has pointed out, there is an analogy between these dehydrogenations and those reported in the Hofmann rearrangement for certain amines of intermediate size [see E. S. Wallis and J. F. Lane, *Org. Reactions*, **3**, 267 (1946)]. One could postulate the formation of *N*-fluoroamine intermediates in these oxidations, as *N*-bromoamines were considered to be intermediates in the hypobromite oxidations (R. C. Fuson, *Advanced Organic Chemistry*, John Wiley and Sons, New York, 1950, p. 538), but no evidence was found for such species. The basic fractions of these reactions, and of those mentioned later, were not examined for coupling products.

(4) E. Farenhorst and E. C. Kooyman, *Rec. trav. chim.*, **72**, 993 (1953).

TABLE I

IODINE PENTAFLUORIDE REACTIONS

Organic Compound	Solvent[a]	Substrate, mmoles	IF_5, mmoles	Reaction Conditions	Products, mmoles
Benzylamine	C	40	43	15°, 2 hr.	Benzaldehyde, 8[b] Benzonitrile, 4[b]
Benzylamine	CP	40	43	15°, 2 hr.	Benzonitrile, 36[b] Benzaldehyde, Trace
Hexylamine	CP	70	71	25°, 4 hr.	Hexanenitrile, 36
Butylamine	CP	40	43	20°, 2 hr.	Butyronitrile, 17
Isobutylamine	CP	40	43	20°, 2 hr.	Isobutyronitrile, 14[b] Isobutyraldehyde, 10[b]
t-Butylamine	CP	100	70	−10°, 1 hr. 3°, 1 hr.	Azoisobutane, 24 (48%)
Hydrazobenzene	C	29	14	3°, 1 hr.	Azobenzene, 10.5 (74%)
Dibenzylamine	CP	20	43	15°, 2 hr.	Benzaldehyde, 16
Tribenzylamine	C	20	43	15°, 2 hr.	Benzaldehyde, 18 Dibenzylamine, 12
Cyclohexanone oxime	C	43	43	3°, 1 hr. 15°, 1 hr.	ϵ-Caprolactam, 12.5
Benzophenone oxime	C	43	43	3°, 1 hr. 15°, 1 hr.	*N*-Phenylbenzamide, 32
Acetophenone oxime	C	43	43	3°, 1 hr. 15°, 1 hr.	Acetophenone, 9 Acetanilide, 9.3 *p*-Iodoacetanilide, 2.3

[a] Solvent C is methylene chloride; CP is a methylene chloride–pyridine mixture. [b] Yield determined by vapor phase chromatography.

A 0.26-g. portion of the reaction product was added to a solution of 2,4-dinitrophenylhydrazine; a total of 0.45 g. (67%) of the 2,4-dinitrophenylhydrazone of benzaldehyde was collected, m.p. and mixture m.p. 235–236°.

When the reaction was conducted as described above, except that 13 ml. (0.16 mole) of pyridine was added to the solution, there was obtained 3.86 g. of residue. This residue was analyzed by vapor phase chromatography and was found to contain benzonitrile, 3.68 g. (89%), and a little benzaldehyde (about 3%).

(b) *Hexylamine.* A solution containing 5.0 ml. (0.071 mole) of iodine pentafluoride, 23 ml. (0.28 mole) of pyridine, and 150 ml. of methylene chloride was stirred at 3° while 9.3 ml. (0.070 mole) of hexylamine in 20 ml. of methylene chloride was added dropwise. The mixture was stirred at 25° for 4 hr, then water was added and the organic layer was separated. The methylene chloride solution was washed successively with water, dilute hydrochloric acid, water, 5% aqueous sodium thiosulfate, and water. The methylene chloride was removed by distillation and the residue was distilled to give hexanenitrile, 3.67 g. (52%), b.p. 72° (33 mm.), n_D^{20} 1.4069. The nitrile sample gave only a single peak on examination by vapor phase chromatography; the retention time was the same as that of the authentic sample. However, the authentic sample contained a second small peak that was not removed by distillation, and the lack of a pure reference sample prevented a v.p.c. yield from being determined.

(c) *Hydrazobenzene.* A solution of 5.35 g. of hydrazobenzene in 40 ml. of methylene chloride was added to a stirred solution of 1.0 ml. (0.014 mole) of iodine pentafluoride in 50 ml. of methylene chloride. A cooling bath maintained an internal temperature of −10° to −5° during the addition; the mixture then was stirred 1 hr. at 3°. The reaction mixture was quenched in water, and the organic layer was processed as usual. The residue obtained on evaporation of the methylene chloride was chromatographed on silica gel. Azobenzene, 3.84 g. (74%), m.p. 66–67°, was obtained on evaporation of the pentane–methylene chloride eluate. The product was identified by mixture melting point and infrared spectrum.

(d) *t-Butylamine.* A solution containing 120 ml. of methylene chloride, 18 ml. of pyridine, and 5.0 ml. (0.07 mole) of iodine pentafluoride was stirred at −10° while 7.3 g. (0.10 mole) of *t*-butylamine in 10 ml. of methylene chloride was added dropwise. The mixture then was stirred at −10° for 1 hr. and at 0° for 1 hr. Water was added and the organic layer was separated and washed with water, dilute hydrochloric acid, 5% aqueous sodium thiosulfate, and water. The methylene chloride was removed through a Holzman column and the residue was distilled through the same column. 2,2′-Dimethyl-2,2′-azopropane, 3.40 g., b.p. 53° (70 mm.), n_D^{20} 1.4133, reported[4] b.p. 109° (45°/50 mm.), n_D^{20} 1.4091. The vapor phase chromatogram of the material on Perkin Elmer Column A at 75° exhibited 2 trace impurities. A redistilled center cut had n_D^{20} 1.4193; the trace impurity peaks were still present in the vapor phase chromatogram.

Anal. Calcd. for $C_8H_{18}N_2$: C, 67.55; H, 12.75; N, 19.70. Found: C, 67.83; 11.71; N, 19.72.

Reaction of acetophenone orime and iodine pentafluoride. A stirred solution of 3.0 ml. (0.043 mole) of iodine pentafluoride in 120 ml. of methylene chloride was cooled in an ice bath while 5.8 g. (0.043 mole) of acetophenone oxime in 30 ml. of methylene chloride was added dropwise. Stirring was continued for 1 hr. at 3° and for 1 hr. at 15°. Water was then added and the organic layer was separated and washed with 15% aqueous sodium thiosulfate and water. The residue obtained on evaporation of the methylene chloride was chromatographed on silica gel. The first fraction eluted from the column was acetophenone, 1.09 g. (21%), identified as its 2,4-dinitrophenylhydrazone, m.p. 235–237°, mixture m.p. 236–237° (authentic sample m.p. 242–243°); the infrared spectrum of the derivative was identical with that of acetophenone 2,4-dinitrophenylhydrazone. A second fraction (3.33 g.) was eluted by methylene chloride–methanol. This was recrystallized from ethanol-water to give (a), 0.83 g., m.p. 162–166°, (b) 0.83 g., m.p. 108–111°, (c) 0.46 g., m.p. 113–114°, and (d) 0.14 g., m.p. 113–114°. The last 2 fractions were acetanilide; a mixture m.p. with acetanilide was 113–114°. The (a) and (b) crops were recrystallized from ethanol to give *p*-iodoacetanilide, 0.55 g., m.p. 180–182°; a mixture m.p. with an authentic sample (m.p. 184–186°) was 182–184°. A second crop of less pure *p*-iodoacetanilide, 0.06 g., m.p. 168–172 was also obtained. A final crop of acetanilide, 0.67 g., 109–111°, mixture m.p. 112–113°

was obtained from the mother liquors of the (a) and (b) recrystallization.

ROHM & HAAS CO.
REDSTONE ARSENAL RESEARCH DIV.
HUNTSVILLE, ALA.

Evidence for the Expansion of the Valence Shell of Divalent Sulfur[1]

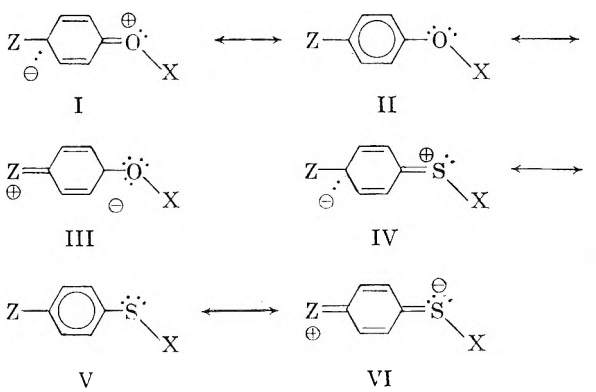
ROBERT R. BEISHLINE

Received September 15, 1960

Because sulfur has unoccupied 3*d*-orbitals, it has the possibility of expanding its valence shell through electron-pair acceptor type conjugation. When sulfur is attached directly to a phenyl ring this electron-pair acceptor conjugation presumably occurs *via* overlap between a π-orbital on carbon and an unoccupied 3*d*-orbital on sulfur to form a $(p\text{-}d)\pi$ bond.

Bordwell and Boutan[2] concluded on the basis of pK_a data and a qualitative Hammett σ treatment that electron-pair acceptor type conjugation for divalent sulfur is usually small or negligible. Application of recent modifications of the Hammett σ treatment[3] which allow semiquantitative evaluation of resonance effects demonstrates that some revision of these conclusions is necessary.

Bordwell and Boutan reasoned that if sulfur expanded its valence shell the resonance form (VI) would be more important than form (III) and a −R *para-* substituent (Z) would be more electron donating by resonance in the ionization of a substituted thiophenol than in the ionization of the corresponding phenol, *i.e.*, the resonance effect of a −R *para-* substituent (Z) would have a larger negative value in the ionization of a thiophenol than in that of the corresponding phenol.[4]



They looked for this resonance effect, but their treatment of the data did not show it (*cf.* results listed in Table I) and it was therefore assumed to be absent. However, they arrived at their conclusions *via* the qualitative relationship:

$$\sigma_p - \sigma_m \cong \textit{para}\text{-resonance effect}$$

which neglects small but significant resonance effects due to *meta-* substituents. Resonance values ($\bar{\sigma}_R$) calculated by the method of Taft and Lewis[3] (given in Table I), which considers resonance interactions from the *meta-* position, show that the effect is present, and although small, is outside of experimental error.

TABLE I

COMPARISON OF $(\sigma_p - \sigma_m)$ VALUES WITH $\bar{\sigma}_R$ VALUES

Z	$\sigma_p - \sigma_m$ (ionization of phenols)	$\sigma_p - \sigma_m$ (ionization of thiophenols)	$\bar{\sigma}_R$[a] (ionization of phenols)	$\bar{\sigma}_R$[a] (ionization of thiophenols)
—OCH_3	−0.24	−0.21	−0.36	−0.48
—$N(CH_3)_2$	−0.16	−0.17	−0.21	−0.33

[a] These $\bar{\sigma}_R$ values were calculated using the ρ_1 values given in Table II of reference (3) and the aliphatic σ_1 values given by Taft and Lewis in Table I of reference (3) and Table II of *J. Am. Chem. Soc.*, **80**, 2436 (1958).

Participation by sulfur in electron-pair acceptor type conjugation should increase as the X-group attached to sulfur becomes more electron withdrawing by inductive and conjugative interaction (as measured *qualitatively* by the σ_p value of the X-group). This follows since such withdrawal would reduce the contribution of resonance form (IV) and also contract the 3*d*-orbitals making them less diffuse and therefore capable of greater overlap with a 2*p*-orbital on carbon. Table II shows that this effect is actually observed. The $\bar{\sigma}_R$ values for —S(:)X qualitatively follow the σ_p values of X, increasing from negative numbers (net electron doner action by —S(:)X) when X is CH_3 to *positive* numbers (net electron acceptor action by —S(:)X) when X is $COCH_3$ and CN. In each case the $\bar{\sigma}_R$ values are *more positive* for the ionization of the substituted phenol than for that of the corresponding substituted benzoic acid, as would be expected

(1) This work was supported in part by the Office of Naval Research, Project NR055-328.

(2) F. G. Bordwell and P. J. Boutan, *J. Am. Chem. Soc.*, **78**, 854 (1956).

(3) R. W. Taft, Jr. and I. C. Lewis, *J. Am. Chem. Soc.*, **81**, 5343 (1959).

(4) As a result of resonance form (VI), valence shell expansion by sulfur would be expected to stabilize the substituted thiophenol relative to the corresponding thiophenylate ion because of the negative charge on sulfur in the anion. This effect should be very much smaller in the case of the substituted phenols; consequently, the ionization constant of thiophenol would be decreased more by the introduction of a −R *para* substituent (Z) than would the ionization constant of phenol.

if sulfur were participating in electron-pair acceptor type conjugation.

TABLE II

QUALITATIVE RELATIONSHIP BETWEEN $\bar{\sigma}_R$ VALUES FOR $-\ddot{S}-X$ AND $\bar{\sigma}_R$ VALUES FOR X

$-\ddot{S}-X$ Group	σ_p for X[a]	$\bar{\sigma}_R$ for $-\ddot{S}-X$[b] (ionization of benzoic acids)	$\bar{\sigma}_R$ for $-\ddot{S}-X$[b] (ionization of phenols)
$-SCH_3$	−0.17	−0.24	−0.03
$-SCOCH_3$	+0.52	+0.10	+0.12
$-SCN$	+0.63	+0.06	+0.14

[a] H. H. Jaffe, *Chem. Revs.*, **53**, 191 (1953). [b] The $\bar{\sigma}_R$ values for $-\ddot{S}-X$ were calculated from the data of Bordwell and Boutan (2) using the ρ_I values given in Table II of reference (3). The aliphatic σ_I values of Taft and Lewis were used (see (*a*), Table I) except for the thiolacetoxy ($-SCOCH_3$) and thiocyanate groups. The σ_I value for the thiolacetoxy group was obtained from the data of Bordwell and Boutan[2] using equations (1) and (6) of reference (3) and the ρ_I and α values given in Table II of reference (3). The σ_I value of the thiocyanate group has not been experimentally determined, and was estimated from the equation:

$$\sigma_{I_{-AX}} = \sigma_{I_{-X}}\left(\frac{1}{2.8}\right) + \sigma_{I_{-AH}}$$

where 1/2.8 is a fall-off factor. This equation comes from unpublished work of R. W. Taft, Jr., and I. C. Lewis which is patterned after earlier work of G. E. K. Branch and M. Calvin, *The Theory of Organic Chemistry*, Prentice-Hall, Inc., New York, N. Y., 1941, pp. 201–225. In general, the method gives good agreement with experimental results.

Although the observed electron-pair acceptor participation by sulfur is small, the $(p\text{-}d)\pi$ conjugation need not necessarily be small since the observed effect could be the net result of $(p\text{-}d)\pi$ conjugation, such as shown in resonance form (VI), acting against a somewhat smaller magnitude of ordinary $(p\text{-}p)\pi$ conjugation of the type shown in resonance forms (IV) and (I).

DEPARTMENT OF CHEMISTRY
THE PENNSYLVANIA STATE UNIVERSITY
UNIVERSITY PARK, PA.

Phosphorus Pentoxide as a Reagent in Peptide Synthesis

BERNARD F. ERLANGER AND NICHOLAS KOKOWSKY

Received October 17, 1960

At the time Schramm and Wissman[1] reported on the use of phosphorus pentoxide for the synthesis of peptides, an essentially identical procedure was being developed in this laboratory. The purpose of this communication is, first of all, to report that, contrary to the findings of the above authors, racemization can occur when acylated peptides are employed as intermediates and, secondly, to supply additional information about the potential usefulness of this synthetic procedure.

The general procedure was as follows: A diethyl phosphite solution containing one mole of acylated amino acid, one mole of amino acid (or peptide) ester hydrochloride, and two moles of tri-*n*-butylamine, was added to a solution of phosphorus pentoxide in diethylphosphite. After being heated on a steam bath for forty minutes, the reaction mixture was poured into an aqueous sodium bicarbonate solution. Crystallization frequently occurred at this point. The reaction was carried out in a hood, since phosphine appeared as a by-product.

A number of the compounds not hitherto synthesized by this method are listed in Table I and include peptides containing the following amino acid residues: glycine, D-alanine, L-phenylalanine, L-tyrosine, L-tryptophan, ε-*N*-carbobenzoxy-L-lysine, and L-glutamic acid dibenzyl ester. The protecting groups include *N*-benzoyl, *N*-carbobenzoxy,

TABLE I

PEPTIDE DERIVATIVES

Compound[a]	Yield,[b] %	M.P., found	M.P., lit.
Z·Gly-Phe·OH(DL)	70[c]	160	160[d]
Z·Gly-Phe·OH(L)	64[c]	125–126	125–126[e]
Z·Ala-Gly·OBz(L)	85	112	111[f]
Z·Ala-Ala·OBz(D-D)	75	138	138[g]
Z·Phe-Gly·OC_2H_5(L)	77	109	109–110[h]
B·Gly-Z·Lys·OCH_3(L)[i]	75	145	145[j]
Tr·Gly-Gly·OC_2H_5	65	161	163[k]
Z·Ala-Tyr·OC_2H_5(L-L)	50	136	137[l]
Z·Try-Gly·OH(L)	32[c]	156	156[m]
Z·Gly-Try·OH(L)	50[c]	142	142[m]
Z·Ala-Glu·$(OBz)_2$(L-L)	65	103	104–105[n]

[a] The abbreviations are those of E. Brand and B. F. Erlanger, *J. Am. Chem. Soc.*, **73**, 3508 (1951). Tr = trityl = triphenylmethyl; B = benzoyl; Z = carbobenzoxy; Bz = benzyl. [b] Yield of purified products. [c] Over-all yield of coupling reaction and subsequent saponification of methyl ester. [d] J. Vaughan, Jr., and R. L. Osato, *J. Am. Chem. Soc.*, **74**, 676 (1952). [e] K. Hofmann and M. Bergmann, *J. Biol. Chem.*, **134**, 225 (1940) report $[\alpha]_D^{25}$ +38.5 (5.0% in ethanol); we find $[\alpha]_D^{25}$ +37.8 (0.5% in ethanol). [f] B. F. Erlanger and E. Brand, *J. Am. Chem. Soc.*, **73**, 3508 (1951). [g] This is m.p. of L-L isomer as reported in ref. *f*. [h] G. W. Anderson and R. W. Young, *J. Am. Chem. Soc.*, **74**, 5308 (1952). They also report $[\alpha]_D^{25}$ −16.0 (2% in ethanol); we find $[\alpha]_D^{25}$ −17.3 (2% in ethanol). [i] This compound was saponified and converted, by hydrogenolysis, to hippuryl L-lysine: $[\alpha]_D^{25}$ −5.2 (2.5% in water); ref. *e* reports the same rotation. [j] M. Bergmann, L. Zervas, and F. Ross, *J. Biol. Chem.*, 111, 245 (1935). [k] G. Amiard, R. Heymes, and L. Velluz, *Bull. Soc. Chim. France*, 191 (1955). [l] M. Bergmann and J. S. Fruton, *J. Biol. Chem.*, **145**, 247 (1942). [m] E. L. Smith, *J. Biol. Chem.*, **175**, 39 (1948). [n] H. Sachs and E. Brand, *J. Am. Chem. Soc.*, **75**, 4608 (1953). They also report $[\alpha]_D^{25}$ −16.6 (2% in glacial acetic acid); we find $[\alpha]_D^{25}$ −16.8 (2% in glacial acetic acid).

(1) G. Schramm and A. Wissman, *Ber.*, **91**, 1073 (1958).

and *N*-trityl. Except for the peptide containing tyrosine and one containing tryptophan, the yields are good. The yield of tyrosine peptides could probably be increased by protecting the phenolic hydroxyl group.[2]

In order to ascertain whether racemization would occur when an acylated dipeptide was used as an intermediate, the sensitive test of Anderson and co-workers[3] was applied. Carbobenzoxyglycyl L-phenylalanine was condensed with glycine ethyl ester hydrochloride in the presence of tri-*n*-butylamine and the products were examined. Approximately 40% of the total product was found to be carbobenzoxyglycyl DL-phenylalanylglycine ethyl ester. The experimental conditions were modified in a number of ways without effecting a decrease in the extent of racemization (see Experimental section).

Schramm and Wissman[1] reported that no racemization occurred when carbobenzoxyglycyl L-leucylglycine ethyl ester was synthesized by the condensation of carbobenzoxyglycyl L-leucine with glycine ethyl ester hydrochloride in the presence of tri-*n*-butylamine and phosphorus pentoxide. Since their procedure was quite similar to the one used in our laboratory, the degree of racemization must be influenced by the nature of peptide being synthesized. Our experiments demonstrate, however, that racemization is possible when acylated peptides are employed as intermediates in this reaction.

It would appear from our work, as well as from that of Schramm and Wissman,[1] that phosphorus pentoxide is a valuable reagent for the synthesis of simple peptide derivatives of amino acids which lack reactive groups in their side chains or whose reactive groups are suitably protected. It is especially adaptable to the synthesis of large quantities of peptides in small reaction volumes, as illustrated in the Experimental section by the preparation of 90 g. carbobenzoxyglycyl L-phenylalanine. It has also been found to be a useful reagent for the preparation of hydroxamic acids and anilides directly from carboxylic acids. The synthesis of hexanohydroxamic acid from the acid and hydroxylamine hydrochloride is described in another paper,[4] as is the synthesis of a new substrate for trypsin, benzoyl DL-arginine-*p*-nitroanilide hydrochloride.[5]

EXPERIMENTAL

The following procedure was used to prepare all compounds listed in Table I. In crystallizing these compounds, the solvents used were the same as those described in the literature for the particular peptide derivative (see Table I).

Standard procedure: Carbobenzoxyglycyl L-phenylalanine. A suspension of 85.5 g. (0.397 mole) of L-phenylalanine methyl ester hydrochloride (Mann Research Laboratories), 83.2 g. (0.397 mole) of carbobenzoxyglycine,[6] and 148 g. (190 ml., 0.795 mole) of tri-*n*-butylamine in 125 ml. of diethylphosphite was added to a solution of 56 g. (0.397 mole) of phosphorus pentoxide (Mallinckrodt, A.R.) in 175 ml. of diethylphosphite (Victor Chemical Works) (warming is necessary to effect solution of the phosphorus pentoxide). The reaction mixture was heated on a steam bath for 40 min., poured into 700 ml. of water containing an excess of sodium bicarbonate, and the resulting oil extracted into ethyl acetate. After washing with dilute hydrochloric acid and water, the ethyl acetate extract was dried over anhydrous sodium sulfate and concentrated *in vacuo* to yield 145 g. of an oil. The above procedure should be carried out in a hood, since a considerable quantity of phosphine appears as a by-product.

The oily ester was saponified by allowing it to stand in a solution of 236 ml. 2*N* of sodium hydroxide in 500 ml. of methanol for 90 min. at room temperature. It was then acidified with concentrated hydrochloric acid, concentrated in volume *in vacuo* and poured into 200 ml. of water. The resulting oil was extracted into ethyl acetate, washed with water, and dried over anhydrous sodium sulfate. Removal of the solvent *in vacuo* gave a solid mass which could be crystallized from ethyl acetate–ether. The yield was 45 g. The mother liquor was found to contain unsaponified ester which was allowed to react for an additional hour at room temperature with a solution of 150 ml. 2*N* of sodium hydroxide in 200 ml. of methanol. The reaction mixture was treated as above and yielded 51 g. of material, which was combined with the 45 g. obtained previously and recrystallized from ethyl acetate–ether. The yield was 90 g. (64% over-all yield for both steps); m.p. 125–127°; $[\alpha]_D^{24}$ +37.5 (0.5% in ethanol); reported,[7] m.p. 125–126°, $[\alpha]_D^{24}$ +38.5 (5% in ethanol).

Racemization studies: Carbobenzoxyglycyl-L-phenylalanylglycine. Carbobenzoxyglycyl-L-phenylalanine (356 mg., 1 mmole), glycine ethyl ester hydrochloride (140 mg., 1 mmole), and 0.48 ml. (2 mmoles) of tri-*n*-butylamine were suspended in 5.0 ml. of diethylphosphite. This mixture was added to a solution of 142 mg. (1 mmole) of phosphorus pentoxide in 5.0 ml. of diethylphosphite and the whole reaction mixture heated on a steam bath for 20 min. After this heating period, it was poured into 15 ml. of water, extracted into ethyl acetate, and the ethyl acetate extract was washed successively with water, dilute hydrochloric acid, and dilute sodium bicarbonate. After drying over anhydrous sodium sulfate, the ethyl acetate was removed *in vacuo*, the residue was dissolved in absolute alcohol and allowed to crystallize in the refrigerator; yield, 140 mg. (32%), m.p. 130°, $[\alpha]_D^{25}$ 0 (*c*, 2, ethanol). According to Anderson and Callahan,[3] this is the racemized product, *i.e.*, carbobenzoxyglycyl-DL-phenylalanylglycine ethyl ester.

The mother liquor was taken to dryness *in vacuo* and the residue crystallized from ethyl acetate-petroleum ether; yield, 140 mg., m.p. 118–120°, $[\alpha]_D^{25}$ −12.8 (*c*, 2, ethanol). Literature[3] reports m.p. 120–120.5° and $[\alpha]_D^{25}$ −13.2 (*c*, 2, ethanol) for carbobenzoxyglycyl L-phenylalanylglycine ethyl ester.

Essentially the same results were obtained when experimental conditions were changed as follows: (a) decreasing the reaction time to 10 min.; (b) using free glycine ethyl ester in place of the hydrochloride and 1 mole of tri-*n*-butylamine; (*c*) heating the glycine ethyl ester with phosphorus pentoxide for 10 min. prior to addition of other rea-

(2) *Cf.* K. Blau and S. G. Waley, *Biochem. J.*, **57**, 538 (1954); S. G. Waley and J. Watson, *Biochem. J.*, **57**, 529 (1954); E. Wunsch, G. Fries, and A. Zwick, *Ber.*, **91**, 542 (1958).

(3) G. W. Anderson and F. M. Callahan, *J. Am. Chem. Soc.*, **80**, 2902 (1958).

(4) W. Cohen and B. F. Erlanger, *J. Am. Chem. Soc.*, **82**, 3928 (1960).

(5) B. F. Erlanger, N. Kokowsky, and W. Cohen, in preparation.

(6) M. Bergmann and L. Zervas, *Ber.*, **65**, 1192 (1932).

(7) K. Hofmann and M. Bergmann, *J. Biol. Chem.*, **134**, 225 (1940).

gents; (d) decreasing the volume in order to discourage intramolecular reactions; (e) carrying out the reaction at room temperature for 45 min. (the yield was decreased considerably but the same degree of racemization occurred); and (f) adding only 1 mole of tri-*n*-butylamine to the reaction mixture.

Acknowledgment. This work was supported in part by contract Nonr-266(44) with the Office of Naval Research.

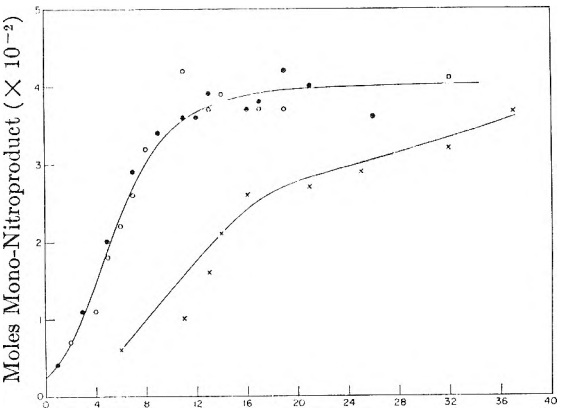
DEPARTMENT OF MICROBIOLOGY
COLLEGE OF PHYSICIANS AND SURGEONS
COLUMBIA UNIVERSITY
NEW YORK, N. Y.

Nitration with Uranium Nitrate–Nitrogen Tetroxide–Water Complex in the Presence of Acetic Anhydride[1]

JOHN R. LACHER, JEAN SCHWARZ, AND J. D. PARK

Received September 29, 1960

The type of influence which acetic anhydride has on the nitrating ability of nitric acid is not definitely understood. Menke[2] examined the nitrating abilities of inorganic nitrates with acetic anhydride. He found that nitrates of metals such as Fe^{+3}, Cu, Ni, Co, Al, Ce, and UO_2^{++} acted as very strong nitrating agents in acetic anhydride. Menke suggested possibly that acetyl nitrate is formed in the nascent state and this is then decomposed as the temperature rises. Also, he found that the velocity of nitration could be modified by a change in temperature, the choice of inorganic nitrate, and by using mixtures of acetic anhydride and acetic acid in various proportions. Putokhin[3] nitrated thiopene with cupric nitrate–trihydrate in acetic anhydride and obtained good results. He found the reaction quieter with 80% acetic acid in place of acetic anhydride and almost nil with 60% acetic acid. Dewar and Maitlis[4] nitrated quinoline using lithium nitrate with a little copper nitrate in acetic anhydride at 100°. Traverso[5] examined the nitration of tetralin with copper and aluminum nitrates in acetic acid and acetic anhydride. Borewell and Garbisch[6] in a recent study of the behavior of acetic anhydride and 70% nitric acid feel that the exothermic reaction between these compounds forming acetyl nitrate is essential for successful nitrations, and the acetyl nitrate so formed is the nitrating agent.



Nitrations with I. $UO_2(NO_3)_2 \cdot N_2O_4 \cdot H_2O$. II. $UO_2(NO_3)_2 \cdot 6H_2O$

○ Nitrobenzene I
× Nitrobenzene II
● Nitro-o-xylenes I

We initially intended to nitrate aromatic compounds with uranium nitrate–nitrogen tetroxide–water complex[7] in acetic anhydride. It was noted that as the quantity of acetic anhydride was increased the reaction became increasingly vigorous. We therefore, investigated the influence of increasing amounts of acetic anhydride on the amount of mononitration products of benzene and *o*-oxylene. An excess of aromatic compound was used as a solvent. Nitration with uranyl nitrate hexahydrate was also investigated for comparison to the above uranyl nitrate complex.

EXPERIMENTAL

Benzene, 25 cc. and varying quantities of acetic anhydride (from 0.02 to 0.40 mole) were mixed in a 125 cc. Erlenmeyer flask immersed in an ice bath with a magnetic stirrer. Uranium nitrate–nitrogen tetraoxide-water complex (0.02 mole) was slowly added to this mixture with constant stirring. Approximately 20 min. was taken for addition. A slight exothermic reaction occurred during addition of complex while the reaction flask was in the ice bath. When all the complex had been added and the solution was well stirred, it was removed from the ice bath and stirring was continued at room temperature. A very vigorous exothermic reaction occurred, and a yellow precipitate settled out of the solution. The temperature was kept below 60° until the reaction had subsided. The yellow precipitate has been identified as uranyl acetate. The entire reaction mixture was then washed twice with ice water and once with 5% sodium carbonate solution. The resulting organic layer was vacuum distilled. The nitrobenzene obtained was weighed and the amount in moles was recorded in Fig. 1 as a function of the moles of acetic anhydride used.

Benzene nitrations were also carried out using uranyl nitrate hexahydrate (0.02 mole) in the same manner as above with the exception that addition of the solid nitrate was at room temperature, as the reaction was much less vigorous than that with the complex.

(1) This work was supported by a grant from the Chemistry Branch of the Division of Research, United States Atomic Energy Commission.

(2) J. B. Menke, *Rec. Trav. Chim.*, **44**, 141 (1925).

(3) N. I. Putokhin, *Sbornik Nauch. Trudov Kuibyshev, Ind. Inst. im. V. V. Kuibyshiva*, No. 5, 271 (1955).

(4) M. J. S. Dewar, P. M. Maitlis, *Chem. & Ind.*, **48**, 685 (1955).

(5) Georgio Traverso, *Ann. Chim.*, **45**, 706 (1955).

(6) F. G. Bordwell and C. W. Garbisch, Jr., *J. Am. Chem. Soc.*, **82**, 3588 (1960).

(7) J. R. Lacher, Keith Ensley, Anne Tenge, and J. D. Park, *J. Org. Chem.*, **24**, 1347 (1959).

o-Xylene (25 cc.) was mixed with varying quantities of acetic anhydride and the complex was slowly added in a manner similar to that above. When mixed at room temperature, the exothermic reaction was not allowed to exceed 30°.[8] The same yellow precipitate mentioned above formed in this reaction from a dark red-brown solution. Washing and vacuum distillation were carried out in the same manner as previously described. No attempt was made to separate the isomeric mixture obtained. Very large amounts of acetic anhydride (eg. 0.35 mole) could not be used because of increasing amounts of tarry oxidation products coating the distilling flask.

The yield of mononitro products obtained in all cases with the uranium nitrate–nitrogen tetroxide–water complex seemed to increase almost linearly with increasing amounts of acetic anhydride between 0.02 and 0.12 mole and then leveled off to an average of approximately 0.04 mole of nitro product. The yield then became independent of the amount of acetic anhydride used. With uranyl nitrate hexahydrate the yield increased linearly with amounts of acetic anhydride between 0.06 and 0.18 mole and the yield increased slowly.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF COLORADO
BOULDER, COLO.

(8) A. W. Crossley and N. Renouff, *J. Chem. Soc.*, 95, 202 (1909).

Poly(diphenylvinylphosphine Oxide)[1]

K. DARRELL BERLIN[2] AND GEORGE B. BUTLER

Received October 10, 1960

In previous studies concerned with cyclic polymerization involving tertiary phosphine oxides it was postulated that a radical could form on a carbon atom adjacent to a phosphoryl function.[3,4] To our knowledge only one report on the polymerization of a vinyl substituted tertiary phosphine oxide has been recorded.[5] Since the completion of the present work, an investigation of the homopolymerization of several vinylphosphonates has been described; low molecular weight polymers were obtained.[6] We now wish to report the synthesis and results of polymerization of diphenylvinylphosphine oxide. This monomer was specifically selected for the study because: (a) there are no alylic hydrogen atoms in the molecule which could take part in degradative chain transfer[7] and (b) the vinyl group is in conjugation with the phosphoryl group which would be adjacent to the propagation radical.

RESULTS AND DISCUSSION

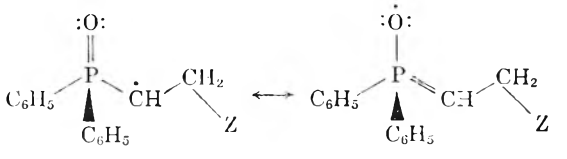
Diphenylvinylphosphine oxide (III) was prepared as depicted in the scheme. In the final step the phosphine II was oxidized to give white crystals of diphenylvinylphosphine oxide in a yield of 47.2%. In addition to the elemental analysis and infrared spectrum which support the structure III, the oxide was reduced under low pressure to the known diphenylethylphosphine oxide (IV).

$$(C_6H_5)_2PCl\ (I) + CH_2{=}CHMgCl \longrightarrow (C_6H_5)_2PCH{=}CH_2\ (II)$$

$$(C_6H_5)_2P(O)CH_2CH_3\ (IV) \xleftarrow{H_2/Pt} (C_6H_5)_2P(O)CH{=}CH_2\ (III) \xleftarrow{H_2O_2} (II)$$

In contrast to vinyl phenyl ketone which is unstable and polymerizes upon standing,[8] diphenylvinylphosphine oxides (III) is stable in air and does not polymerize in storage for several months. However, in the presence of radical initiators this monomer homopolymerized in bulk or in solution. The polymer is soluble in dimethylformamide and alcohol, and one sample (m.p. 220–242°) in alcohol gave a value of 0.047 for its intrinsic viscosity.

Although the monomer III does not seemingly contain such active hydrogen as were present in the compounds described in the studies mentioned previously,[3,4,6] the intrinsic viscosity measurement obtained on the sample of poly(diphenylvinylphosphine oxide) suggests the polymer is of low molecular weight. The degree of stabilization of the propagation radical through enolic-like structures involving the phosphoryl function may influence chain growth. Since the *d*-orbitals of the phosphorus atom would participate in the stabilization of the radical, such contributing structures as V may have different steric requirements from those of a carbon-carbon double bond composed of only



Z = polymer chain

V

(1) This research was supported in part by the United States Air Force through the Air Force Office of Scientific Research of the Air Research and Development Command, under Contract Number AF 33(616)-6887. Reproduction in whole or in part is permitted for any purpose of the United States government. Partial support by the Research Foundation of the Oklahoma State University is acknowledged.

(2) Present address: Department of Chemistry, Oklahoma State University, Stillwater, Okla.

(3) K. D. Berlin and G. B. Butler, *J. Am. Chem. Soc.*, 82, 2712 (1960).

(4) K. D. Berlin and G. B. Butler, *J. Org. Chem.*, 25, 2006 (1960).

(5) An attempted preparation of di-*n*-propenylphenylphosphine oxide and diisopropenylphenylphosphine oxide *via* Grignard reaction resulted in polymerization of the monomers *in situ*. See C. G. Gebelein and E. Howard, Jr., Abstracts of Papers, Third Delaware Regional Meeting, Philadelphia, February 25, 1960, p. 79.

(6) R. M. Pike and R. A. Cohen, *J. Poly. Sci.*, 44, 531 (1960).

(7) R. C. Labile, *Chem. Revs.*, 58, 807 (1958).

(8) For a discussion of vinyl ketone polymers see: C. E. Schildknecht, *Vinyl and Related Polymers*, John Wiley & Sons, Inc., New York, 1952, Chap. 14.

p-orbitals. To be specific the requirement that all atoms attached to a carbon-phosphorus multiple bond must lie in or near a common plane may no longer hold.[9] Thus, greater shielding of the propagation radical by the phenyl groups and the oxygen atom might result. Molecular models support this postulation. Efforts are underway to further investigate the chemistry of this oxide III and related monomers.

EXPERIMENTAL[10]

Diphenylvinylphosphine (II). To 0.4 mole of the vinyl Grignard reagent in 400 ml. of tetrahydrofuran was added dropwise, with stirring and cooling, a solution of 55.1 g. (0.25 mole) of diphenylchlorophosphine[11] in 100 ml. of dry benzene. The addition required 1.5 hr. and was regulated to sustain a gentle reflux which was then maintained for 20 hr. Decomposition was effected with 300 ml. of 10% aqueous ammonium chloride to a chilled reaction mixture. The water layer was extracted three times with ether and finally with 400 ml. of hot benzene. After drying overnight, the organic phase was fractionated to give 30.0 g. (56.8%) of the colorless phosphine II; b.p. 104° (0.25 mm.), $n^{24.5}$ 1.6260.

Anal.[12] Calcd. for $C_{14}H_{13}P$: C, 79.24; H, 6.13; P, 14.62. Found: C, 79.43; H, 6.12; P, 14.43.

The infrared spectrum of the phosphine has major peaks at 3025, 3000, 1580, 1475, 1435 (phenyl-phosphorus), 1385, 1260, 1095, 1065, 1025, 1000, 980, 950, 925, 745, and 700 cm.$^{-1}$

Diphenylvinylphosphine oxide (III). A solution of 42.2 g. (0.2 mole) of diphenylvinylphosphine (II) in 200 ml. of dry benzene was treated dropwise with 28.5 ml. of 30% hydrogen peroxide. The addition (3 hr.) was adjusted to maintain a gentle boil in the solution. After an additional 3 hr. at reflux, the solution was allowed to cool to room temperature and was then poured into 100 ml. of water. The aqueous portion was extracted with ether, the extracts were dried over sodium sulfate, and the organic solvent was distilled under aspirator pressure. The residual oil was treated with a boiling solution of 1:1 benzene-petroleum ether (b.p. 70–90°). Upon cooling the solution deposited white crystals which were washed with petroleum ether; yield 22.0 g. (48.0%), m.p. 115–117°.

Anal. Calcd. for $C_{14}H_{13}OP$: C, 73.66; H, 5.70; P, 13.59. Found: C, 73.40; H, 5.88; P, 13.60.

An infrared analysis revealed absorption at 3025, 2990 1590 (doublet), 1475, 1435(phenyl-phosphorus), 1375, 1300, 1190 (phosphoryl group), 1100, 1065, 1000, and 970 cm.$^{-1}$ There are also broad bands from 700 to 760 cm.$^{-1}$

The oxide was reduced in a Paar instrument over platinum at a pressure of 35–45 lb./sq. in. over a 24-hr. period. The yield of diphenylethylphosphine oxide (IV) was nearly quantitative, m.p. 118.5–120.5° (recorded[13] m.p. 121°). The infrared spectrum has major bands at 3025, 2950, 1435, 1175, 1115, 1065, 1025, 995, 750, and 710 cm.$^{-1}$

Poly(diphenylvinylphosphine oxide). The polymerizations were carried out in an atmosphere of nitrogen at a constant temperature. The apparatus consisted of a reaction tube which was fitted with a condenser and a nitrogen inlet. Partial purification was achieved by dissolving the polymer in a minimum of absolute alcohol and reprecipitating with cold, dry ether.

Bulk polymer. A weighed amount of the monomer III and di-*t*-butyl peroxide (1.0% by weight of the monomer) were placed in the reaction tube which was then immersed in a bath at 140° for 24 hr. The polymer solidified to a mass and was purified as described above. The polymer exhibited absorption in the infrared at 3025, 2975, 1435 (phenyl-phosphorus bond) 1175 (phosphoryl group), 1115, 740, 720 and 700 cm.$^{-1}$ There were also small peaks for water at 3400 cm.$^{-1}$ and 1624 cm.$^{-1}$ The yield was nearly quantitative, and the highest melting fraction (m.p. 220–242°) was isolated in 20%. The intrinsic viscosity measurement of the highest melting fraction was obtained with alcoholic solutions (concentrations were less than 1%) using a modified Ubbelohde viscometer.

Solution polymer. The same apparatus as described earlier was used. Equal amounts of monomer and dimethylformamide were placed in the reaction tube along with the catalyst (AIBN-1% by weight of monomer). The temperature was maintained at 65° for 120 hr. The infrared spectrum of this polymer was nearly superimposable on that of the bulk polymer. Although elaborate precautions (nitrogen atmosphere) were taken to maintain anhydrous conditions during the purification of the polymer, the hot polymerization mixture was found to be extremely sensitive to moisture. This is reminiscent of earlier work.[3,4] The elemental analysis of the bulk or solution polymer suggested the presence of water as indicated by the infrared spectra also.

Anal. Calcd. for $C_{14}H_{13}OP$: C, 73.66; H, 5.70; P, 13.59. Calcd. for $C_{14}H_{13}OP.H_2O$: C, 68.29; H, 6.09; P, 12.60. Found: C, 67.74; 67.85; H, 5.71, 5.99; P, 11.79.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF FLORIDA
GAINESVILLE, FLA.

DEPARTMENT OF CHEMISTRY
OKLAHOMA STATE UNIVERSITY
STILLWATER, OKLA.

(9) This type of bonding may find its analogy under the classification of *d*-orbital resonance as was suggested to explain the acidity of an α-hydrogen in a bicyclic trisulfone: W. Von E. Doering and L. K. Levy, *J. Am. Chem. Soc.*, **77**, 509 (1955).

(10) All boiling points are uncorrected. All melting points are corrected.

(11) A generous supply of this compound was obtained from the Victor Chemical Co.

(12) The microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

(13) G. M. Kosolapoff, *Organophosphorus Compounds*, John Wiley & Sons, Inc., New York, 1950, p. 116.

Fluorocarbon Sulfides. II. Synthesis and Physical Properties of Thiaperfluorocyclopentane

GEORGE VAN DYKE TIERS

Received October 3, 1960

It is well known from careful studies of the reactions of perfluoroalkyl iodides with elementary sulfur[1–3] that bis(perfluoroalkyl) disulfides and trisulfides are formed readily and in good yields at 250° with at best only traces of the corresponding monosulfides being found.[1,2] Above 300°, however, a small amount of monosulfide is obtained.[3]

It was therefore quite surprising to discover that the reaction of 1-4,-diodoperfluorobutane with

(1) M. Hauptschein and A. V. Grosse, *J. Am. Chem. Soc.*, **73**, 5461 (1951).

(2) G. R. A. Brandt, H. J. Emeleus, and R. N. Haszeldine, *J. Chem. Soc.*, 2198 (1951).

(3) G. V. D. Tiers, *J. Org. Chem.*, **26**, in press.

(excess) sulfur, which proceeded smoothly at 250° provided an extremely high yield of the cyclic monosulfide $(CF_2)_4S$, thiaperfluorocyclopentane.[3a] This compound, owing to its "globular" shape and weak intermolecular forces, resembles cyclohexane and perfluorocyclohexane in having a relatively high freezing point (−6.5°) and a very low entropy of fusion (*ca.* 2 e.u.), which corresponds to very little inhibition of motion in the crystal. At −127.2° there is a solid state transition with an entropy change of 18 e.u., a more nearly "normal" value for the immobilizing of fluorocarbons.[4]

EXPERIMENTAL

Thiaperfluorocyclopentane. Into each of five 30-ml. heavy-walled borosilicate glass ampoules was placed 7.0 g. of 1,4-diiodoperfluorobutane,[5] n_D^{25} 1.4265, (total 0.077 mole) and 1.0 g. of sulfur (total 0.156 g.-atom). These were sealed *in vacuo*, heated for 20 hr. at 250° in a rocking tube-oven, then chilled in liquid air, opened cautiously, and warmed to room temperature. The crude liquid reaction product, decanted from the solid lumps of iodine and unchanged sulfur, weighed 17.0 g. A portion, 11.7 g., was distilled in an efficient 10-cm. packed[6] fractionating column, and from it there was obtained 9.8 g. of thiaperfluorocyclopentane, $(CF_2)_4S$, (0.042 mole), corresponding to a yield of 79% from the diiodide.

Anal.[7] Calcd. for C_4F_8S; C, 20.70; S, 13.82. Found: C, 20.8; S, 13.9.

Thiaperfluorocyclopentane has b.p. 40.7°, n_D^{25} 1.3052, d_4^{25} 1.6339 ± .0003, f.p.[4,8,9] −6.5°, and solid state transition point,[4,9] −127.2°. The heat of fusion was estimated as 0.5 kcal./mole (entropy of fusion *ca.* 2 e.u.) and the heat of transition as approximately 2.6 kcal./mole (entropy of transition *ca.* 18 e.u.) by the relative area method,[9] the equipment having been calibrated with cyclohexane, toluene, and other similar materials. The observed molar refraction, 26.92 cc., leads[10] to an atomic refraction of 7.40 for sulfur, a value lower than the usual Eisenlohr values due to electron withdrawal by the perfluorinated group. The strongest bands in the infrared spectrum of the vapor are at 7.42, 7.76, 8.22, 8.75, and 10.10 microns.

The ultraviolet spectrum (0.1% in isooctane) shows a single band having λ_{max} = 2211 Å., ϵ_{max} = 50, and width at half-height $W_{1/2}$ = 6920 cm.$^{-1}$

Acknowledgment. I thank B. W. Nippoldt, P. B. Olson, and A. Duncan for elementary analysis and especially for the development of a modified procedure for compounds of this type[7]; and Dr. J. J. McBrady for infrared spectroscopy.

CONTRIBUTION NO. 185 FROM THE
CENTRAL RESEARCH DEPARTMENT
MINNESOTA MINING AND MFG. CO.
ST. PAUL 19, MINN.

(3a) ADDED IN PROOF: This compound was recently claimed in U.S. Patent 2,931,803 (C. G. Krespan, to the Du Pont Co.), and was made by the thermal reaction of tetrafluoroethylene with sulfur.

(4) L. L. Burger and G. H. Cady, *J. Am. Chem. Soc.*, **73**, 4243 (1951); also V. E. Stiles and G. H. Cady, *J. Am. Chem. Soc.*, **74**, 3771 (1952).

(5) M. Hauptschein, C. S. Stokes, and A. V. Grosse, *J. Am. Chem. Soc.*, **74**, 1974 (1952).

(6) "Helipak" packing; Podbielniak Co., Chicago, Ill.

(7) H. E. Freier, B. W. Nippoldt, P. B. Olson, and D. G. Weiblen, *Anal. Chem.*, **27**, 146 (1955). Furnace temp. 1200°.

(8) E. L. Skau, *Proc. Am. Acad. Arts Sci.*, **67**, 551 (1932).

(9) J. M. Sturtevant, Chap. X in *Physical Methods of Organic Chemistry*, Vol. I, Part I, A. Weissberger *ed.*, Interscience, N. Y., 1945, pp. 397–402.

(10) A. V. Grosse and G. H. Cady, *Ind. Eng. Chem.*, **39**, 367 (1947).

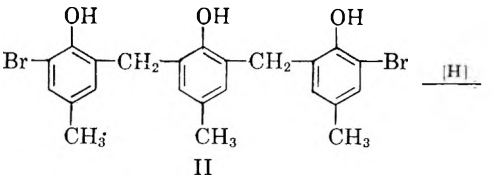
Phenol-Formaldehyde Condensations

H. M. FOSTER AND D. W. HEIN

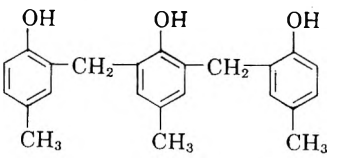
Received September 25, 1959

The condensation of 2-6-dihydroxymethyl-*p*-cresol with excess *p*-cresol gives a well defined crystalline product, m.p. 215°.[1–3] The structure of this compound has been in some doubt since both a linear "tri-nuclear" dibenzylphenol structure[1,3] and a cyclic "tetra-nuclear" structure[2] have been suggested. Very recently, Hayes and Hunter[4] presented good evidence for the linear "tri-nuclear" structure.

We have confirmed the findings of Hayes and Hunter by the unambiguous synthesis of 2,6-bis-(2-hydroxy-5-methylbenzyl)-*p*-cresol, I, *via* debromination of 2,6-bis(2-hydroxy-3-bromo-5-methylbenzyl)-*p*-cresol, II.



II



I

The condensation product of 2,6-dihydroxymethyl-*p*-cresol and excess *p*-cresol was identical by microanalysis, melting point, mixed melting point, and infrared absorption spectrum with I.

As supporting evidence for the "tetra-nuclear," 2:2 (2,6-dihydroxymethyl-*p*-cresol: *p*-cresol) structure, Niederl and McCoy[2] reported that the equimolar condensation of 2,6-dihydroxymethyl-*p*-cresol with *p*-cresol yielded a crystalline, well defined product. We attempted to repeat this experiment, although we could not reproduce the

(1) M. Koebner, *Z. Angew. Chem.*, **46**, 252 (1933).

(2) J. B. Niederl and J. S. McCoy, *J. Am. Chem. Soc.*, **65**, 629 (1943).

(3) S. R. Finn and G. J. Lewis, *J. Soc. Chem. Ind. (London)*, **69**, 132 (1950).

(4) B. T. Hayes and R. F. Hunter, *J. Appl. Chem.*, **8**, 743 (1958).

experimental conditions exactly, and obtained only resinous material.

On the other hand, condensation of 2,6-dihydroxymethyl-*p*-chlorophenol with excess *p*-cresol proceeded in a completely analogous manner as when 2,6-dihydroxymethyl-*p*-cresol was condensed with excess *p*-cresol. A well defined, crystalline product, m.p. 222–223°, was obtained. Because of the presence of chlorine, microanalyses clearly permitted a choice in favor of the "tri-nuclear," 1:2 (2,6-dihydroxymethyl-*p*-chlorophenol:*p*-cresol) condensation product, 2,6-bis(2-hydroxy-5-methylbenzyl)-*p*-chlorophenol; a "tetra-nuclear," 2:2 condensation product is clearly ruled out. Similarly, condensation of 2,6-dihydroxymethyl-*p*-cresol with either *p*-chlorophenol or *p*-bromophenol gave in each case, the "tri-nuclear," 1:2 (2,6-dihydroxymethyl-*p*-cresol: *p*-halophenol) condensation product, characterized as such by microanalysis.

EXPERIMENTAL[5]

2,6-Bis(2-hydroxy-3-bromo-5-methylbenzyl)-p-cresol.[3] A mixture of 8.4 g. (0.05 mole) of recrystallized 2,6-dihydroxymethyl-*p*-cresol and 65 g. (large excess) of 2-bromo-*p*-cresol was warmed on the steam bath until nearly all the dihydroxymethyl derivative had dissolved. The mixture was cooled to 40°, and treated with 1 ml. of concd. hydrochloric acid. After a short time, the mixture was treated with 50 ml. of petroleum ether (b.p. 30–60°) and permitted to stand.

After a week, the reaction mixture was diluted with 100 ml. of petroleum ether, the solid product was filtered and washed copiously with petroleum ether.

The solid was recrystallized from alcohol-water, acetic acid–water (several times) and finally from acetic acid to give a colorless, microcrystalline product, m.p. 175–177°; lit., m.p. 176°.

2,6-Bis(2-hydroxy-5-methylbenzyl)-p-cresol. A sample of the dibromo compound (1.8 g., 0.0035 mole) was dissolved in 50 ml. of 95% ethanol and 4 ml. of 10% sodium hydroxide. The solution was further treated with 0.1 g. of palladium-carbon catalyst and hydrogenated in a Parr apparatus for several days. The catalyst was then filtered, and the clear filtrate diluted with an equal volume of water. The solution was then neutralized with several drops of concentrated hydrochloric acid and the now cloudy solution concentrated on the steam bath. The solid which separated from solution was filtered and recrystallized from acetic acid. The crystalline solid, still moist with acetic acid, was digested with boiling benzene for several minutes, filtered, washed copiously with petroleum ether, and dried to give a very pure sample, m.p. 215–217°.

Anal. Calcd. for $C_{23}H_{24}O_3$: C, 79.28; H, 6.94; mol. wt., 348. Found: C, 79.45; H, 7.17; mol. wt.,[6] 331 ± 10.

A sample of the condensation product of the dihydroxymethyl-*p*-cresol with a large excess of *p*-cresol,[2] purified as above, melted at 215–217°, also; mixed m.p. 214–216°.

Anal. Calcd. for $C_{23}H_{24}O_3$ ("tri-nuclear" product): C, 79.28; H, 6.94; mol. wt., 348. Calcd. for $C_{32}H_{32}O_4$ ("tetra-nuclear" product): C, 79.97; H, 6.71; mol. wt., 481. Found: C, 79.09; H, 6.91; mol. wt.,[6] 298 ± 10.

Comparison of the infrared absorption spectra of the two samples furnished additional evidence of their identity.

Equimolar condensation of 2,6-dihydroxymethyl-p-cresol and p-cresol. A mixture of 8.4 g. (0.05 mole) of recrystallized 2,6-dihydroxymethyl-*p*-cresol, 5.4 g. (0.05 mole) *p*-cresol, and 50 ml. of glacial acetic acid was warmed on the steam bath to give a clear solution (a solution did not form at room temperature), chilled in ice, and the slurry saturated with anhydrous hydrogen chloride during cooling in ice water. The solution which formed was permitted to stand at room temperature. After 1 week, the solid product which had separated from solution was filtered and drained with suction. The solid was nonhomogeneous and could be separated into three fractions: soluble in cold acetic acid, soluble in hot acetic acid, and insoluble in acetic acid. All three fractions melted over wide ranges and could not be recrystallized from acetic acid, aqueous acetic acid, alcohol or aqueous alcohol.

2,6-Dihydroxymethyl-p-chlorophenol. A solution of 28 g. (0.25 mole) of *p*-chlorophenol, 12.5 g. of sodium hydroxide and 15 ml. of water was cooled to about 15° and treated with 55 ml. of 37% formalin solution. The mixture was permitted to stand at room temperature. After several days the reaction mixture had set to a very stiff paste. The mixture was diluted with 60 ml. of 15% brine solution and was stirred until fairly uniform. The solid was filtered, washed with 40 ml. of 15% brine solution, and drained with suction. After neutralization of an aqueous solution of the sodium salt with dilute acetic acid, the product was dissolved in methanol, a small amount of acetic acid was added, the solution was clarified and poured into a large volume of water. The nearly colorless product was filtered, washed with water, drained with suction, and dried at 55°. The yield of pure product was 10.8 g., m.p. 162–163°C.; lit.,[7] m.p. 165°.

2,6-Bis(2-hydroxy-5-methylbenzyl)-p-chlorophenol. To a mixture of 4.8 g. (0.025 mole) of 2,6-dihydroxymethyl-*p*-chlorophenol and 30 ml. (large excess) of *p*-cresol was added 10 drops of concd. hydrochloric acid. No visible reaction occurred. The mixture was treated with 25 ml. of petroleum ether (b.p. 30–60°), warmed gently on the steam bath until all the petroleum ether had been evaporated and again treated with 25 ml. of petroleum ether. The reaction mixture was permitted to stand at room temperature. After several days, the reaction mixture had completely solidified. The solid mass was triturated with 50 ml. of petroleum ether, the slurry stirred until uniform, and the solid filtered. The solid was washed with petroleum ether, and drained dry with suction. A sample was twice recrystallized from glacial acetic acid, m.p. 220–222°. The sample appeared to be partially solvated.

Anal. Calcd. for $C_{22}H_{21}ClO_3 \cdot {}^1/_3\ CH_3CO_2H$: C, 70.00; H, 5.79; Cl, 9.12. Found: C, 70.00; H, 6.47; Cl, 8.99.

The sample was desolvated by digestion with boiling benzene, followed by digestion and washing with boiling hexane; m.p. 222–223°.

Anal. Calcd. for $C_{22}H_{21}ClO_3$: C, 71.63; H, 5.74; Cl, 9.61. Found: C, 71.88; H, 5.656; Cl, 9.34.

The benzene extract from above was permitted to cool yielding a small amount of colorless needles. After another recrystallization from benzene and washing with hexane the sample melted at 222–224°.

Anal. Calcd. for $C_{22}H_{21}ClO_3$: Cl, 9.61. Found: Cl, 9.82.

2,6-Bis(2-hydroxy-5-chlorobenzyl)-p-cresol. Recrystallized 2,6-dihydroxymethyl-*p*-cresol (4.2 g., 0.025 mole) was dissolved in 35 g. (large excess) of previously melted *p*-chlorophenol. A few milliliters of hexane were added to prevent crystallization of the starting materials, and the mixture further treated with 10 drops of concd. hydrochloric acid. The reaction mixture which became milky was heated on the steam bath for a short time and then permitted to stand at room temperature. The gummy, semi-solid product was

(5) All melting points are uncorrected. Microanalyses were obtained by the late Mr. O. E. Sundberg and associates.

(6) Abraham Wilson, Louis Bini, and Robert Hofstader, *Anal. Chem.*, **33**, 135 (1961).

(7) M. Weiler and K. Berres, German Patent 510,447 (1930).

filtered and washed with a little benzene. The still gummy material was suspended in cold benzene, the slurry stirred until uniform, and the solid filtered. The more granular product was then digested with boiling benzene. The quite pure product was easily recrystallized from glacial acetic acid (twice) and then digested with boiling benzene. The product was subsequently washed with benzene and hexane, m.p. 242–244°; lit.,[3] m.p. 239–240°. At this stage, microanalyses indicated that the sample was partially solvated with benzene. The sample was desolvated by digestion with boiling hexane and drying at 55° in vacuum for several days.

Anal. Calcd. for $C_{21}H_{18}Cl_2O_3$: C, 64.79; H, 4.66; Cl, 18.22. Found: C, 65.18; H, 4.45; Cl, 18.41.

Another sample was recrystallized from acetic acid. After preliminary drying at 50° for several days the sample was further dried in vacuum at 100° for 24 hr.

Anal. Calcd. for $C_{21}H_{18}Cl_2O_3$: C, 64.79; H, 4.65; Cl, 18.22. Found: C, 64.65; H, 4.87; Cl, 17.84, 17.79.

2,6-Bis(2-hydroxy-5-bromobenzyl)-p-cresol. To a partial solution of 35 g. (large excess) of *p*-bromophenol and 35 ml. of hexane at steam-bath temperature, was added 4.2 g. (0.025 mole) of recrystallized 2,6-dihydroxymethyl-*p*-cresol. The mixture was then treated with 10 drops of concd. hydrochloric acid, whereupon a vigorous exothermic reaction ensued. A dense, semi-solid mass separated from the reaction mixture. The supernatant was decanted and the residue treated with benzene. This treatment promoted rapid crystallization of the product. The product was filtered and washed with benzene. Then it was suspended in cold benzene, filtered, and digested with boiling benzene. Finally, the product was recrystallized from acetic acid (twice) followed by digestion with boiling benzene. The sample was washed with benzene and hexane and dried, m.p. 231–232° dec., with prior sintering and discoloration beginning at 215°. The sample appeared to be partially solvated with benzene. The sample was desolvated by digestion with hexane, followed by drying at 100° in vacuum for 24 hr.

Anal. Calcd. for $C_{21}H_{18}Br_2O_3$: C, 52.74; H, 3.79; Br, 33.43. Found: C, 52.59; H 3.88; Br, 33.24.

RESEARCH DEPARTMENT
ORGANIC CHEMICALS DIVISION
AMERICAN CYANAMID CO.
BOUND BROOK, N. J.

Reactions of Antimony Pentachloride and Ferric Chloride with Deactivated Aromatic Compounds[1]

PETER KOVACIC AND ALLEN K. SPARKS[2]

Received August 3, 1960

Earlier publications in this series have dealt with the interaction of antimony pentachloride[3] and ferric chloride[4] with simple alkyl- and halobenzenes. This investigation is concerned with the scope of the reaction of these metal halides with deactivated aromatic compounds. Benzotrifluoride, nitrobenzene and benzaldehyde were selected for study.

Benzotrifluoride. Products obtained from antimony pentachloride and benzotrifluoride included *m*-chloro-α,α,α-trifluorotoluene,[5] *m*-benzoyl-α,α,α-trifluorotoluene, benzoic acid and tarry polymer. The compounds derived from side-chain attack might arise from precursors[6–10] such as $C_6H_5CX_2^+$ (X = F or Cl). It is presumed that *m*-benzoyl-α,α,α-trifluorotoluene is formed by hydrolysis[11] of the intermediate *m*-$C_6H_5CX_2C_6H_4CF_3$ (X = F or Cl). Similar condensations of benzotrichloride with itself,[12] phenols[13,14] and benzene[15] have been reported.

On the other hand, ferric chloride reacted exclusively with the trifluoromethyl group of benzotrifluoride, yielding *m*-benzoyl-α,α,α,-trifluorotoluene and benzoic acid as the only isolable products after hydrolysis, in addition to tar.

Nitrobenzene. Antimony pentachloride combined with nitrobenzene at 103–118° to give a 64% yield of chloronitrobenzene (predominantly *meta*).

In contrast, ferric chloride exhibited a quite different mode of reaction. Chloronitrobenzene, *p*-chloroaniline, 2,4,6-trichloroaniline, and chloranil were isolated in low yields. It seems reasonable that the amines rose *via* reduction of nitrobenzene by ferrous chloride. Robertson and Evans have discussed[16] the relationship between the nature of the reducing system and chloroaniline formation in the reduction of nitrobenzene. The generation of chloranil is somewhat reminiscent of conversion of a *p*-aminophenol to a chloroquinone by oxidation with ferric chloride.[17–19] Although the reaction sequences leading to the various products are un-

(1) Part X of a series on *Reactions of Metal Halides with Organic Compounds;* from the Ph.D. thesis of A. K. Sparks, Case Institute of Technology, 1960.

(2) Allied Chemical Corp. Fellow, 1958–1960.

(3) P. Kovacic and A. K. Sparks, *J. Am. Chem. Soc.*, 82, 5740 (1960).

(4) P. Kovacic, C. Wu and R. W. Stewart, *J. Am. Chem. Soc.*, 82, 1917 (1960); P. Kovacic and N. O. Brace, *J. Am. Chem. Soc.*, 76, 5491 (1954).

(5) E. Wertyporoch, *Ann.*, 493, 153 (1932).

(6) A. L. Henne and M. S. Newman, *J. Am. Chem. Soc.*, 60, 1697 (1938).

(7) G. M. Le Fave, *J. Am. Chem. Soc.*, 71, 4148 (1949).

(8) Antimony pentachloride and ferric chloride are known to catalyze hydrolysis of the trichloromethyl group (M. E. Hill, *J. Org. Chem.*, 25, 1115 (1960)).

(9) M. Prober, *J. Am. Chem. Soc.*, 76, 4189 (1954).

(10) C. I. Tewksbury and H. M. Haendler, *J. Am. Chem. Soc.*, 71, 2336 (1949).

(11) (a) B. Bensley and G. Kohnstam, *J. Chem. Soc.*, 3408 (1955); (b) A. L. Henne and H. M. Leicester, *J. Am. Chem. Soc.*, 60, 864 (1938).

(12) A. Wohl and E. Wertyporoch (Ann., 481, 30 (1930)) describe the formation of *m*-$C_6H_5CCl_2C_6H_4CCl_3$, *m*-$C_6H_5CCl_2$-$C_6H_4CCl_2C_6H_4CCl_2$-*m*, and resin from benzotrichloride and aluminum chloride.

(13) O. Doebner and W. Stackmann, *Ber.*, 9, 1918 (1876).

(14) M. S. Newman and A. G. Pinkus, *J. Org. Chem.*, 19, 985, 992 (1954).

(15) J. B. Lal and S. Dutt, *J. Indian Chem. Soc.*, 12, 389 (1935); *Chem. Abstr.*, 30, 452 (1936).

(16) G. R. Robertson and R. A. Evans, *J. Org. Chem.*, 5, 142 (1940).

(17) J. Cason, *Org. Reactions*, 4, 311 (1948).

(18) L. I. Smith and W. B. Irwin, *J. Am. Chem. Soc.*, 63, 1036 (1941).

(19) L. I. Smith and J. A. King, *J. Am. Chem. Soc.*, 63, 1887 (1941).

known, the following processes might reasonably be involved at one stage or another: oxidation and nuclear chlorination by ferric chloride, rearrangements of the phenylhydroxylamine or Bamberger[20] type.

Quite recently, Miller and White reported[21] the formation of hexachlorobenzene, together with a trace of chloranil, from the reaction of nitrobenzene with excess anhydrous ferric chloride at 190–195°.

Benzaldehyde. The reaction of benzaldehyde with ferric chloride or antimony pentachloride[22] resulted in the formation of dark, polymeric solid accompanied by the evolution of copious quantities of gas containing hydrogen chloride. In the case of ferric chloride, carbon monoxide[23,24] was also detected in the effluent vapor.

EXPERIMENTAL[25]

Antimony pentachloride and benzotrifluoride. Antimony pentachloride (144 g., 0.48 mole) was added slowly to benzotrifluoride (292 g., 2 moles) with stirring under nitrogen at 30–94° during 90 min. After 1 hr. at 90–95°, work-up of the reaction mixture, including refluxing with water, yielded benzoic acid (2 g.) and a liquid (21.2 g.), b.p. 57–58° (40 mm.), identified as chloro-α,α,α-trifluorotoluene (91% *meta*) by infrared analysis (authentic isomers as reference standards) and by hydrolysis[7] to *m*-chlorobenzoic acid, m.p., 152.5–153° from toluene; lit.[26] m.p. 153°.

Anal. Calcd. for $C_7H_5O_2Cl$: Neut. equiv., 156.6 Found: 157.

The liquid, 33.2 g., b.p. 105.5–106.5° (0.6 mm.), turned to a white solid, m.p. 49–50.5°. A mixture melting point with authentic *m*-benzoyl-α,α,α-trifluorotoluene from the ferric chloride-benzotrifluoride reaction showed no depression.

The distillation residue consisted of brown solid (9.1 g.).

Ferric chloride and benzotrifluoride.[27] A mixture of benzotrifluoride (2 moles) and anhydrous ferric chloride (1 mole) was heated under nitrogen at reflux for 4 hr. Work-up, including refluxing with water, yielded benzoic acid (6.6 g.) and *m*-benzoyl-α,α,α-trifluorotoluene, 29.6 g., b.p. 121–123° (1.5 mm.), m.p. 51.5–53° from aqueous methanol.

Anal. Calcd. for $C_{14}H_9F_3O$: C, 67.20; H, 3.62; F, 22.78. Found: C, 67.16; H, 3.77; F,[28] 23.14.

Hydrolysis of a portion of this fraction with sulfuric acid[7] gave a 95% yield (crude) of *m*-benzoylbenzoic acid, m.p. 159.5–161° from toluene; lit.[29] m.p. 161°.

Anal. Calcd. for $C_{14}H_{10}O_3$: Neut. equiv., 226. Found: 228.

The distillation residue consisted of dark brown, brittle solid (60 g.).

Antimony pentachloride and nitrobenzene. A mixture of antimony pentachloride (69.9 g., 0.23 mole) and nitrobenzene (111.4 g., 0.91 mole) was heated at 108–118° under nitrogen for 4.5 hr. Chloronitrobenzene, 23.5 g., b.p. 108.5–109.5° (11 mm.) was obtained. The product was a mixture of isomers, predominantly *meta*, as determined by infrared analysis.

Ferric chloride and nitrobenzene. A mixture of ferric chloride (0.5 mole) and nitrobenzene (1 mole) was heated during 4 hr. with stirring under nitrogen to 142° and then at 182–204° for 1 hr.

The reaction mixture was steam distilled and the steam-volatile material was fractionated, yielding a yellow liquid, 1.7 g., b.p. 103–105° (10 mm.), which was identified as a mixture of chloronitrobenzenes by comparison of the infrared spectrum with those of the authentic materials. The brown distillation residue (1.3 g.) was crystallized from toluene to yield 0.71 g. of chloranil, m.p. 289.5–290.5°; lit.[30] m.p. 290°.

Anal. Calcd. for $C_6Cl_4O_2$: C, 29.31; H, 0.00; Cl, 57.68. Found: C, 29.21; H, 0.06; Cl, 57.33.

The pot residue from steam distillation was made basic and the steam distillation continued. A small amount of solid (0.29 g.), m.p. 74.5–76° from dilute ethanol, was collected from the condenser. A mixture melting point with authentic 2,4,6-trichloroaniline showed no depression.

The remaining steam-volatile material was distilled to give a brown oil (0.1 g.), b.p. 64–96° (11 mm.). The infrared spectrum contained all the peaks of *p*-chloraniline, in addition to bands indicative of a nitro compound contaminant. Reaction of a portion of this fraction with benzoyl chloride gave a white solid, m.p. 188–190.5°, which did not depress the melting point of authentic *N*-(*p*-chlorophenyl)benzamide.

Antimony pentachloride and benzaldehyde. Antimony pentachloride (0.15 mole) was added to benzaldehyde (1.22 moles) at 120–156° under nitrogen. After 30 min. at 130–140°, work-up of the reaction mixture yielded black solid as the main product.

Anal. Found: C, 63.43; H, 3.96; Cl, 7.24.

The infrared spectrum of a gas sample collected over water during the early stages of reaction revealed no trace of carbon monoxide.

Ferric chloride and benzaldehyde.[31] A mixture of benzaldehyde (425 g., 4 moles) and ferric chloride (162 g., 1 mole) was heated under nitrogen at 145–160° for 1 hr. A gas sample[23] showed very weak infrared absorption bands of similar intensity at 2120 and 2180 cm.$^{-1}$, characteristic of carbon monoxide; lit.[32] 2135 and 2196 cm.$^{-1}$ (approx.). The reaction mixture yielded insoluble, infusible black solid (30 g.).

Anal. Found: C, 76.26; H, 3.22; Cl, 0.14 Fe, 0.73.

Acknowledgment. We gratefully acknowledge the support of part of this work by the National Science Foundation.

DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING
CASE INSTITUTE OF TECHNOLOGY
CLEVELAND 6, OHIO

(20) E. O. Bamberger, *Ann.*, **424**, 233, 297 (1921).
(21) R. E. Miller and W. A. White, *J. Org. Chem.*, **25**, 1249 (1960).
(22) R. Gnehm and E. Bänziger, *Ann.*, **296**, 62 (1897).
(23) D. H. Hey, *J. Chem. Soc.*, **72**, (1935).
(24) H. E. Ungnade and E. W. Crandall, *J. Am. Chem. Soc.*, **71**, 2209 (1949).
(25) Melting points and boiling points are uncorrected; elemental analyses were performed by Drs. Weiler and Strauss, Oxford, England.
(26) J. C. Smith, *J. Chem. Soc.*, 213 (1934).
(27) F. J. Donat and C. K. Wilkins assisted with this experiment.
(28) We are indebted to the Dow Chemical Co. for this analysis.
(29) P. Senff, *Ann.*, **220**, 225 (1883).
(30) C. Graebe, *Ann.*, **263**, 16 (1891).
(31) Experiment performed by C. Wu.
(32) R. H. Pierson, A. N. Fletcher, and E. Gantz, *Anal. Chem.*, **28**, 1218 (1956).

Reaction of Organophosphorus Acids with Isocyanates[1]

ROBERT B. FOX AND WILLIAM J. BAILEY

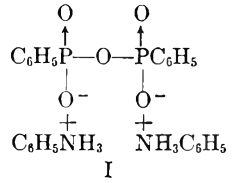
Received April 29, 1960

In a recent report,[2] it was shown that the tertiary amine salts of phenylphosphinic acid and the cor-

responding half-salts of phosphonic acids condense with isocyanates to give good yields the *P*- and *O*-carbamoyl derivatives, respectively. The acids themselves react with isocyanates and isocyanate adducts in quite a different manner, with the major isolated products being ureas and compounds formed by intermolecular dehydration of the phosphorus acids.

Such behavior is somewhat analogous to that observed by Naegeli and Tyabji[3] in the reactions of carboxylic acids with isocyanates, in which both ureas and anhydrides are formed along with amides and carbon dioxide. The carbon dioxide has been shown to arise from the isocyanate.[4]

We have found that both phenylphosphinic and phenylphosphonic acid react with phenyl isocyanate in an inert solvent at ordinary temperatures to give dianilinium diphenylpyrophosphonate (I) as the only isolable phosphorus containing product. The salt is readily hydrolyzed to a relatively un-



I

stable acid which appears to be a dihydrate of diphenylpyrophosphonic acid. Upon being heated, this acid is rapidly converted to phenylphosphonic acid to produce water as the only volatile product of the reaction. The identity of I was confirmed through its independent preparation from aniline and the anhydrous diphenylpyrophosphonic acid formed by the restricted hydrolysis of phenylphosphonic dichloride.[5]

A facile method of synthesis of the salt I involves the reaction of phenylphosphonic acid and an isocyanate adduct, such as *sym*-diphenylurea or methyl carbanilate at about 210°. It is noteworthy that monoanilinium phenylphosphonate did not appear to dehydrate to give I at 210°, although the acid itself has been stated[6] to form diphenylpyrophosphonic acid at this temperature.

The mechanism of the formation of I from phenylphosphinic acid has not been elucidated with certainty, although it is apparent that an oxidation step is involved. Disproportionation of the acid to the phosphonic acid and phenylphosphine may be tentatively discounted on the basis of the lack of the very penetrating odor of the phosphine at any point during the reaction. Yields of diphenylurea and of gases (probably carbon dioxide) absorbable by Ascarite were always high in the reactions with both the phosphinic and the phosphonic acid. It would be logical to assume that, analogously with the reactions of carboxylic acids,[3] I is formed through intermolecular dehydration of the phosphonic acid and subsequent reaction of the resulting acid with the aniline generated simultaneously from the isocyanate.

EXPERIMENTAL

Phenylphosphinic acid, m.p. 84°, and phenylphosphonic acid, m.p. 163.5–164°, were recrystallized commercial products. A Perkin-Elmer model 21 recording infrared spectrophotometer was used for the infrared spectra. Microanalyses are by Oakwold Laboratories, Alexandria, Va., Dr. Mary Aldridge, American University, and Mrs. Kathryn Gerdeman Baylouney, University of Maryland. All melting points are corrected, and those accompanied by decomposition gave a gas without sintering.

Reaction of phenylphosphinic acid with phenyl isocyanate. To a stirred suspension of 71.0 g. (0.5 mole) of phenylphosphinic acid in 750 ml. of dry toluene in an ice bath was added dropwise in a 45 min. period 71.4 g. (0.6 mole) of phenyl isocyanate. During the addition, much of the solid dissolved. In the course of stirring in the ice bath for an additional 2 hr. a precipitate formed; the evolution of a gas was evident throughout the reaction, and these gases were allowed to pass through an Ascarite tube. After being allowed to stand at room temperature overnight, the mixture was stirred 2 hr. at 75° and then 1 hr. at 100°. A total of 15.4 g. of a product was absorbed by the Ascarite tube. Filtration and concentration of the reaction mixture afforded 85.6 g. of crude crystalline material (an oily residue was discarded), which upon repeated recrystallization from hot isopropyl alcohol gave, in addition to diphenylurea, m.p. 248° dec., 25.0 g. (10%) of dianilinium diphenylpyrophosphonate, m.p. 211–213° dec.

Anal. Calcd. for $C_{24}H_{26}N_2O_5P_2$: C, 59.47; H, 5.31; P, 12.79. Found: C, 59.98; H, 5.18; P, 11.91.

The use of other inert solvents or a variation in reactant ratios had an adverse effect on the yield. In acetone, the reaction followed a different course and gave an unidentified *acid*, m.p. 199.5–200°, which may have been $C_6H_5P(O)(OH)C(CH_3)_2OCONHC_6H_5$, but was not further characterized.

Reaction of phenylphosphonic acid with phenyl isocyanate. To a stirred solution of 15.8 g. (0.1 mole) of phenylphosphonic acid in 100 ml. of dry acetone at room temperature was added as rapidly as possible 13.1 g. (0.11 mole) of phenyl isocyanate. Within 30 min. the mixture had warmed slightly and an Ascarite tube appended to the reflux condenser had become quite hot, indicating the efflux of an absorbable gas. After the mixture had been heated under reflux for 2 hr., filtration and further concentration gave 22.0 g. of crude solids; the Ascarite tube gained 5.2 g. Repeated recrystallization of the crude material (which contained about 50% diphenylurea) from hot isopropyl alcohol gave a product, m.p. 210–212°, which on the basis of its infrared spectrum and a mixed melting point determination, appeared identical with the dianilinium diphenylpyrophosphonate obtained from phenylphosphinic acid.

Anal. Calcd. for $C_{24}H_{26}N_2O_5P_2$: C, 59.47; H, 5.31; P, 12.79; N, 5.78. Found: C, 60.70; H, 5.28; P, 12.00; N, 5.89.

Reaction of phenylphosphonic acid with phenyl isocyanate adducts. A mixture of 7.9 g. (0.05 mole) of phenylphosphonic acid and 10.6 g. (0.05 mole) of *sym*-diphenylurea was heated at 210° for 10 min. in an open test tube with a thermometer-stirring rod. One recrystallization of the cooled reaction

(1) Based on a portion of a thesis submitted in June 1959 by Robert B. Fox to the Graduate School of the University of Maryland in partial fulfillment of the requirements of the degree of Doctor of Philosophy.

(2) R. B. Fox and W. J. Bailey, *J. Org. Chem.*, **25**, 1447 (1960).

(3) C. Naegeli and A. Tyabji, *Helv. Chim. Acta*, **17**, 931 (1934); **18**, 142 (1935).

(4) A. Fry, *J. Am. Chem. Soc.*, **75**, 2686 (1953).

(5) L. Anschütz and H. Wirth, *Chem. Ber.*, **89**, 688 (1956).

(6) A. Michaelis and C. Mathias, *Ber.*, **7**, 1070 (1874).

mass from 2.5 l. of hot isopropyl alcohol afforded 7.5 g. (62%) of dianilinium diphenylpyrophosphonate, m.p. 215–217°, identified through a comparison of its infrared spectrum with that of an authentic specimen.

A repetition of this experiment with methyl carbanilate in place of the urea gave similar results.

Dianilinium diphenylpyrophosphonate (I). A mixture of 5.5 g. (0.028 mole) of phenylphosphonic dichloride and 0.76 g. (0.042 mole) of water in 35 ml. of ether was shaken for 45 min., with occasional cooling under a water tap. Most of the volatile material in the resulting heavy oil was removed under water-aspirator pressure. Treatment with 10 ml. of cold water gave a crystalline precipitate which was washed with cold water, slurried with ether, and dried in air to yield without further purification, 2.3 g. (55%) of slightly hygroscopic diphenylpyrophosphonic acid, m.p. 81.5–82.5°[6].

Anal. Calcd. for $C_{12}H_{12}P_2O_5$: C, 48.30; H, 4.06; neut. equiv., 149.1. Found: C, 47.87; H, 4.04; neut. equiv., 150.4.

The dianilinium salt of this acid was prepared by the addition of 3 drops of aniline to a solution of 0.2 g. of the acid in 2 ml. of cold water; the resulting precipitate was recrystallized from hot isopropyl alcohol. The infrared spectrum and properties of this salt are identical in every respect with those of the salt prepared as described above. Aqueous solutions of dianilinium diphenylpyrophosphonate are acidic and fairly stable. Titration with alkali shows a sharp break at *p*H 8.5 with a neutralization equivalent of 241 ± 1 (calcd. 242).

An attempt to prepare this salt by heating a sample of monoanilinium phenylphosphonate (m.p. 210–213° dec.) at 210° failed to show evidence of dehydration. The infrared spectra of this salt and that of dianilinium diphenylpyrophosphonate are quite dissimilar.

Hydrolysis of dianilinium diphenylpyrophosphonate. A mixture of 2 g. of the dianilinium salt and 20 ml. of 10% aqueous sodium hydroxide was heated just to the boiling point, cooled, and extracted with ether to remove aniline (identified as acetanilide, m.p. 113–114°, and benzenesulfonanilide, m.p. 110–111°). Careful treatment of the aqueous alkaline solution with excess concentrated hydrochloric acid caused the precipitation of a crude acid, m.p. 75–77° dec. Recrystallization from *cold* acetone gave material, m.p. 82.5–83°, which was titrated as a strong monobasic acid with a neutralization equivalent of 169 ± 2 (calculated for diphenylpyrophosphonic acid dihydrate, 167). Crystallization of this substance from hot acetone gave material which exhibited a neutralization curve with two unequally spaced breaks. The infrared spectrum of the volatile material obtained by heating a sample of the acid at 100° showed the presence only of water. The spectrum of the residue or of a sample recrystallized from boiling toluene was identical with that of phenylphosphonic acid.

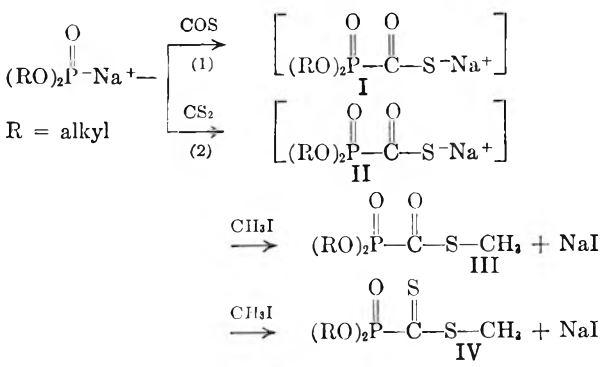
U. S. Naval Research Laboratory
Washington 25, D. C.
Department of Chemistry, University of Maryland
College Park, Md.

The Reactions of Sodium Dialkyl Phosphonates with Carbonyl Sulfide and with Carbon Disulfide

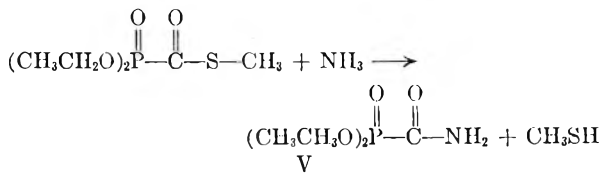
Daniel W. Grisley, Jr.

Received October 10, 1960

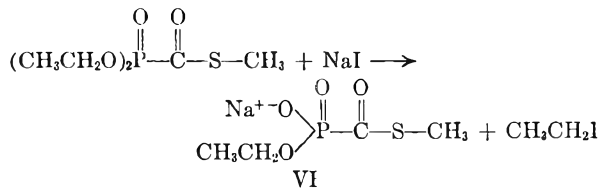
The nucleophilic characteristics of the alkali metal dialkyl phosphonates, especially toward carbonyl groups,[1] prompted an investigation of their reactivity toward carbonyl sulfide and toward carbon disulfide. It was found that both reagents reacted with sodium dialkyl phosphonates to form a new phosphorus-carbon bond. The salts (I) and (II) were not isolated, but were allowed to react further to produce the corresponding thiolformate (III) and dithioformate (IV) esters. Structure III



(R = ethyl) was indicated by a carbonyl absorption in the infrared spectrum at 6.15[2] μ. In addition, the NMR peak of III (R = ethyl) at +4.6 p.p.m., is within the range of the structurally similar acyl phosphonates which have a chemical shift of + 2 ± 1 p.p.m.[3] Finally, *S*-methyl diethoxyphosphinylthiolformate was amidated to yield the known amide (V) in 75% yield.[4] Diethoxyphosphinylformamide had characteristic amide carbonyl (6.0 μ) and N–H (3.0 μ and 3.15 μ) peaks in its infrared spectrum.[5] The NMR spectrum of V had a single peak at +1.4 p.p.m.



It was found that *S*-methyl diethoxyphosphinylthiolformate was easily dealkylated with sodium iodide to yield *O*-ethyl-*O*-sodium carbomethylthiophosphonate (VI). The NMR peak of VI



(1) A. N. Pudovik, *Uspekhi Khim.*, **23**, 547 (1954).

(2) It is stated in L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley & Sons, Inc., New York, 1954, p. 160, that the carbonyl frequencies of a number of thiol esters occur at 1675 cm.$^{-1}$ (5.96 μ).

(3) J. Van Wazer, C. Callis, J. Shoolery, and R. Jones, *J. Am. Chem. Soc.*, **78**, 5715 (1956).

(4) P. Nylen, *Ber.*, **57**, 1023 (1924).

(5) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley & Son, Inc., New York, 1954, p. 176 indicates the carbonyl absorption of primary amides at 1650 cm.$^{-1}$ (6.06 μ).

at +3.2 p.p.m. is in agreement with the structure as shown. VI has a carbonyl peak in its infrared spectrum at 6.17 μ with a shoulder at 6.13 μ. Similar dealkylation reactions of phosphonate esters,[6] phosphate esters,[6,7] and pyrophosphates[8] by nucleophiles in general and by inorganic iodides in particular, have been reported.

Indeed, the dealkylation of *S*-methyl diethoxyphosphinylthiolformate by sodium iodide formed in reaction (1) could have accounted for the low yield of III (R = ethyl), (48%). Moreover, formation of the theoretically[9] less readily dealkylated isopropyl analog (III) in substantially higher yield (70%) under similar conditions supports this idea.

In the reaction of sodium diisopropyl phosphonate with carbon disulfide followed by reaction with methyl iodide (reaction (2)) choice of the structure (IV) (R = isopropyl) was based upon its NMR spectrum. *S*-Methyl diisopropoxyphosphinyldithioformate had a P^{31} chemical shift of +4.2 p.p.m. The similarity of this peak shift to that of the thiol ester (III) (R = isopropyl) (+6.5 p.p.m.) indicates a structure of the type IV. It is interesting that whereas the thiol esters (III) are colorless liquids, the dithio ester (IV) and *S*-*p*-chlorobenzyl diisopropoxyphosphinyldithioformate are by contrast, deeply red colored.

EXPERIMENTAL[10,11]

Materials. Sodium hydride was a 50.9% suspension in mineral oil purchased from Metal Hydrides Co. Tetrahydrofuran used as a reaction mixture solvent was Matheson (b.p. 64–66°). It was distilled from sodium hydride directly into the reaction flask immediately before use. Hexane, used to free the sodium hydride from mineral oil, was distilled. The first 10% of the distillate was discarded and the fraction b.p. 66–67° was collected. Diethyl hydrogen phosphonate (Virginia-Carolina Chemical Co.) was distilled at reduced pressure and a middle cut was taken. Diisopropyl hydrogen phosphonate, b.p. 81–82°/15 mm., n_D^{25} 1.4066, was prepared by the reaction of gaseous hydrogen chloride with triisopropyl phosphite purchased from the Virginia-Carolina Chemical Co. Carbonyl sulfide (Matheson) was purified by passing it through a series of three traps each containing approximately 700 ml. of a saturated lead acetate solution in water and then through a Drierite column before admitting the gas to the reaction mixture. Carbon disulfide (Baker and Adamson Reagent) was dried over anhydrous magnesium sulfate. Gaseous ammonia was Matheson. Methyl iodide was Matheson, b.p. 42–44°. Sodium iodide (Baker and Adamson Reagent) was dried *in vacuo* at 100°. *p*-Chlorobenzyl chloride was obtained from Matheson.

The reaction of sodium diethyl phosphonate with carbonyl sulfide followed by reaction with methyl iodide. Diethyl hydrogen phosphate (27.6 g., 0.2 mole) was added dropwise to a stirred slurry of sodium hydride (50.9% dispersion in mineral oil) (9.6 g., 0.2 mole) in tetrahydrofuran (200 ml.) at 25–30° in a dry atmosphere. The reaction was stirred and refluxed until hydrogen evolution ceased. The reaction mixture was cooled to 6°. Carbonyl sulfide gas was passed over the mixture at 2–5° until the mixture had absorbed a total of 13.3 g. (0.22 mole). Methyl iodide (28.4 g., 0.2 mole) was added to the stirred mixture at 3–5° over 10 min. The mixture was poured into 1 l. of ice water; an oil separated. The oil was extracted into ether (200 ml.). The water layer was saturated with salt and then extracted with ether (200 ml.). The ether layers were combined, dried (magnesium sulfate), filtered, and evaporated to yield a colorless oil. The oil was distilled through a 10-in. vacuum jacketed Vigreux column to yield a main fraction, *S*-methyl diethoxyphosphinylthioformate (20.5 g., 0.1 mole, 48%), b.p. 80–81°/0.1 mm. The infrared spectrum[12] (neat) had a peak at 6.15 μ (C=O); it was identical with that of an authentic sample prepared in the same manner. The authentic sample had b.p. 116–118°/1.7 mm., n_D^{25} 1.4705.

Anal. Calcd. for $C_6H_{13}O_4PS$: C, 33.96; H, 6.17; P, 14.60; S, 15.11. Found: C, 34.24; H, 5.98; P, 14.92; S, 15.34.

The NMR spectrum[13] had a P^{31} chemical shift of +4.6 p.p.m.

The reaction of sodium diisopropyl phosphonate with carbonyl sulfide followed by reaction with methyl iodide. The reaction conditions and work-up procedure used were the same as those used for sodium diethyl phosphonate. The amounts used were diisopropyl hydrogen phosphonate (33.2 g., 0.2 mole), sodium hydride (50.9% dispersion in mineral oil) (9.6 g., 0.2 mole), carbonyl sulfide (25.1 g., 0.43 mole), methyl iodide (28.4 g., 0.2 mole), and tetrahydrofuran (200 ml.). There was obtained *S*-methyl diisopropoxyphosphinylthiolformate (33.8 g., 0.14 moles, 70%), b.p. 100–101°/0.5 mm., n_D^{25} 1.4634. The infrared spectrum (neat) was identical with that of an authentic sample prepared in the same manner. The NMR spectrum had a P^{31} chemical shift of +6.5 p.p.m. The authentic sample had b.p. 76–77°/0.1 mm. and n_D^{25} 1.4630.

Anal. Calcd. for $C_8H_{17}O_4PS$: C, 39.98; H, 7.13, P, 12.89; S, 13.34. Found: C, 40.10; H, 7.16; P, 12.97; S, 13.32.

The reaction of S-methyl diethoxyphosphinylthiolformate with ammonia. Ammonia was bubbled into a solution of *S*-methyl diethoxyphosphinylthiolformate (4.24 g., 20 mmoles) in tetrahydrofuran (30 ml.) at room temperature for 3 hr. The white crystals were filtered; the filtrate was concentrated *in vacuo* to yield solid. The crystalline sclids were combined, washed with ether, filtered, and dried at 70°/20 mm. to yield diethoxyphosphinylformamide (2.80 g., 15 mmoles, 75%), m.p. 138–139° (lit.[4] m.p. 134–135°). A small sample was recrystallized from hot ethyl acetate and was dried at room temperature *in vacuo*, to yield crystals, m.p. 138–139°.

Anal. Calcd. for $C_5H_{12}NO_4P$: C, 33.16; H, 6.68; N, 7.74; P, 17.10. Found: C, 33.03; H, 6.73; N, 7.84; P, 17.19.

The infrared spectrum (potassium bromide) had peaks at 3.0 μ and 3.15 μ (N—H), and a peak at 6.0 μ (C=O). The nuclear magnetic resonance spectrum had a P^{31} chemical shift at +1.4 p.p.m. (15.9% solution in acetone).

The reaction of S-methyl diisopropoxyphosphinylthiolformate with ammonia. The procedure was essentially the same as that used for *S*-methyl diethoxyphosphinylthiolformate. *S*-Methyl diisopropoxyphosphinylthiolformate (4.9 g., 21 mmoles) was amidated to yield a white solid, diisopropoxyphosphinylformamide (3.3 g., 16 mmoles, 76%), m.p. 94–96°. A small sample was recrystallized from hot ethyl acetate to yield colorless needles, m.p. 95–97°.

Anal. Calcd. for $C_7H_{16}NO_4P$: C, 40.19; H, 7.71; P, 14.81; N, 6.70. Found: C, 40.09; H, 7.51; P, 14.72; N, 6.73.

(6) R. Cremlyn, G. Kenner, J. Mather, and A. Todd, *J. Chem. Soc.*, 528 (1958).

(7) L. Zervas and I. Dilaris, *J. Am. Chem. Soc.*, 77, 5354 (1955).

(8) L. Zervas and I. Dilaris, *Ber.*, 89, 925 (1956).

(9) A. Streitwieser, Jr., *Chem. Rev.*, 56, 586 (1956).

(10) All melting and boiling points are uncorrected.

(11) Elemental analyses were performed by the Galbraith Laboratories, P. O. Box 4187, Knoxville, Tenn.

(12) Infrared spectra were run on a Baird Infra-Red Recording Spectrophotometer Model B.

(13) All measurements were performed with a Varian Dual-Purpose Nuclear Magnetic Resonance Spectrometer. 9400 gauss. 16.2 mc. Ref. 85% phosphoric acid.

The infrared spectrum (Nujol slurry) had peaks at 3.05 μ and 3.15 μ (N—H), and a peak at 6.05 μ (C=O). The NMR spectrum had a P^{31} chemical shift of +2.7 p.p.m. and a minor resonance at +5.1 p.p.m. (15.9% solution in acetone).

The reaction of S-methyl diethoxyphosphinylthiolformate with sodium iodide. A solution of *S*-methyl diethoxyphosphinylthiolformate (10.61 g., 50 mmoles) and sodium iodide (7.49 g., 50 mmoles) in tetrahydrofuran (100 ml.) was stirred in a dry atmosphere at 25° for 9.5 hr. The reaction mixture contained solid. The mixture was cooled to 0°. The solid was filtered, was washed with ether, and was dried at 60°/20 mm. for 1 hr. to yield *O*-ethyl *O*-sodium carbomethylthiophosphonate (9.50 g., 46 mmoles, 92%), m.p. 205°–210°. The hydroscopic product was recrystallized twice from hot acetone to yield white crystals, 7.17 g., m. p. 205–207°.

Anal. Calcd. for $C_3H_8NaO_4PS$: C, 23.31; H, 3.91; P, 15.03; S, 15.56. Found: C, 23.19; H, 3.61; P, 15.29; S, 15.74.

The infrared spectrum (potassium bromide) had a peak at 6.17 μ with a shoulder at 6.13 μ (C=O). The NMR spectrum had a P^{31} chemical shift of +3.2 p.p.m.

The reaction of sodium diisopropylphosphonate with carbon disulfide followed by reaction with methyl iodide. Sodium diisopropyl phosphonate was prepared in the usual manner. A solution of sodium diisopropylphosphonate (0.2 mole) in tetrahydrofuran (200 ml.) was added to well stirred carbon disulfide (76 g., 1 mole) at 2–8° over 15 min. The solution became deep red colored. Methyl iodide (30 g., 0.21 mole) was added to the stirred solution at 5° during 5 min. The reaction mixture was stirred for an additional 5 min. at 5°. The homogeneous dark-red mixture was poured into ice water (750 ml.). The organic phase was extracted into ether (300 ml.). The ether phase was washed with water (4 × 500 ml.). The organic phase was dried, (magnesium sulfate), filtered, and evaporated to yield an oil. The oil was distilled through a 10-in. vacuum jacketed Vigreux column to yield a main fraction, a dark red-colored liquid, *S*-methyl diisopropoxyphosphinyldithioformate (30.8 g., 0.12 mole, 60%), b.p. 116–117°/0.4 mm., n_D^{25} 1.5168.

Anal. Calcd. for $C_8H_{17}O_3PS_2$: C, 37.49; H, 6.69; P, 12.09; S, 25.02. Found: C, 37.75; H, 7.07; P, 11.88; S, 24.72.

The NMR spectrum had a P^{31} chemical shift of +4.2 p.p.m.

The reaction of sodium diisopropyl phosphonate with carbon disulfide followed by reaction with p-chlorobenzyl chloride. In this experiment the sodium hydride (50.9% dispersion in mineral oil) (4.8 g., 0.1 mole) was freed of mineral oil by washing with hexane (3 × 300 ml.). The supernatant liquor was removed by means of nitrogen pressure by filtering through a dip tube having a frittered glass tip. The sodium diisopropyl phosphonate (0.1 mole) was prepared in tetrahydrofuran (100 ml.) in the usual manner. The tetrahydrofuran solution of the sodium diisopropyl phosphonate was added to carbon disulfide (38 g., 0.5 mole) as before. A solution of *p*-chlorobenzyl chloride (14.5 g., 0.09 mole) in tetrahydrofuran (100 ml.) was added to the reaction mixture at 1–3° over 5 min. The reaction mixture was stirred in a nitrogen atmosphere at room temperature for 19 hr. The mixture was then refluxed for 1 hr. Ether was added to the mixture. The mixture was washed with water (3 × 500 ml.). The organic phase was dried, (magnesium sulfate), filtered and evaporated *in vacuo* at 80° to yield a dark red oil. The oil was evacuated at 80°/0.1 mm. for 1 hr. and then at room temperature at 0.1 mm. for 20 hr. to yield a deep red oil, *S*-*p*-chlorophenyl diisopropoxyphosphinyldithioformate (27.4 g., 0.075 mole, 83%).

Anal. Calcd. for $C_{14}H_{20}ClO_3PS_2$: C, 45.83; H, 5.49; P, 8.44; S, 17.48. Found: C, 45.98; H, 5.75; P, 8.14; S, 17.77.

The NMR spectrum (neat) had P^{31} chemical shifts of +4.2 p.p.m., 0.0 p.p.m. and −16.1 p.p.m. The peak at +4.2 p.p.m. accounted for >95% of the combined areas under the peaks.

Acknowledgment. The author wishes to thank Mr. John Pustinger and Dr. Gail Birum for their valuable assistance in this work. He wishes to thank Mr. John W. Cooper for the infrared spectra and Messrs. William S. Coakley, Robert E. Dorsett and John E. Strobel for the NMR data.

CHEMICAL RESEARCH DEPARTMENT
RESEARCH AND ENGINEERING DIVISION
MONSANTO CHEMICAL CO.
DAYTON 7, OHIO

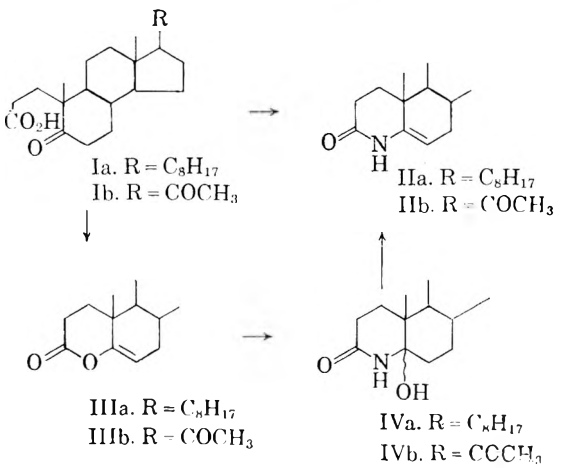
Steroids. II. 4-Aza-5-cholesten-3-one and 4-Aza-5-pregnene-3,20-dione[1,2]

NORMAN J. DOORENBOS, CHIEN LI HUANG,[3] C. RICHARD TAMORRIA,[4] AND MU TSU WU

Received September 28, 1960

The synthesis of 4-aza-5-cholesten-3-one (IIa), m.p. 252–253°, from 3,5-seco-4-norcholestan-5-on-3-oic acid (Ia) by reaction with ammonia at 140° has been reported by our laboratory.[5] Wildi[6] described a similar preparation for this compound. Recently the synthesis of IIa with a much lower melting point, m.p. 189°, by the reaction of ammonia with 4-oxa-5-cholesten-3-one (IIIa) at 25° was announced.[7] The reported spectra of these compounds were similar and it was thought that they might be different crystalline forms.

The procedure of Uskoković and Gut[7] was



(1) For paper I in this series see R. E. Havranek and N. J. Doorenbos, *J. Am. Pharm. Assoc., Sci. Ed.*, **49**, 328 (1960).

(2) This work was supported by Research Grant CY-4132 from the National Cancer Institute, National Institutes of Health.

(3) Sterling-Winthrop Research Fellow, 1958–59.

(4) H. A. B. Dunning Research Fellow, 1959–60.

(5) N. J. Doorenbos and C. L. Huang, Abstract, 136th National A.C.S. Meeting, 30-O, Atlantic City, September 1959.

(6) R. S. Wildi, U. S. Patent 2,897,202, July 28, 1959.

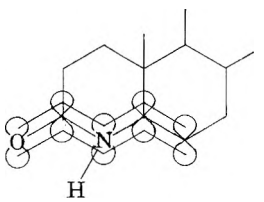
(7) M. Uskoković and M. Gut, *Helv. Chim. Acta*, **42**, 2258 (1959).

repeated in this laboratory. The high yield reported was approached only after allowing the reaction to proceed for one week. As the reaction time was shortened, increased amounts of IIIa were recovered. The product of this reaction, m.p. 190–192°, was shown to be 4-azacholestan-5ξ-ol-3-one (IVa) and not IIa as reported.[7] The structure was established by analysis and spectra. The 5-hydroxy derivative (IVa) was easily dehydrated to IIa by acid catalysts at 25° or by heating above 100°. Perhaps the previous investigators had dehydrated IVa to IIa by drying at 100° before determining the analysis and spectra.

The synthesis of 4-aza-5-pregnen-3,20-dione (IIb) from 4-oxa-5-pregnen-3,20-dione (IIIb) was also reported.[7] The reaction intermediate, 4-aza-5ξ-hydroxypregnane-3,20-dione (IVb) was isolated and reported to have the same melting point as IIb, m.p. 288–289°. 4-Aza-5-pregnene-3,20-dione (IIb) had been prepared previously in this laboratory and it was felt that IVb should have a lower m.p. than IIb. 4-Aza-5ξ-hydroxypregnane-3,20-dione (IVb) was prepared as described[7] and found to have a melting point of 212–214°. IVb was readily dehydrated to IIb by acid catalysts at 25° or by heating above 100°.

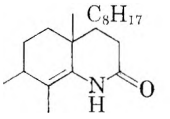
The melting points of IVa and IVb must be taken with care since they rapidly lose water at their melting point. The samples were prepared for analysis by drying for twelve hours at 25°/0.1 mm.

The methods used to convert IVa into IIa and IVb into IIb suggest that the 5,6-double bond is more stable than the 4,5-double bond in these lactams. Differences in resonance stabilization of these isomers might account for these observations. The 5-ene could have three pentacentric molecular orbitals (V), as a result of the filled *p*-orbital of nitrogen with the adjacent unsaturated atoms, whereas the 4-ene could have only two tetracentric molecular orbitals.

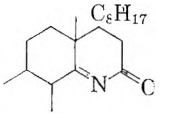


V

In comparison, it should be noted that Tsuda and Hayatsu[8] were able to isomerize 15-aza-D-homo-5α-cholest-8(14)-en-3β-ol-16-one benzoate (VI) into 15-aza-D-homo-5α-cholest-14-en-3β-ol-16-one benzoate (VII) by treatment with hydrochloric acid. VI is probably less stable for steric reasons. The double bond is exocyclic to two six-membered rings including a rather rigid ring B.



VI



VII

EXPERIMENTAL[9]

4-Aza-5-cholesten-3-one (IIa). 3,5-Seco-4-norcholestan-5-on-3-oic acid[10] (4.0 g., 0.010 mole) was dissolved in 200 ml. of concd. aqueous ammonium hydroxide and heated in a pressure vessel under a nitrogen atmosphere at 200° for 6 hr. The mixture was cooled, filtered, and dried to yield 3.80 g. (99%) of 4-aza-5-cholesten-3-one (IIa), m.p. 250–253°. One crystallization from acetone-ethanol yielded 3.56 g. of an analytical sample, m.p. 255–256° (reported m.p. 249–250°[6]; m.p. 189°[7]); $[\alpha]_D^{29}$ −82°; λ_{max} 233 mμ, log ε 4.13; infrared 2.95 (NH stretching), 3.15 (NH, H-bond), 5.96 (C=C), and 6.04 μ (C=O) (reported $[\alpha]_D$ −77°; λ_{max} 235 mμ, log ε 4.13).[7]

Anal. Calcd. for $C_{26}H_{43}ON$: C, 80.98; H, 11.24; N, 3.63. Found: C, 81.29; H, 11.55; N, 3.48.

4-Aza-5ξ-hydroxycholestan-3-one (IVa). IVa was prepared from 4-oxa-5-cholesten-3-one[10] (IIIa) by the procedure of Uskoković and Gut.[7] The following data were obtained on the product after drying for 12 hr. at 25°/0.1 mm.[11]: m.p. m.p. 190–192° dec.; $[\alpha]_D^{29}$ +86°; no peaks above 210 mμ in the ultraviolet; infrared 2.77 (OH stretching), 2.95 (OH, H-bond), and 6.02 μ (C=O).

Anal. Calcd. for $C_{26}H_{45}O_2N$: C, 77.36; H, 11.24; N, 3.47. Found: C, 77.75; H, 10.94; N, 3.73.

Thermal dehydration of IVa. A 100-mg. sample of IVa was heated in a nitrogen atmosphere at 250° for 1 min. Bubbles of water vapor could be observed for about 10 seconds. A solid residue, m.p. 244–247°, was obtained upon cooling. One crystallization from acetone-ethanol yielded a crystalline solid, m.p. 255–256°, which was shown to be identical to IIa by mixed melting point and a comparison of spectra.

Acid catalyzed dehydration of IVa. Samples of IVa were dehydrated by treatment with hydrochloric acid in acetic acid or boron trifluoride in acetic anhydride at room temperature. The latter experiment was an attempt to acetylate the hydroxyl group. The identity of the product in each of these reactions was established by mixed melting point and a comparison of spectra.

4-Aza-5-pregnene-3,20-dione (IIb). 3,5-Seco-4-norpregnan-5-on-3-oic acid[12] (Ib) (10.0 g., 0.03 mole) was dissolved in 260 ml. of absolute ethanol, which had been saturated previously with dry ammonia gas at 0°. The solution was heated in a sealed reaction vessel at 150° for 11 hr. The white crystalline solid which separated on cooling was filtered and crystallized from ethanol-ether to yield 6.0 g. (64%) of 4-aza-5-pregnene-3,20-dione (IIb), m.p. 295–296°; $[\alpha]_D^{25}$ −34°; λ_{max} 233 mμ, log ε 4.13; infrared 2.95 (NH stretching), 3.15 (NH, H-bond), 5.87 (ketone C = O), 5.96 (C=C), and 6.03 μ (lactam C=O); (reported m.p. 288–289°; $[\alpha]_D^{21}$ −4°; λ_{max} 233 mμ, log ε 4.13).[7]

Anal. Calcd. for $C_{20}H_{29}O_2N$: C, 76.15; H, 9.27; N, 4.44. Found: C, 76.31; H, 9.59; N, 4.33.

(8) K. Tsuda and R. Hayatsu, *J. Am. Chem. Soc.*, **78**, 4107 (1956).

(9) Melting points were taken on a Thomas-Hoover m.p. apparatus and are uncorrected. Specific rotations were determined on 1% solutions in chloroform. Ultraviolet data were obtained with a Spectracord on solutions in 95% ethanol. Infrared data were obtained with an Infracord using chloroform solutions. Analyses were obtained from Drs. Weiler and Strauss, Oxford, England. The steroid intermediates were furnished by the National Service Center for Cancer Chemotherapy.

(10) R. B. Turner, *J. Am. Chem. Soc.*, **72**, 579 (1950).

(11) A portion of this sample was dried an additional 12 hr. under these conditions without a further loss in weight.

(12) C. C. Bolt, *Rec. trav. chim.*, **T70**, 940 (1951).

4-Aza-5ξ-hydroxypregnane-3,20-dione (IVb). IVb was prepared from 4-oxa-5-pregnen-3,20-dione[13] (IIIb) by the procedure of Uskoković and Gut.[7] The following data were obtained on this product after drying for 12 hr. at 25°/0.1 mm.[11]: m.p. 212–214° dec.; $[\alpha]_D^{28}$ + 171°; no peaks in the ultraviolet above 210 mμ; infrared 2.77 (OH stretching), 2.95 (OH, H-bond), 5.87 (ketone C=O), and 6.03 μ (lactam C=O); (reported m.p. 288–289°; $[\alpha]_D^{21}$ +173°).[7]

Anal. Calcd. for $C_{20}H_{31}O_3N$: C, 72.03; H, 9.37; N, 4.20. Found: C, 72.51; H, 9.25; N, 4.09.

Dehydration of IVb. IVb was dehydrated to IIb by the same procedures described above for IVa. The identity of the product, IIb, in each of these procedures was established by mixed melting point and a comparison of spectra.

Department of Pharmaceutical Chemistry
School of Pharmacy
University of Maryland
Baltimore 1, Md.

(13) M. Gut, *Helv. Chim. Acta*, **36**, 906 (1953).

Steroids. III. Synthesis of Some 3-Aza-A-homocholestanes by the Beckmann and Schmidt Rearrangements in Polyphosphoric Acid[1,2]

Norman J. Doorenbos and Mu Tsu Wu

Received September 28, 1960

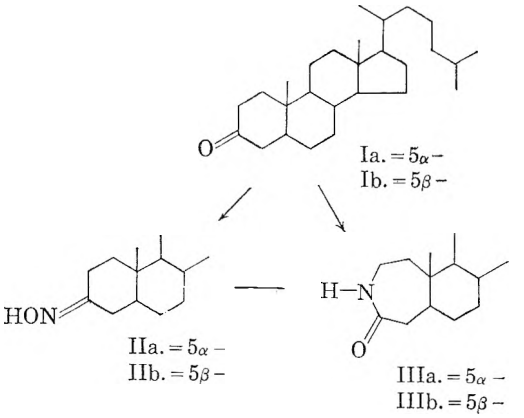
The great value of steroids in modern medicine and the interesting pharmacological properties of steroid alkaloids have brought about an increasing interest in aminosteroids and azasteroids. Over thirty papers and patents on azasteroids alone have appeared.[3]

The Beckmann and Schmidt rearrangements have offered two convenient methods for introducing a heterocyclic nitrogen into the steroid ring system. Many azasteroids have been prepared by the Beckmann rearrangement using a variety of solvents and such catalysts as tosyl chloride,[4–9] thionyl chloride,[10,11] phosphorus pentachloride,[4,5] *p*-acetylaminobenzenesulfonyl chloride,[7] and *p*-aminobenzenesulfonyl chloride.[12,13]

The Schmidt rearrangement has been applied to a few steroid ketones[4,5] with sulfuric acid being used as the catalyst in the presence of a suitable organic solvent.

The yields obtained by these methods have been variable and often below 60%. Recently Conley[14] reported polyphosphoric acid to be superior to other catalysts in the Beckmann and Schmidt rearrangements. Polyphosphoric acid is a mild catalyst and a good solvent for most organic compounds.

In 1957, a general study of heterocyclic steroids was begun in this laboratory. In order to obtain a preliminary evaluation of the usefulness of polyphosphoric acid for the synthesis of azasteroids, two azasteroids were synthesized by the Beckmann and Schmidt rearrangements using both polyphosphoric acid and more conventional methods. The azasteroids selected were 3-aza-A-homocholestan-4-one (IIIa) and 3-aza-A-homocoprostan-4-one (IIIb) since they may be prepared from readily available ketones. Shoppee and Sly[11] prepared these azasteroids by the Beckmann rearrangement of cholestan-3-one oxime (IIa) and coprostan-3-one oxime (IIb), using thionyl chloride as the catalyst and dioxane as the solvent. The crude yields, after purification by chromatography, were 63% for IIIa and 36% for IIIb. These chromatographed fractions were subjected to sublimation and repeated crystallizations in order to obtain analytically pure products. We obtained similar results with this procedure.



In this laboratory, it has been demonstrated that azasteroids may be prepared in high yield by either the Beckmann or Schmidt rearrangements, if polyphosphoric acid is used as the catalyst. No solvent was needed since polyphosphoric acid is a good solvent for cholestan-3-one (Ia) and coprostan-

(1) For paper II in this series see N. J. Doorenbos, C. L. Huang, C.R. Tamorria, and M. T. Wu, *J. Org. Chem.*, **26**, 2546 (1961).

(2) (a) This work was supported by Research Grant CY-4132 from the National Cancer Institute, U. S. Public Health Service; (b) presented at the 1960 A.A.A.S. meeting in New York City, December 29.

(3) Chien Li Huang, Ph.D. thesis, University of Maryland, 1960.

(4) S. Hara, *Pharm. Bull. (Japan)*, **3**, 209 (1955).

(5) S. Hara, *Yakugaku Zasshi*, **78**, 1027 (1958).

(6) S. Hara, *Yakugaku Zasshi*, **78**, 1030 (1958).

(7) S. Kaufmann, *J. Am. Chem. Soc.*, **73**, 1779 (1951).

(8) R. H. Mazur, *J. Am. Chem. Soc.*, **81**, 1454 (1959).

(9) K. Tsuda and R. Hayatsu, *J. Am. Chem. Soc.*, **78**, 4107 (1956).

(10) B. M. Regan and F. N. Hayes, *J. Am. Chem. Soc.*, **78**, 639 (1956).

(11) C. W. Shoppee and J. C. Sly, *J. Chem. Soc.*, 3458 (1958).

(12) H. Heusser, J. Wohlfahrt, M. Muller, and R. Anliker, *Helv. Chim. Acta*, **38**, 1399 (1955).

(13) R. Anliker, M. Muller, J. Wohlfahrt, and H. Heusser, *Helv. Chim. Acta*, **38**, 1404 (1955).

(14) R. T. Conley, *J. Org. Chem.*, **23**, 1330 (1958).

3-one (Ib) and their oxime derivatives, IIa and IIb. The yield of analytically pure product was at least 86% in each example. Analytical samples were obtained readily by one or two crystallizations.

Each azasteroid was prepared also by the Schmidt rearrangement with sulfuric acid as the catalyst. The yields were lower than those obtained with polyphosphoric acid. It is expected that polyphosphoric acid would offer even greater advantages in the Schmidt rearrangement of many of the steroids which contain functional groups sensitive to sulfuric acid.

EXPERIMENTAL[15]

Beckmann rearrangement of cholestan-3-one oxime (IIa). A mixture of 2.00 g. (0.005 mole) of cholestan-3-one oxime and 60 g. of polyphosphoric acid was heated with manual stirring at 120–130° for 30 min. The mixture was then poured onto 500 g. of crushed ice, neutralized with cold 50% sodium hydroxide, and extracted with ether (5 × 100 cc.). Removal of the solvent, after drying over magnesium sulfate, yielded 1.85 g. (93%) of 3-aza-A-homocholestan-4-one (IIIa), m.p. 270–274°. An analytical sample was prepared by crystallization from benzene-ether, m.p. 275.5–276.5° (reported[11] m.p. 268–271°).

Anal. Calcd. for $C_{27}H_{47}ON$: C, 80.73; H, 11.79; N, 3.50. Found: C, 80.80; H, 11.62; N, 3.43.

The infrared spectrum was identical with that of a sample prepared by Shoppee's method[11] and a mixed melting point gave no depression.

Beckmann rearrangement of coprostan-3-one oxime (IIb). A mixture of 700 mg. (0.0017 mole) of coprostan-3-one oxime and 21 g. of polyphosphoric acid was heated, with manual stirring, to 120° and maintained at this temperature for 10 min. Then the mixture was poured onto 200 g. of crushed ice, neutralized with cold sodium hydroxide, and extracted with ether (4 × 100 cc.). Removal of the solvent, after drying over sodium sulfate, gave a solid residue. This residue was crystallized from ether to yield 630 mg. (90%) of 3-aza-A-homocoprostan-4-one (IIIb), m.p. 173–175° (reported[11] m.p. 166–174°).

Anal. Calcd. for $C_{27}H_{47}ON$: C, 80.73; H, 11.79; N, 3.50. Found: C, 80.32; H, 11.58; N, 3.37.

The infrared spectrum was identical with that of a sample prepared by Shoppee's method[11] and a mixed melting point gave no depression.

Schmidt rearrangement of cholestan-3-one (Ia). Sodium azide (0.68 g., 0.011 mole) was added with slow agitation to a mixture of 3.86 g. (0.01 mole) of cholestan-3-one and 100 g. of polyphosphoric acid at 50–60°. This temperature was maintained by means of a water bath for 10 hr. Then the mixture was poured onto crushed ice, made alkaline with cold 50% potassium hydroxide, extracted with chloroform (4 × 100 cc.), and washed with water. Removal of the solvent, after drying over sodium sulfate, yielded 3.46 g. (86%) of 3-aza-A-homocholestan-4-one (IIIa), m.p. 275–277°.

Schmidt rearrangement of coprostan-3-one (Ib). The Schmidt rearrangement of coprostan-3-one (Ib) in polyphosphoric acid was carried out using the procedure outlined above for Ia. 3-Aza-A-homocoprostan-4-one (IIIb) was obtained in 88% yield, after one crystallization from ether, m.p. 172–174°.

(15) Melting points were taken on a Fisher-Johns block and are uncorrected. Analyses were performed by Sterling-Winthrop Research Institute and Drs. Weiler and Strauss, Oxford, England. Steroid intermediates were furnished by the National Service Center for Cancer Chemotherapy, National Institutes of Health.

Schmidt rearrangement of cholestan-3-one (Ia) (*sulfuric acid method*). Twelve cubic centimeters of a 4.7% solution of hydrazoic acid (0.013 mole) was added slowly with stirring at room temperature to a solution of 3.86 g. (0.01 mole) of cholestan-3-one and 5 cc. of sulfuric acid in 30 cc. of benzene. After 1 hr. the solution was poured into ice water. The benzene layer was separated and washed with dilute sodium hydroxide and water. Removal of the solvent, after drying over sodium sulfate, yielded 3.25 g. (81%) of 3-aza-A-homocholestan-4-one (IIIa), m.p. 270–273°. Two crystallizations from ether-methanol yielded an analytical sample, m.p. 275–276.5°.

Schmidt rearrangement of coprostan-3-one (Ib) (*sulfuric acid method*). The Schmidt rearrangement of coprostan-3-one (Ib) in sulfuric acid was carried out using the procedure outlined above for Ia. 3-Aza-A-homocoprostan-4-one (IIIb) was obtained in 72% yield, m.p. 164–170°, after one crystallization from ether. Two recrystallizations from ether raised the m.p. to 171–174°.

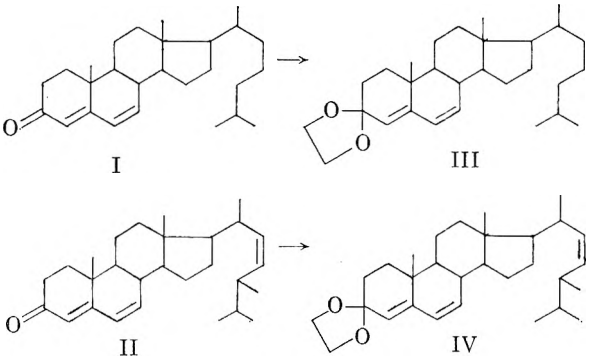
DEPARTMENT OF PHARMACEUTICAL CHEMISTRY
SCHOOL OF PHARMACY
UNIVERSITY OF MARYLAND
BALTIMORE 1, MD.

Cycloethylene Ketals of $\Delta^{4,6}$-3-Ketosteroids

GERHARD J. FONKEN

Received September 29, 1960

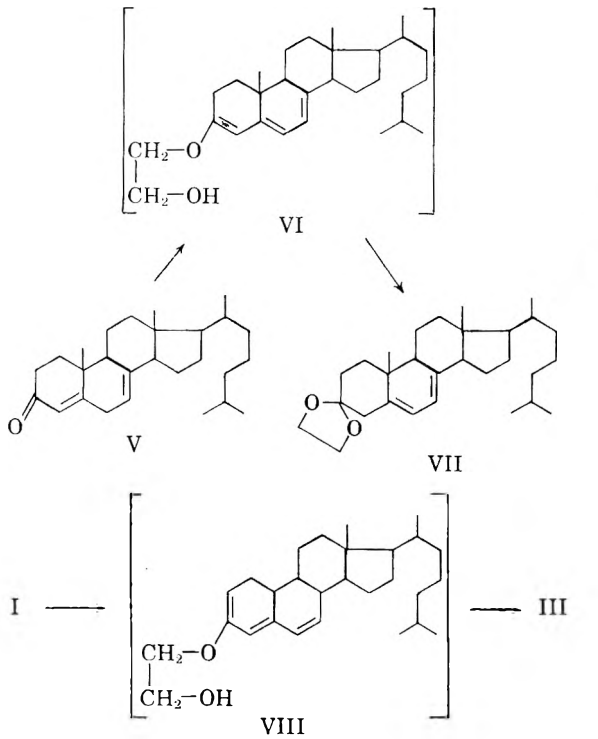
In the course of another investigation, the cycloethylene ketal derivatives of $\Delta^{4,6}$-cholestadiene-3-one, I, and $\Delta^{4,6,22}$-ergostatriene-3-one, II, were prepared. In contrast to the well established rearrangement of the Δ^4-double bond to the Δ^5-position on formation of the cycloethylene ketals of Δ^4-3-ketosteroids,[1] the $\Delta^{4,6}$-3-ketosteroids give rise to ketal derivatives in which the double bonds remain in their original position. Thus, I forms $\Delta^{4,6}$-cholestadiene-3-one-3-cycloethylene ketal, III and II gives rise to the corresponding $\Delta^{4,6,22}$-ergostatriene-3-one-3-cycloethylene ketal, IV.



(1) (a) E. Fernholz and H. E. Stavely, *Abstracts of the 102nd Meeting of the American Chemical Society*, Atlantic City, N. J., 1941, p. 39M; (b) F. Fernholz, U. S. Patents 2,356,154 and 2,378,918; (c) R. Antonucci, S. Bernstein, R. Littel, K. Sax, and J. H. Williams, *J. Org. Chem.*, 17, 1341 (1952); (d) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, 75, 422 (1953); (e) J. A. Zderic, D. C. Limon, H. J. Ringold, and C. Djerassi, *J. Am. Chem. Soc.*, 81, 3120 (1959).

The same ketal derivatives were obtained by both the acid catalyzed reaction of the ketones with ethylene glycol and by the exchange dioxolanation method.[2]

The proposed mechanism of ketal formation[3] suggests that double bond isomerization in the course of cycloethylene ketal formation of a Δ^4-3-ketosteroid results from the formation of an intermediate $\Delta^{3,5}$-dienol ether species. Thus, $\Delta^{4,7}$-cholestadiene-3-one, V, forms $\Delta^{5,7}$-cholestadiene-3-one-3 cycloethylene ketal VII *via* the probable intermediate VI.



In the case of the $\Delta^{4,6}$-3-ketosteroids, the process may involve the intermediate $\Delta^{2,4,6}$-trienol ether VIII rather than the isomeric species VI. The intermediate trienols VI and VIII apparently are not capable of interconversion under the reaction conditions employed and examination of the mother liquors from the preparation of III by ultraviolet spectroscopy gave no indication of the isomeric cycloethylene ketal VII.

The structural assignments of the cycloethylene ketals were verified by reversion of each ketal to its parent $\Delta^{4,6}$-3-ketosteroid precursor upon acid hydrolysis and by the characteristic ultraviolet absorption of each derivative. The $\Delta^{4,6}$-cholestadiene-3-one-3-cycloethylene ketal III exhibited λ_{max} 236 mμ (ϵ = 18,700) and the corresponding $\Delta^{4,6,22}$-ergostatriene-3-one-3-cycloethylene ketal IV had λ_{max} 235 mμ (ϵ = 19,200) which is characteristic of the $\Delta^{4,6}$-diene system ascribed.[4] The isomeric $\Delta^{5,7}$-cholestadiene-3-one-3-cycloethylene ketal VI,[1c] absorbs at λ_{max} 271, 282, 293 mμ. The ergosterol analog exhibits similar absorption.[1c] Hydrolysis of the $\Delta^{5,7}$-3-keto-3-cycloethylene ketals yields the $\Delta^{4,7}$-3-ketosteroids.[1c]

EXPERIMENTAL

$\Delta^{4,6}$-Cholestadiene-3-one-3-cycloethylene ketal. A solution of 200 mg. (0.523 mmole) of $\Delta^{4,6}$-cholestadiene-3-one, 10 mg. of *p*-toluenesulfonic acid, 10 ml. of ethylene glycol, and 50 ml. of benzene was allowed to reflux for 5 hr. The water which separated was collected in a Dean-Stark phase separator. When the reflux period had ended, the solution was poured into 100 ml. of a 5% aqueous sodium carbonate solution and the mixture was extracted with two 100-ml. portions of ether. The ether extracts were washed with water, combined and dried over anhydrous sodium sulfate, and evaporated to dryness at reduced pressure. The residual pale yellow oil crystallized upon trituration with acetone and there was obtained 193 mg. of pale yellow needles, m.p. 112–114.5°. Two recrystallizations from acetone afforded 142 mg. (64%) of colorless needles, m.p., 116–117.5°, $[\alpha]_D^{25}$ + 57° ($CHCl_3$) λ_{max}^{CaSOH} 236 mμ (ϵ = 18,700).

Anal. Calcd. for $C_{29}H_{46}O_2$: C, 81.63; H, 10.87. Found: C, 81.69; H, 11.04.

$\Delta^{4,6,22}$-Ergostatriene-3-one-3-cycloethylene ketal. A solution of 800 mg. (2.01 moles) of $\Delta^{4,6,22}$-ergostatriene-3-one, 40 mg. of *p*-toluenesulfonic acid, 30 ml. of ethylene glycol, and 100 ml. of benzene was allowed to reflux for 6 hr. The water which separated was collected in a Dean-Stark separator. Upon completion of the reflux period, the cooled mixture was poured into 300 ml. of a 5% aqueous sodium carbonate solution. The benzene layer was separated and the aqueous phase was extracted with 100 ml. of ether. The combined benzene and ether extracts were washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness at reduced pressure. The yellow residual oil crystallized upon trituration with acetone. The crude crystalline product was twice recrystallized from acetone and afforded 672 mg. (77%) of colorless leaflets, m.p. 129–130°, $[\alpha]_D^{25}$ ± 0.0° ($CHCL_3$), λ_{max}^{CaSOH} 235 mμ (ϵ = 19,200).

Anal. Calcd. for $C_{30}H_{46}O_2$: C, 82.13; H, 10.57. Found: C, 82.30; H, 10.41.

Department of Chemistry
University of Texas
Austin 12, Tex.

(2) H. J. Dauben, B. Loken, and H. J. Ringold, *J. Am. Chem. Soc.*, **76**, 1359 (1954).

(3) C. Djerassi and M. Gorman, *J. Am. Chem. Soc.*, **75**, 3704 (1953).

(4) L. Dorfman, *Chem. Rev.*, **53**, 47 (1953).

Conformational Analysis. XV. The Dipole Moment of 2-Fluorocholestanone[1,2]

Norman L. Allinger, Herbert M. Blatter, Margaret A. DaRooge,[2a] and Leslie A. Freiberg

Received October 21, 1960

Since various biologically active steroids have been found to have their activity increased by the

(1) Paper XIV, A. M. Wilson and N. L. Allinger, *J. Am. Chem. Soc.*, **83**, 0000 (1961).

(2) This research was supported by a grant from the National Science Foundation.

substitution of fluorine for hydrogen,[3] a number of compounds have recently been prepared containing a fluorine atom on a carbon adjacent to a carbonyl group.[3-5] This paper is concerned with the determination of the conformation of the fluorine atom in such compounds.

2-Bromo- and 2-chlorocyclohexanone derivatives have been studied in great detail with regards to conformation (or in rigid systems, configuration).[6] It has been shown that the conformation of the halogen (bromine or chlorine) can be determined in a variety of ways, namely by dipole moment,[7] infrared spectra,[8] ultraviolet spectra,[9] rotatory dispersion measurements,[10] nuclear magnetic resonance spectra,[11] or polarographic reduction potential.[1] The method of choice depends on the system involved.

The 2-fluorocyclohexanones are rather less well studied with regard to conformation. From the small amount of available data it would seem that the carbonyl shifts in the infrared will be of limited use.[3,12] Equatorial fluorine causes the carbonyl stretching frequency to be raised by about 30 cm.$^{-1}$, while for the axial fluorine the shift is about 20 cm.$^{-1}$. Very few ultraviolet data are available[12,13] for conformationally pure compounds. Many of the steroidal systems described[3,4] are of the 2-fluoro-3-keto-Δ^4 type and only the wave length of the $\pi \rightarrow \pi^*$ transition has usually been reported. Rotatory dispersion measurements appear to be of limited use for fluoro ketones,[13] and the NMR and polarographic methods have not been extensively used as of yet.

The measurement of the dipole moment appears to offer an unambiguous way for determining the conformation of a 2-fluorocyclohexanone, within certain well defined limitations, and was the method used in this work. Since 2-fluorocholestanone is more or less the "parent" steroid example of the system in question, it was the compound studied. Earlier workers[5] have assumed the fluorine was α (equatorial) in this compound, based on the shift of the carbonyl stretching frequency, and by analogy to the conclusions drawn by Kende[14] regarding 2-fluorocyclohexanone.

While the qualitative conclusion of Kende that the equatorial conformer is more stable has been confirmed,[12] the difference in stability between the conformers is much less than Kende has indicated. The carbonyl band in 2-fluorocholestanone is shifted[5] by 26 cm.$^{-1}$, and the configuration previously assigned to the compound was not therefore regarded as unequivocal.

The angle between the dipoles of a 2-halocyclohexanone was calculated earlier[15] using the model of Corey and Sneen[16] for both the axial and equatorial conformations. Ideal geometry was assumed. This assumption is an approximation which will be satisfactory if the difference in the calculated moments for the epimers is sufficiently large, which is the case here.

The dipole moment of 3-cholestanone was measured and found to have the value 3.01 D in benzene solution. This value is very close to that of cyclohexanone (3.08 D).[17] Because of the relatively high polarizability of the carbonyl oxygen (0.84×10^{-24} cm.^{3}),[18] the moment induced in the C=O group by the neighboring equatorial C—F dipole must be taken into account. The value 3.01 D is consequently used for the C=O dipole when the fluorine is axial, and 2.84 D is used when it is equatorial. The latter value is arrived at by assuming the moment induced in the carbonyl by the C—F dipole has the same magnitude as that induced by the C—Br dipole, which must be very nearly true. The value in the case of the C—Br dipole is known experimentally.[19]

Since the polarizability of the fluorine (0.38×10^{-24} cm.^{3})[18] is the same as that of a hydrogen (0.42×10^{-24} cm.^{3}),[18] the same value for the C—F bond moment,[20] 1.90 D, is used throughout the calculations.

From these bond moments and the known angles between the dipoles (109°51′ axial and 51°54′

(2a) Predoctoral U. S. Public Health Service Fellow, General Division of Medical Sciences, 1960-62.

(3) For references see: (a) A. H. Nathan, B. J. Magerlein, and J. A. Hogg, *J. Org. Chem.*, **24**, 1517 (1959); (b) H. M. Kissman, A. M. Small, and M. J. Weiss, *J. Am. Chem. Soc.*, **82**, 2312 (1960); (c) J. S. Mills, A. Bowers, C. Djerassi, and H. J. Ringold, *J. Am. Chem. Soc.*, **82**, 3399 (1960); (d) J. Edwards and H. J. Ringold, *J. Am. Chem. Soc.*, **81**, 5262 (1959).

(4) A. H. Nathan, J. C. Babcock, and J. A. Hogg, *J. Org. Chem.*, **24**, 1395 (1959).

(5) R. B. Gabbard and E. V. Jensen, *J. Org. Chem.*, **23**, 1406 (1958).

(6) For leading references, see Ref. (1).

(7) N. L. Allinger, J. Allinger, and N. A. LeBel, *J. Am. Chem. Soc.*, **82**, 2926 (1960).

(8) (a) R. N. Jones, D. A. Ramsay, F. Herling, and K. Dobriner, *J. Am. Chem. Soc.*, **74**, 2828 (1952); (b) E. J. Corey, *J. Am. Chem. Soc.*, **75**, 2301 (1953).

(9) (a) N. L. Allinger and J. Allinger, *J. Am. Chem. Soc.*, **80**, 5476 (1958); (b) R. C. Cookson, *J. Chem. Soc.*, 3847 (1957).

(10) (a) C. Djerassi, J. Osiecki, R. Riniker, and B. Riniker, *J. Am. Chem. Soc.*, **80**, 1216 (1958); (b) C. Djerassi, I. Fornaguera, and O. Mancera, *J. Am. Chem. Soc.*, **81**, 2385 (1959); N. L. Allinger, J. Allinger, L. E. Geller, and C. Djerassi, *J. Org. Chem.*, **25**, 6 (1960).

(11) E. J. Corey, private communication.

(12) H. M. Blatter, unpublished work.

(13) C. Djerassi, *Optical Rotatory Dispersion: Applications to Organic Chemistry*, McGraw-Hill Co., New York, 1960, p. 115.

(14) A. S. Kende, *Tetrahedron Letters*, No. 14, 13 (1959).

(15) J. Allinger and N. L. Allinger, *Tetrahedron*, **2**, 64 (1958).

(16) E. J. Corey and R. A. Sneen, *J. Am. Chem. Soc.*, **77**, 2505 (1955).

(17) H. H. Günthard and T. Gaumann, *Helv. Chem. Acta*, **34**, 39 (1951).

(18) J. A. A. Ketelaar, *Chemical Constitution*, Elsevier Publishing Co., New York, 1958, p. 91.

(19) W. D. Kumler and A. C. Huitric, *J. Am. Chem. Soc.*, **78**, 3369 (1956).

TABLE I

DIPOLE MOMENT DATA

N_2	d_{12}	ϵ_{12}
Cholestan-3-one		
0.00000000	0.873735	2.2729
0.00069839	0.874023	2.2831
0.00137615	0.874371	2.2929
0.00298159	0.875150	2.3141
0.00429121	0.875814	2.3312
α 13.531	ϵ_1 2.2736	d_1 0.87371
β 0.488	$P_{2\infty}$ 315.7	M_R 118.73
(Pe + Pa) 130.60	μ 3.01 D	
2-Fluorocholestan-3-one		
0.00000000	0.873579	2.2743
0.00038680	0.873977	2.2858
0.00080923	0.874248	2.2974
0.00096282	0.874377	2.3012
0.00111752	0.874433	2.3057
α 27.913	ϵ_1 2.2746	d_1 0.87361
β 0.776	$P_{2\infty}$ 524.2	M_R 118.51
(Pe + Pa) 130.36	μ 4.39 D.	

equatorial),[15] the moment for 2α-fluorocholestanone was calculated to be 4.28 D, while that of 2β-fluorocholestanone was calculated to be 2.95 D.

The dipole moment of the only known 2-fluorocholestanone was measured in benzene solution, and the value found was 4.39 D. The configuration at C-2 is therefore unequivocally established as α and the earlier configurational assignment is confirmed.

EXPERIMENTAL

Cholestanone, m.p. 130–130.5°, was prepared from cholesterol in the usual way. The 2-fluorocholestanone, m.p. 173.0–173.5° was used as received after drying under vacuum for a few hours.

Dipole moment apparatus. The Dipolemeter DM01 manufactured by Wissenshaftlich-Technische Werkstatten obtainable through the Kahl Scientific Instrument Corporation, El Cajon, Calif., was used for the measurements reported herein. The apparatus utilizes the heterodyne beat method and operates at 1,800 kilocycles. It is internally thermostated and of good stability. The cell used was of metal with a gold plated interior and had an effective capacity of about 35$\mu\mu$F with a volume of 40 ml. It was thermostated at 25° ±0.01°.

The dipole moments were measured in benzene solution. The moments were calculated by essentially the method of Halverstadt and Kumler[21] utilizing an IBM 650 computer programmed as described earlier.[22] Since the cholestanone derivatives are of such high molecular weight the usual neglect of the atomic polarization may introduce some error[23] in the present case. Unfortunately there is no very good, simple method for determining the atomic polarization. What has been done in the present case is to set it equal to 10% of the molar refractivity, for both cholestanone and the fluoro derivative. The effect of taking the atomic polarization into account is to lower the experimental moment of cholestanone from 3.10 to 3.01 D, and the moment of the fluoro compound is similarly lowered from 4.46 to 4.39 D. These changes are not of great significance since the experimental error is about 0.03 D, but the values which take atomic polarization into account have been used throughout the paper. The data are summarized in Table I.

Acknowledgment. The authors are indebted to Dr. E. V. Jensen of the University of Chicago for furnishing them with the sample of 2-fluorocholestanone used in this work.

DEPARTMENT OF CHEMISTRY
WAYNE STATE UNIVERSITY
DETROIT 2, MICH.

(20) This is an average of values reported for a number of aliphatic fluorides by M. T. Rogers and J. D. Roberts, *J. Am. Chem. Soc.*, 68, 843 (1946) and by M. T. Rogers, *J. Am. Chem. Soc.*, 69, 457 (1947).

(21) I. F. Halverstadt and W. D. Kumler, *J. Am. Chem. Soc.*, 64, 2988 (1942).

(22) N. L. Allinger and J. Allinger, *J. Org. Chem.*, 24, 1613 (1959).

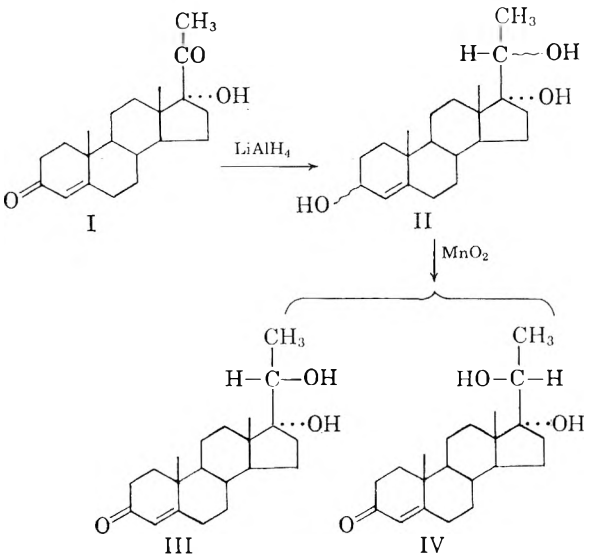
(23) L. E. Sutton in E. A. Braude and F. C. Nachod's *Determination of Organic Structures by Physical Methods*, Academic Press Inc., New York, 1955, p. 378.

17α,20α-Dihydroxy-4-pregnene-3-one

P. NARASIMHA RAO AND LEONARD R. AXELROD

Received November 18, 1960

Presumptive evidence for the presence of 17α,-20α-dihydroxy-4-pregnene-3-one in biological material was presented by Sandor and Lanthier,[1] but no physical constants were given and only chromatographic behavior of the compound was included. A search of the literature revealed that this compound was not previously synthesized and we wish to report its synthesis. 17α-Hydroxyprogesterone (I) was reduced with lithium aluminum



hydride. The resulting mixture of epimeric 3ξ,-17α,20ξ-glycols (II) was oxidized with manganese dioxide[2] at room temperature to give a mixture

(1) T. Sandor and A. Lanthier, *Can. J. Biochem. and Biophys.*, 38, 1167 (1960).

(2) F. Sondheimer, C. Amendolla, and G. Rosenkranz, *J. Am. Chem. Soc.*, 75, 5930 (1953).

of 17α,20α-dihydroxy-4-pregnene-3-one (III) and 17α,20β-dihydroxy-4-pregnene-3-one (IV). The 17α,20-glycols (III and IV) were separated by paper chromatography using the solvent system benzene-formamide[3] (formamide diluted with an equal volume of methanol). Although it was previously shown[4] that reduction of 17α-hydroxy-20-keto-steroids with lithium aluminum hydride affords predominantly the 17α,20α-dihydroxy epimer, we have observed in the present instance that the 17α,20β-isomer constitutes the major product (70%). By a similar reduction of a 17α-hydroxy-progesterone derivative Romo *et al.*[5] have obtained only the 17α,20β-dihydroxy epimer IV. However, it has been possible for us to isolate the 17α,20α-dihydroxy epimer in 30% yield, and as expected it was more polar than the 17α,20β-dihydroxy epimer[4a] and the molecular rotation was lower than its 17α,20β-isomer IV.

EXPERIMENTAL[6]

Melting points. All melting points were determined on samples dried under high vacuum at 60° for 24 hr. and were uncorrected.

Absorption spectra. The ultraviolet absorption spectra were determined in methanol on a Cary Recording Spectrophotometer (Model 11 MS). The infrared absorption spectra were determined in potassium bromide disks on a Perkin-Elmer infrared spectrometer (Model 21).

Optical rotations. All optical rotations were measured in chloroform solution.

Lithium aluminum hydride reduction of I. A solution of 2 g. of 17α-hydroxyprogesterone (I) in 60 ml. of tetrahydrofuran was added with stirring to 3.5 g. of lithium aluminum hydride in 110 ml. of tetrahydrofuran over a period of 15 min., and the mixture was then heated under reflux for 2 hr. The excess reagent was decomposed by addition of ethyl acetate. A saturated solution of sodium sulfate was then added until the precipitate began to adhere to the sides of the flask. Finally 20 g. of solid sodium sulfate was added and the solution was filtered from the salts. Evaporation of the filtrate gave 2 g. of a mixture of epimeric 4-pregnene-3ξ, 17α,20ξ-triols (II) as a crystalline solid. Without further purification this mixture was subjected to manganese dioxide oxidation.

Manganese dioxide oxidation of the mixture of triols II. To a solution of 2 g. of the mixture of aforementioned triols in 100 ml. of tetrahydrofuran 10 g. of manganese dioxide[7] was added and stirred at room temperature (25°) for 4 hr. The solution was then filtered from the catalyst and after evaporating the solvent, 1.8 g. of a mixture of 17α, 20α-dihydroxy-4-pregnene-3-one (III) and 17α,20β-dihydroxy-4-pregnene-3-one (IV) was obtained as a solid.

Separation of III and IV by paper chromatography. One gram of the mixture of III and IV was chromatographed on 200 Whatman No. 1 paper grams in the solvent system benzene-formamide[3] (formamide diluted with an equal volume of methanol) for 5 hr. The positions of III and IV were demonstrated by means of a 2,4-dinitrophenylhydrazene reagent[7] and iodine reagent.[8] Both compounds reacted with the 2,4-dinitrophenylhydrazene reagent to give orange colors on the paper, whereas the iodine reagent gave a blue color with the more polar 17α,20α-dihydroxy-4-pregnene-3-one (III) and a brown color with the less polar 17α,20β-dihydroxy-4-pregnene-3-one (IV). The compounds were then separately eluted from the papers with a mixture of equal volumes of methanol and chloroform. The solvent was evaporated under a stream of nitrogen *in vacuo* at 45° in each case and the residue was crystallized. 17α,20α-Dihydroxy-4-pregnene-3-one (III) which was obtained in 30% yield crystallized from methanol as stout needles, m.p. 208–210°, $(\alpha)_D^{22°}$ + 20.4°, MD + 67.7°; $\lambda_{max}^{CH_3OH}$ 242 mμ, ε = 19,210), ν_{max}^{KBr} 3483, 2965, 1660, and 1615 cm.$^{-1}$

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.71. Found: C, 75.70; H, 9.53.

17α,20β-Dihydroxy-4-pregnene-3-one (IV) was obtained in 70% yield and crystallized from acetone as prisms, m.p. 204–205.5°, $(\alpha)_D^{22}$ + 72.7°, MD + 241.6°, $\lambda_{max}^{CH_3OH}$241 mμ (ε = 16,030), ν_{max}^{KB} 3465, 2960, 1660, and 1615 cm.$^{-1}$

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.71. Found: C, 75.93; H, 9.70. [Lit.[6] m.p. 201–204°, $(\alpha)_D^{20}$ +68.2°, λ_{max} 240 mμ (log ε, 4.29).]

The mixture melting point of III and IV showed depression and melted over a range 190–198°.

Acknowledgment. This work was supported by grant No. A-3270 from the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Md.

DEPARTMENT OF PHYSIOLOGY AND BIOCHEMISTRY
SOUTHWEST FOUNDATION FOR RESEARCH AND EDUCATION
SAN ANTONIO, TEX.

(3) A. Zaffaroni and R. B. Burton, *J. Biol. Chem.*, **193**, 749 (1957).

(4) (a) D. K. Fukushima and Evelyn D. Meyer, *J. Org. Chem.*, **23**, 174 (1958); (b) H. Hirschmann and F. B. Hirschmann, *J. Biol. Chem.*, **187**, 137 (1950); (c) R. B. Turner, *J. Am. Chem. Soc.*, **75**, 3489 (1953).

(5) J. Romo, M. Romero, C. Djerassi, and G. Rosenkranz, *J. Am. Chem. Soc.*, **73**, 1528 (1951).

(6) Analyses were performed by Micro Tech Laboratories, Skokie, Ill.

(7) O. Mancera, G. Rosenkranz, and F. Sondheimer, *J. Chem. Soc.*, 2189 (1953).

(8) L. R. Axelrod, *J. Biol. Chem.*, 205, 173 (1953).

Reactions of Vanillin and Its Derived Compounds. XXX.[1] The Reduction of 4,4′-Dibenzyloxy-3,3′-dimethoxybenzil

IRWIN A. PEARL

Received December, 12, 1960

Earlier studies on the synthesis of 4,4′-dihydroxy-3,3′-dimethoxybenzophenone from vanillil (4,4′-dihydroxy-3,3′-dimethoxybenzil) (I)[2] indicated that the bisbenzyl ether of vanillil, 4,4′-dibenzyloxy-3,3′-dimethoxybenzil (II) was more amenable to rearrangement with alkali than was the parent I. This greater specific reactivity of bisbenzyl ethers led to the preparation of bisbenzyl ethers of several reduction products of I needed for preparative studies related to products isolated from lignosulfonate oxidation mixtures.[3–5] The present paper

(1) For paper XXIX of this series, see *J. Org. Chem.*, 25, 1449 (1960).

(2) I. A. Pearl, *J. Am. Chem. Soc.*, **76**, 3635 (1954).

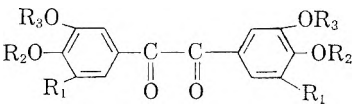
(3) I. A. Pearl and E. E. Dickey, *J. Am. Chem. Soc.*, **74**, 614 (1952).

reports the preparation of the bisbenzyl ethers of several reduction products of I by the reduction of II.

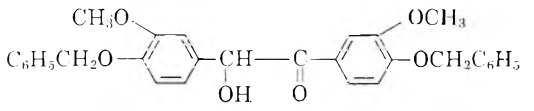
Reduction of II under conditions previously employed for the reduction of I[6] gave three monomolecular reduction products of II, but there appeared to be very little correlation between reductions of II and those of I, syringil (III),[7] and 3,3′-4,4′-tetrahydroxybenzil (IV).[1]

EXPERIMENTAL[8]

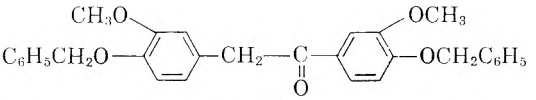
4,4′-Dibenzyloxy-3,3′-dimethoxybenzoin (V). A solution of 10 g. of II[2] in 150 ml. of glacial acetic acid was heated to boiling, removed from the source of heat, and treated with an excess (10 g.) of reduced iron powder. The mixture was shaken for approximately 15 min. during which time the color of the solution changed from yellow to brown. The mixture was filtered, and the brown filtrate was diluted with ten volumes of water. The resulting white precipitate was



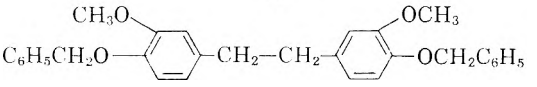
I. $R_1 = R_2 = H$; $R_3 = CH_3$
II. $R_1 = H$; $R_2 = C_6H_5CH_2$; $R_3 = CH_3$
III. $R_1 = OCH_3$; $R_2 = H$; $R_3 = CH_3$
IV. $R_1 = R_2 = R_3 = H$



V



VI



VII

filtered, washed with water, and allowed to air dry to yield 7.2 g. of yellowish horny solid. This product was recrystallized from methanol and from ethanol to yield colorless crystals of V melting at 110–111° and not depressing a mixed melting point with authentic V prepared by condensing *O*-benzylvanillin with potassium cyanide.[2] The ultraviolet absorption spectrum showed the following maxima: λ_{max} 232 mμ, ε 25680; λ_{max} 280 mμ, ε 14250; λ_{max} 310 mμ, ε 10103.

Anal. Calcd. for $C_{30}H_{28}O_6$: C, 74.36; H, 5.83. Found: C, 74.33; H, 5.92.

V was also prepared by reduction of II with tin granules in boiling glacial acetic acid in the presence of a few crystals of mercuric chloride.

4,4′-Dibenzyloxy-3,3′-dimethoxydeoxybenzoin (VI). A warm (65°) solution of 10 g. of II in 150 ml. of glacial acetic acid was treated with 10 g. of zinc dust, and the mixture was shaken. After a few minutes, decolorization was complete. The mixture was heated on the steam bath for 30 min. and filtered hot. The filtrate was cooled and diluted with ten volumes of water. The precipitate was filtered, washed with water, and air dried to yield 7.6 g. of colorless crystals melting at 142–143°. Recrystallization from methanol and then from ethanol yielded crystals of pure VI melting at 144–145° and having the following maxima in its ultraviolet absorption spectrum: λ_{max} 230 mμ, ε 26350; λ_{max} 27 mμ, ε 14920; λ_{max} 305 mμ, ε 10320. The ultraviolet spectrum was almost identical with that for V, thus establishing the similarity of the structure between the benzylated guaiacyl units in the compounds.

Anal. Calcd. for $C_{30}H_{28}O_5$: C, 76.90; H, 6.02. Found: C, 76.91; H, 6.41.

4,4′-Dibenzyloxy-3,3′-dimethoxybibenzyl (VII). A mixture of 4 g. of II and 400 ml. of 95% ethanol was heated to boiling and removed from the source of heat. The hot mixture was treated with 20 g. of granulated zinc and then with concentrated hydrochloric acid in small portions. Each addition of acid caused the mixture to boil, and boiling was allowed to subside before the next addition. After approximately 75 ml. of acid had been added, the yellow color of the solution disappeared. The colorless mixture was filtered, and the zinc was washed with a little hot ethanol. The crystalline precipitate which separated on cooling was filtered and recrystallized from acetic acid to yield colorless crystals (3.0 g.) of VII melting at 129–130° and having the following maxima in its ultraviolet absorption spectrum: λ_{max} 230 mμ, ε 18900; λ_{max} 280 mμ, ε 6910. VII has a strong white fluorescence under ultraviolet light.

Anal. Calcd. for $C_{30}H_{30}O_4$: C, 79.27; H, 6.65. Found: C, 79.26; H, 7.12.

VII was also prepared in almost quantitative yield by reduction of II with amalgamated zinc and hydrochloric acid in ethanolic solution.

Unsuccessful reductions of II. Attempted reductions of II with granulated tin and hydrochloric acid, Raney nickel in alkaline solution, sodium hydrosulfite in alkaline solution, magnesium amalgam in acetic acid solution, and aluminum amalgam in acetic acid solution under conditions reported previously[6,7,9] resulted in either the recovery of starting material or in the production of unidentified mixtures.

THE INSTITUTE OF PAPER CHEMISTRY
APPLETON, WIS.

(4) I. A. Pearl and D. L. Beyer, *J. Am. Chem. Soc.*, **76**, 6106 (1954).
(5) I. A. Pearl and D. L. Beyer, *Tappi*, **39**, 171 (1956).
(6) I. A. Pearl, *J. Am. Chem. Soc.*, **74**, 4593 (1952).
(7) I. A. Pearl, *J. Org. Chem.*, **22**, 1229 (1957).
(8) All melting points are uncorrected. Ultraviolet spectral data are for solutions in 95% ethanol (concentration, 0.02 g. per liter). Analyses and spectra were determined by the Analytical Department of The Institute of Paper Chemistry.
(9) I. A. Pearl and W. M. Dehn, *J. Am. Chem. Soc.*, **60**, 57 (1938).

Amide Derivatives of D-Glucosamine

WILLIAM A. BONNER AND PHILIP I. MCNAMEE[1]

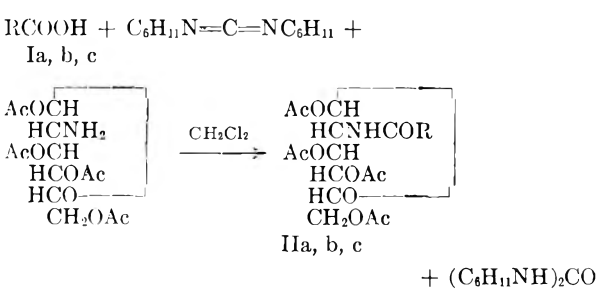
Received November 18, 1960

In connection with a problem requiring the availability of sulfur-containing amide derivatives of D-glucosamine we have been interested in the development of a simple, acceptable-yield procedure for the *N*-acylation of *O*-acetylated D-glucosamine with a variety of acyl functions. Bergmann and Zervas[2] as well as Link and co-workers[3]

(1) The authors are indebted to the U. S. Army Medical Research and Development Command (Contract DA-49-193-MD-2070) for its generous support of this investigation.
(2) M. Bergmann and L. Zervas, *Ber.*, **65**, 1201 (1932).

have prepared several amino acid amide derivatives of D-glucosamine, the so-called "glucopeptides," by interaction of carbobenzoxy derivatives of amino acid chlorides with 1,3,4,5-tetra-*O*-acetyl-β-D-glucosamine. While the final step in these reactions took place in acceptable yield the need for preparing the intermediate acid chloride appeared to us a disadvantage, and we accordingly elected to attempt an adaptation of the "carbodiimide" synthesis of Sheehan[4] and du Vigneaud,[5] wherein a carboxylic acid interacts with an amine in the presence of *N,N'*-dicylohexylcarbodiimide to produce a carboxamide and *N,N'*-dicyclohexylurea. Our preliminary efforts to employ this reaction to the synthesis of acyl derivatives of D-glucosamine are summarized in Chart I, where the preparations of a "glucopeptide" as well as two other amide derivatives of 1,3,4,6-tetra-*O*-acetyl-β-D-glucosamine are summarized. Yields ranged from about 55 to

Chart I



Ia, IIa. R = CH_3COSCH_2—
Ib, IIb. R = $PhCH_2SCH_2$—
Ic, IIc. R = $PhCH_2SCH_2CH(NHCOOCH_2Ph)$—

80% and the brief required reaction time of fifteen minutes permitted the frequently analytically pure product to be obtained in less than an hour. In contrast, the acid chloride procedure[2,3] requires more than a day to complete and extensive purification by acid and alkali washes are necessary during product isolation.

Structure proof of our *N*-(*S*-acetylmercaptoacetyl) - 1,3,4,6 - tetra - *O* - acetyl - β - D - glucosamine (IIa) and *N*-(*S*-benzylmercaptoacetyl)-1,3,4,6-tetra-*O*-acetyl-β-D-glucosamine (IIb) products was undertaken by reductive desulfurization with Raney nickel, wherein each product yielded authentic *N*-acetyl-1,3,4,6-tetra-*O*-acetyl-β-D-glucosamine.

EXPERIMENTAL

N-(S-Acetylmercaptoacetyl)-1,3,4,6-tetra-O-acetyl-β-D-glucosamine (IIa). *S*-Acetylmercaptoacetic acid (Ia; 6.6 g.; 0.05 mole) and 1,3,4,6-tetra-*O*-acetyl-β-D-glucosamine[6] (17.3 g.; 0.05 mole) dissolved in methylene chloride (100 ml.) were treated slowly with a solution of *N,N'*-dicyclohexylcarbodiimide (11.5 g.; 0.055 mole) in methylene chloride (100 ml.). The reaction mixture immediately became warm and *N,N'*-dicyclohexylurea separated from the solution. The latter was filtered and the filtrate was evaporated to dryness, whereupon the residue was dissolved in the minimum amount of hot ethyl acetate and the resulting solution was treated with an equal volume of anhydrous ether, then with sufficient ligroin to engender turbidity. On standing overnight, crude IIa separated, 12.6 g. (55%), m.p. 159–170°. The crude product was recrystallized first from a mixture of ethyl acetate, ether, and ligroin and then from water, to yield the pure materal, m.p. 183–185°, $[\alpha]_D^{23}$ + 25.2° (*c*, 3.37; chloroform).

Anal. Calcd. for $C_{18}H_{25}O_{11}NS$: C, 46.64; H, 5.44; N, 3.02; S, 6.92. Found: C, 46.74, 46.79; H, 5.58, 5.60; N, 3.34; S, 7.20.

N-(S-Benzylmercaptoacetyl)-1,3,4,6-tetra-O-acetyl-β-D-glucosamine (IIb). *S*-Benzylmercaptoacetic acid[7] (Ib; 9.9 g.; 0.055 mole) and 1,3,4,6-tetra-*O*-acetyl-β-D-glucosamine (18.8 g.; 0.054 mole) in methylene chloride (100 ml.) was treated as above with a solution of *N,N'*-dicyclohexylcarbodiimide (11.5 g.; 0.055 mole) in methylene chloride (100 ml.). The mixture was allowed to stand for 6 hr., when the dicyclohexylurea was filtered and the filtrate was evaporated to dryness. The residue was dissolved in hot ethyl acetate (100 ml.) and the solution was treated with anhydrous ether (100 ml.), whereupon the crude IIb product, m.p. 178–180°, 21.5 g. (77%), was precipitated by addition of ligroin. The crude product was recrystallized twice from methanol to yield a sample having m.p. 180–182° and $[\alpha]_D^{23}$ −16.1° (*c*, 3.60; chloroform).

Anal. Calcd. for $C_{23}H_{29}O_{10}NS$: C, 54.00; H, 5.71; N, 2.74; S, 6.27. Found: C, 53.66, 53.72; H, 5.68, 5.86; N, 2.99; S, 6.80.

N-(S-Benzyl-N-carbobenzoxycysteinyl)-1,2,4,6-tetra-O-acetyl - β - D - glucosamine (IIc). *S* - Benzyl - N - carbobenzoxycysteine (Ic; 4.8 g.; 0.014 mole) and 1,3,4,6-tetra-*O*-acetyl-β-D-glucosamine (4.8 g.; 0.014 mole) in methylene chloride (50 ml.) were treated with a solution of *N,N'*-dicyclohexylcarbodiimide (3.0 g.; 0.0146 mole) in the same solvent (50 ml.). After 15 min. the substituted urea precipitate was filtered and the filtrate was stripped of solvent. The residue was dissolved in a minimum of hot ethyl acetate and the IIc product crystallized by the addition of ether, yield 7.4 g. (79%), m.p. 187–189°, $[\alpha]_D^{23}$ + 6.7° (*c*, 4.48; chloroform).

Anal. Calcd. for $C_{32}H_{38}O_{12}N_2S$: C, 56.96; H, 5.68; N, 4.15; S, 4.75. Found: C, 56.98, 57.14; H, 5.74, 5.86; N, 4.24; S, 4.75.

Reductive desulfuration of IIa *and* IIb. The above IIa product (1 g.) and Raney nickel[8] (8 g.) in absolute ethanol (25 ml) were heated under reflux for a period of 5 hr., whereupon the nickel was filtered (Celite) and the filtrate was evaporated to dryness. There resulted 0.6 g. (71%) of crude product which, on recrystallization from 2-propanol, afforded pure *N*-acetyl-1,3,4,6-tetra-*O*-acetyl-β-D-glucosamine have m.p. 182–184° dec. This material showed no mixed melting point depression with an authentic sample of the product, and displayed an infrared spectrum identical in all respects with that of the authentic sample. Precisely similar results were obtained when the above IIb product was subjected to the same desulfuration procedure.

DEPARTMENT OF CHEMISTRY
STANFORD UNIVERSITY
STANFORD, CALIF.

(3) D. G. Doherty, E. A. Popenoe, and K. P. Link, *J. Am. Chem. Soc.*, **75**, 3466 (1953).

(4) J. C. Sheehan and G. P. Hess, *J. Am. Chem. Soc.*, **77**, 1067 (1955).

(5) R. Roeske, F. H. C. Stewart, R. J. Stedman, and V. du Vigneaud, *J. Am. Chem. Soc.*, **78**, 5883 (1956).

(6) Prepared by the method of M. Bergmann and L. Zervas, *Ber.*, **64**, 975 (1931).

(7) G. G. Stoner and G. Dougherty, *J. Am. Chem. Soc.*, **63**, 1481 (1941).

(8) R. Mozingo, *Org. Syntheses*, 21, 15 (1941).

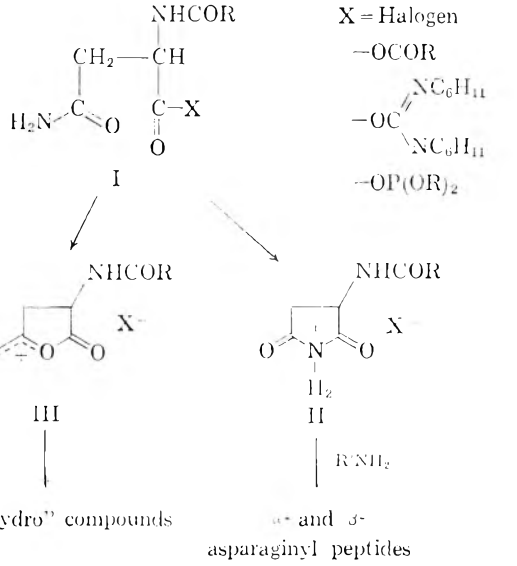
The Synthesis of Two Peptides Containing Methylene-L-asparagine

CHARLES H. STAMMER

Received October 31, 1960

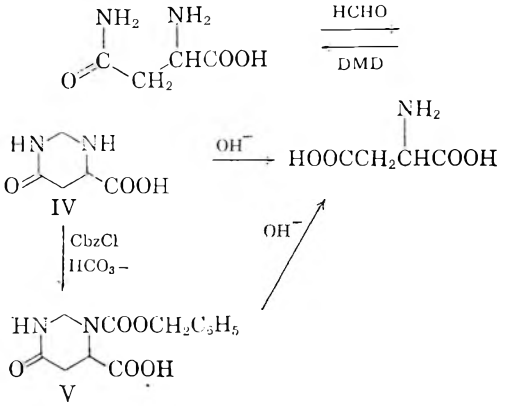
This paper describes attempts to develop a new synthesis of L-asparaginyl peptides using methylene-L-asparagine (IV).[1] Two carbobenzyloxy methylene-L-asparaginyl dipeptides were prepared and attempts to convert them to the corresponding L-asparaginyl peptides were made. Even though dimedone abstracted formaldehyde from IV giving L-asparagine in good yield, it converted methylene-L-asparaginyl peptides into complex mixtures which were not further investigated.

It is well known that the coupling of *N*-acylasparagines with amines is attended by low yields[2] and gives mixtures of products. The coupling reaction is most probably complicated by rearrangement of a reactive intermediate (I) formed from the *N*-acylasparagine and coupling agent. Rearrangement of I to the cyclic imide II followed by reaction with an amine might be expected to yield[3,4]



mixtures of α- and β-asparaginyl peptides. If I rearranged to III, "anhydro" compounds[5,6,7] might be the products. If, as here suggested, the difficulties are due to interaction of the carbamido group with the activated carboxyl, masking of the carbamido function might facilitate formation of the desired products. We hoped that the carbamido function of methylene-L-asparagine would be unable to interact with the activated carboxyl and that, once formed, methylene-L-asparaginyl peptides could be converted back to the corresponding asparaginyl peptides.

Methylene-L-asparagine (IV) was first isolated by Schiff in 1900[1] and its cyclic structure was established by the efforts of several workers.[8] We found that IV could be formed from L-asparagine and formaldehyde in either neutral or alkaline solution and crystallized in about 50% yield. The treatment of methylene-L-asparagine with dimedone[9] (DMD) in aqueous solution liberated[10] L-asparagine which was isolated and identified by its infrared spectrum. The reaction of IV with carbobenzyloxy chloride in alkaline solution gave *N*-carbobenzyloxymethylene-L-asparagine (V).

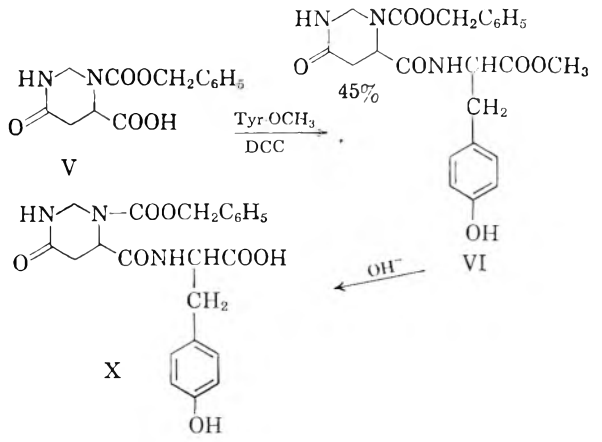


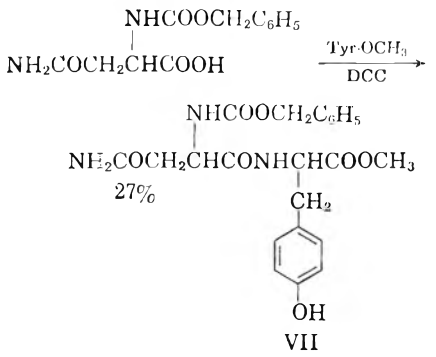
The formation of this *N*-acyl derivative confirms the ring structure of IV since the open-chain methylene-imino (CH_2=N—) form would not be expected to give such a derivative. The decomposition of V in 2*N* lithium hydroxide at room temperature required ten days while a solution of IV in 1*N* lithium hydroxide had reached constant optical rotation in twenty hours. Papergrams indicated that both IV and V were converted to aspartic acid by alkali.

Two derived dipeptides were prepared from V. Tyrosine methyl ester reacted with V in the presence of *N*,*N*′-dicyclohexylcarbodiimide[11,12] (DCC) giving carbobenzyloxy methylene-L-asparaginyl-L-tyrosine methyl ester (VI) in 45% yield. Under the same reaction conditions, carbobenzyloxy-L-asparagine was coupled with tyrosine methyl ester and the carbobenzyloxy dipeptide ester (VII)

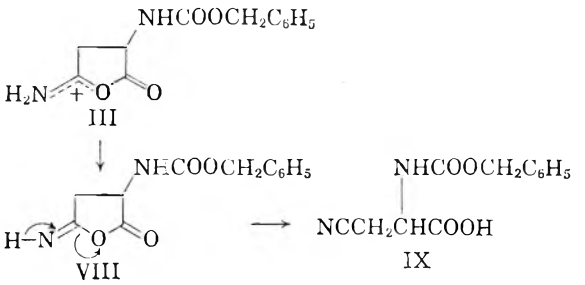
(1) H. Schiff, *Ann.*, **310**, 25 (1900).
(2) S. S. Leach and H. Lindley, *Australian J. Chem.*, **7**, 173 (1954).
(3) A. R. Battersby and J. C. Robinson, *J. Chem. Soc.*, 259 (1955).
(4) E. Sondheimer and R. W. Holley, *J. Am. Chem. Soc.*, **76**, 2467 (1954); *J. Am. Chem. Soc.*, 79, 3767 (1957).
(5) C. Ressler, *J. Am. Chem. Soc.*, **78**, 5956 (1956).
(6) D. T. Gish, P. G. Katsoyannis, G. P. Hess, and R. J. Stedman, *J. Am. Chem. Soc.*, **78**, 5954 (1956).
(7) P. G. Katsoyannis, D. T. Gish, and V. duVigneaud, *J. Am. Chem. Soc.*, **79**, 4516 (1957).
(8) D. French and J. T. Edsall, *Adv. in Prot. Chem.*, Vol. II, Academic Press, Inc., New York, N. Y., 1945, p. 306.
(9) D. Vorlander, *Z. Anal. Chem.*, **77**, 241 (1929).
(10) This ease of hydrolysis is consistent with the work of A. W. Titherly and G. E. K. Branch, *J. Chem. Soc.*, **103**, 330 (1913) on hexahydropyrimidine.
(11) H. G. Khorana, *Chem. Rev.*, **53**, 145 (1953).
(12) J. C. Sheehan and G. P. Hess, *J. Am. Chem. Soc.*, **77**, 1067 (1955).

was obtained in 27% yield. Although the yield of dipeptide was considerably increased by the use of V, further improvement is still desirable.





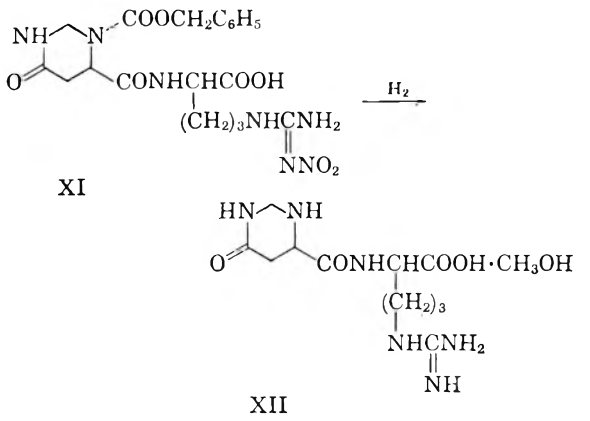
In order to investigate the possibility of participation by the carbamido group in the coupling reaction (as discussed earlier), carbobenzyloxy-L-asparagine was allowed to react with dicyclohexylcarbodiimide in the absence of tyrosine methyl ester. Dicyclohexylurea, in 92% yield, was precipitated and *N*-carbobenzyloxy-β-cyano-L-alanine[13] (IX) was obtained in 42% yield. The formation of IX may have occurred through intermediates such as III and VIII. Carbobenzyloxy-β-cyano-L-alanine (IX) thus becomes readily available and,



since it can be easily converted to asparagine with hydrogen bromide in acetic acid,[12] might be useful in asparaginyl peptide syntheses.

The conversion of carbobenzyloxy methylene-L-asparaginyl-L-tyrosine methyl ester (VI) to the free dipeptide L-asparaginyl-L-tyrosine failed. The ester group was saponified in 0.5*N* sodium hydroxide giving the acid[14] X. Reductive removal of the carbobenzyloxy group gave a mixture of products which reacted with ninhydrin and diazotized sulfanilic acid. Treatment of this crude mixture with aqueous dimedone solution gave the dimedone-formaldehyde adduct in only 47% yield and a new mixture of peptides. The complexity of the mixture made further investigation impractical.

A second methylene-L-asparaginyl peptide was obtained when V was allowed to react through its mixed anhydride[15] with the sodium salt of nitro-L-arginine.[16] The crude dipeptide, obtained in 60% yield, afforded 45% of crystalline carbobenzyloxy methylene-L-asparaginyl-nitro-L-arginine (XI). Hydrogenation of XI in methanol gave crystalline



methylene-L-asparaginyl-L-arginine (XII) as its methanol adduct. When XII was treated with an aqueous dimedone solution, the peptide product showed three ninhydrin-positive components. Attempts to purify this mixture failed.

It is our hope that, even though our results are incomplete, others will be stimulated to use formaldehyde adducts of amino acids in peptide synthesis and that peptide methodology may benefit thereby.

EXPERIMENTAL

General. All melting points were taken on a Kofler Micro Hot Stage.

All paper chromatograms reported were done on 32-cm. Whatman No. 1 circles with a 1-cm. center hole.[17] The development of the chromatograms was carried out between two 12″ Pyrex pie plates. The eluting solvent mixture was

(13) (a) M. Zaoral and J. Rudinger, *Proc. Chem. Soc.*, 176 (1957); (b) *Coll. Czech. Chem. Comm.*, 24, 1993 (1959).

(14) No racemization occurred during this hydrolysis since the optical rotation of the acid X checks that obtained from chymotrypsin hydrolysis of IX. Unpublished results.

(15) J. R. Vaughan and R. L. Osato, *J. Am. Chem. Soc.*, 74, 676 (1952).

(16) K. Hofmann, W. D. Peckham, and A. Rheiner, *J. Am. Chem. Soc.*, 78, 238 (1956).

(17) E. Lederer and M. Lederer, *Chromatography*, Second Ed., Elsevier Publishing Co., New York, N. Y., 1957, p. 134.

contained in a 1″ × 1″ glass cup and was supplied to the paper through a paper wick which passed through the center hole of the circle into the cup. The developing solvent mixtures are designated as below:

BAW—butanol:acetic acid:water—4:1:5. The upper phase was used.
BAm—butanol:1.5*N* ammonium hydroxide—1:1. The upper phase was used.
MPW—methyl ethyl ketone:pyridine:water—4:1:1.6.

The compounds were located on the paper by means of ninhydrin (N), diazotized sulfanilic acid (P), or ultraviolet absorption (UV). A compound which has an R_f value of 0.5 in the MPW system and was located with ninhydrin reagent is reported as R_f^{MPW} 0.5(*N*). R_f's reported consecutively were run on the same sheet. Certain standards (L-asparagine and L-aspartic acid) were often run as reference points, since R_f values varied somewhat from sheet to sheet.

Unless otherwise specified, all analytical samples were dried at 52° and *ca.* 0.1 mm. pressure in the presence of phosphorus pentoxide or Drierite for 2 hr.

Methylene-L-asparagine (IV). (a) *In neutral solution.* One hundred grams of finely pulverized L-asparagine monohydrate was dissolved in 700 ml. of water maintained at 75° during a 1-hr. period. The solution was filtered and allowed to cool to *ca.* 45° when 54 g. (1 equivalent) of 37% aqueous formaldehyde was added. After 25 min., 2 l. of methanol was added slowly and the mixture was placed in a refrigerator for 2 hr. The crude methylene-L-asparagine, collected on a filter and washed with methanol, weighed 57.4 g. (59.5%) after drying in a vacuum oven at 50°. This material showed $[\alpha]_D^{25}$ −63.5° (*c*, 1.07 in water), R_f^{MPW} 0.28 (N, purple), 0.35 (N, brown), 0.40 (N, brown), m.p. 210–260° dec. A 5-g. sample of this material was recrystallized from 170 ml. of water (dissolves slowly) and 100 ml. of methanol at room temperature giving 3.0 g. of methylene-L-asparagine, $[\alpha]_D^{25}$ −73.5° (*c* 2.04 in water), R_f^{MPW} 0.50 (N, brown), m.p. 210–260° dec. infrared showed 3.1 μ (NH), 5.95–6.2 (C=O).

(b) *In alkaline solution.* A solution prepared from 30.0 g. (200 mmoles) of L-asparagine monohydrate, 200 ml. of 1*N* lithium hydroxide, and 18 ml. of 37% aqueous formaldehyde was allowed to stand at room temperature. An hour after mixing, the observed optical rotation was −5.41° (1-dm tube). During the next 48 hr., the observed rotation changed to and became constant at −12.7°. The solution was acidified with 13 ml. of acetic acid and 500 ml. of absolute ethanol was added slowly. The cloudy solution was placed in a refrigerator overnight. The crystalline methylene-L-asparagine weighing 16.3 g. (53%) was collected on a filter and washed with ethanol and ether. The crude product showed: $[\alpha]_D^{25}$ −62.5° (*c*, 2.46 in water); $[\alpha]_D^{25}$ −103.5° (*c*, 7.25 in water containing 1 equivalent of sodium hydroxide); R_f^{MPW} 0.31 (N, purple), 0.44 (N, brown). L-Asparagine: R_f^{MPW} 0.30 (N, brown); L-aspartic acid: R_f^{MPW} 0.32 (N, purple). The crude product was dissolved in 350 ml. of water (required 2 hr. stirring at room temperature), filtered and the filtrate diluted with 350 ml. of methanol. After standing in the refrigerator overnight, the solution was filtered, giving 7.2 g. of crystalline methylene-L-asparagine, $[\alpha]_D^{25}$ −71.2° (*c*, 2.09 in water) and $[\alpha]_D^{25}$ −119° (*c*, 7.32 in water containing 1 equivalent of sodium hydroxide), R_f^{MPW} 0.50 (N, brown). L-Asparagine R_f^{MPW} 0.35 (N, brown); L-aspartic acid: R_f^{MPW} 0.40 (N, purple).

Anal. Calcd. for $C_5H_8N_2O_3$: C, 41.66; H, 5.59; N, 19.44. Found: C, 41.93; H, 5.66; N, 19.61.

Decomposition of methylene-L-asparagine (VI). (a) *In lithium hydroxide.* A solution of 254 mg. of IV in 25.0 ml. of 0.89*N* lithium hydroxide was allowed to stand at room temperature. The initial optical rotation ($[\alpha]_D^{25}$ in 1-dm. tube) of this solution was −109° and after 24 hr. it had become constant at −5.88°. The solution was acidified to *pH* 6 with 2 ml. of glacial acetic acid and lyophilized. Crystallization of the residue from 4 ml. of water and 7 ml. of ethanol gave 173 mg. of solid showing R_f^{BAW} 0.22 (N, blue), R^{MPW} 0.32 (N, blue); DL-aspartic acid: R_f^{BAW} 0.26 (N, blue), R_f^{MPW} 0.36 (N, blue); L-asparagine: R_f^{MPW} 0.29 (N, brown). The crystalline product contained inorganic salts and was not further characterized.

(b) *With dimedone.* To a warm solution of 560 mg. (4 mmoles) of dimedone in 75 ml. of water was added 288 mg. (2 mmoles) of IV. After standing overnight at room temperature, the solution was filtered. The dimedone-formaldehyde adduct weighed 524 mg. (89%). The filtrate was lyophilized and the residue, weighing 217 mg., was extracted three times with 5-ml. portions of hot ethanol. The insoluble material was dissolved in 2 ml. of hot water and 2 ml. of ethanol was added dropwise. The crystals were washed with ethanol and dried. The infrared of this product was identical with that of L-asparagine monohydrate.

Carbobenzyloxy methylene-L-asparagine (V). A solution of 5.0 g. (34.7 mmoles) of methylene-L-asparagine (IV) in 50 ml. of half-saturated potassium bicarbonate solution was stirred magnetically in a 250-ml. round bottomed flask. To this solution was added 4.9 ml. of carbobenzyloxy chloride and the mixture stirred at room temperature for 2.5 hr. The solution was washed with three 50-ml. portions of ether and acidified to *p*H 1.5 with concd. hydrochloric acid. The precipitated oil was extracted into 150 ml. of ethyl acetate. The extract was dried and evaporated to *ca.* 100 ml. and allowed to stand at room temperature. The crystalline carbobenzyloxy methylene-L-asparagine was collected on a filter and washed once with ethyl acetate. It weighed 5.7 g. (59%) and showed m.p. 135–138°, $[\alpha]_D^{25}$ −30° (c, 1.55 in water).

Anal. Calcd. for $C_{13}H_{14}N_2O_5$: C, 56.11; H, 5.07; N, 10.07. Found: C, 56.01; H, 4.80; N, 9.78.

Decomposition of carbobenzyloxy methylene-L-asparagine (V). A solution of 2.78 g. (10 mmoles) of V in 25.0 ml. of 2.13*N* lithium hydroxide was allowed to stand at room temperature. The initial *observed* optical rotation was −7.24° and after 10 days the rotation had become constant at −0.28°. The solution was acidified with 3 ml. of acetic acid and lyophilized. The residue was extracted with three 50-ml. portions of hot ethanol and the insoluble solid, weighing 1.14 g., was collected on a filter and dried. It showed R_f^{MPW} 0.33 (N, blue); DL-aspartic acid, R_f^{MPW} 0.36 (N, blue); L-asparagine, R_f^{MPW} 0.29 (N, brown). The product even after crystallization from water and ethanol, contained inorganic salts and was not further characterized.

Carbobenzyloxy methylene-L-asparaginyl-L-tyrosine methyl ester (VI). A solution of 5.85 g. (30 mmoles) of L-tyrosine methyl ester[18] and 6.18 g. (30 mmoles) of *N,N'*-dicyclohexylcarbodiimide in 50 ml. of dry dimethylformamide was prepared in a 250-ml. Erlenmeyer flask provided with a magnetic stirrer and immersed in an ice bath. A solution of 8.34 g. (30 mmoles) of carbobenzyloxy methylene-L-asparagine in 30 ml. of dry dimethylformamide was added to the stirred amine-carbodiimide solution over a 1-hr. period. After being stirred overnight at room temperature, the reaction mixture was cooled in ice and the precipitated *N,N'*-dicyclohexylurea, weighing 4.55 g. (68%), was collected on a filter. The filtrate was evaporated to dryness and the residue was dissolved in 200 ml. of ethyl acetate. The solution was washed with two 30-ml. portions of 1*N* hydrochloric acid and two 30-ml. portions of saturated potassium bicarbonate solution. The organic phase was dried and evaporated giving 12.9 g. of a crystalline residue. Recrystallization of the crude product from 100 ml. of ethyl acetate gave 6.2 g. (45.5%) of carbobenzyloxy methylene-L-asparaginyl-L-tyrosine methyl ester, m.p. 163–165°, $[\alpha]_D^{24}$ −45.7° (*c*, 1.05 in methanol). A sample recrystallized from 1:3 isopropyl alcohol-water showed m.p. 163–165°, $[\alpha]_D^{25}$ −48° (*c*, 1.0 in methanol), R_f^{MPW} 1.0 (P) R_f^{BAW} 0.89 (P).

Anal. Calcd. for $C_{23}H_{25}N_3O_7$: C, 60.65; H, 5.53; N, 9.23. Found: C, 60.96; H, 5.60; N, 9.62.

(18) H. Schwarz and F. M. Bumpus, *J. Am. Chem. Soc.*, 81, 890 (1959).

Carbobenzyloxy methylene-L-asparaginyl-L-tyrosine (X). A solution of 228 mg. (0.50 mmole) of carbobenzyloxy methylene-L-asparaginyl-L-tyrosine methyl ester in 2.0 ml. of 0.5*N* sodium hydroxide was allowed to stand at room temperature for 2 hr. (At intervals of 0, 15, 35, 60, and 120 min., 5–10 μl. of the reaction mixture was applied to a 32-cm. Whatman No. 1 circle and this sheet was developed in MPW. The spots developed by diazotized sulfanilic acid showed that after 15 min., the saponification was complete and that after 2 hr., the methylene-L-asparaginyl ring had not been destroyed by the alkali present.) The reaction mixture was acidified with 1.0 ml. of 1.0*N* hydrochloric acid and the separated oil extracted into three 3-ml. portions of ethyl acetate. After drying, the organic layer was evaporated giving 228 mg. of crude product. This material was dissolved in 1 ml. of hot isopropyl alcohol, 3 ml. of water added and after 3 hr. at room temperature, the solution was placed in a refrigerator. The crystalline carbobenzyloxy methylene-L-asparaginyl-L-tyrosine, weighing 108 mg. (50%), was collected by centrifugation and washed with 1:4 isopropyl alcohol–water solution. When dry, the product showed m.p. 118–122°, $[\alpha]_D^{25}$ −25.5° (c, 1.06 in pyridine), R_f^{MPW} 0.88 (P, R^{BAm} 0.31 (P). A sample again recrystallized from 1:3 isopropyl alcohol–water melted at 119–122°.

Anal. Calcd. for $C_{22}H_{23}N_3O_7$: C, 59.86; H, 5.25; N, 9.52. Found: C, 60.11; H, 5.53; N, 9.64.

Attempted conversion of X *to* L-*asparaginyl-*L-*tyrosine.* (a) *Reduction.* A solution of 1.2 g. of X in 20 ml. of methanol was hydrogenated overnight at 40 p.s.i. and room temperature using 1.2 g. of 10% palladium-on-carbon as catalyst. The catalyst was filtered and extracted with four 10-ml. portions of hot methanol, four 10-ml. portions of hot water, and four 10-ml. portions of 10% pyridine in hot water. The combined extracts weighed 742 mg. and showed numerous components when paper chromatographed.

(b) *Dimedone treatment.* To a hot solution of 600 mg. of dimedone in 50 ml. of water was added 619 mg. of the reduction product obtained above. After heating the mixture 1.5 hr. on a steam bath, it was placed in the refrigerator. The dimedone-formaldehyde adduct, weighing 274 mg. (47%), was filtered and the filtrate was lyophilized. The residue was was extracted with three 50-ml. portions of hot ethyl acetate leaving 466 mg. (79%) of insolubles which showed multiple spots in both MPW and BAW systems. After trituration with hot isopropyl alcohol, the product weighed 287 mg. and showed R_f^{MPW} 0.30, 0.42, 0.60, 0.79 (N + P). Elemental analysis gave values inconsistent with L-asparaginyl-L-tyrosine.

*Carbobenzyloxy-*L-*asparaginyl-*L-*tyrosine methyl ester.* A solution of 2.66 g. (10 mmoles) of carbobenzyloxy-L-asparagine[19] in 27 ml. of dry dimethylformamide was added during 15 min. to an ice-cold magnetically stirred solution of 2.06 g. (10 mmoles) of *N,N'*-dicyclohexylcarbodiimide and 1.95 g. (10 mmoles) of L-tyrosine methyl ester in 12 ml. of dry dimethylformamide. After *ca.* 20 hr. at room temperature, the mixture was cooled and the precipitated dicyclohexylurea weighing 2.0 g. (89%), was collected on a filter. The filtrate was evaporated to dryness and the residue dissolved in a warm mixture of 100 ml. of ethyl acetate and 25 ml. of butanol. Two 25-ml. washings with 2.5*N* hydrochloric acid removed 0.5 g. of L-tyrosine methyl ester, m.p. 133–136°, B_f^{BAm} 0.86 (P), and two 25-ml. washings with half-saturated potassium bicarbonate solution removed 0.8 g. of acidic components, R_f^{BAm} 0.13 (P), 0.36 (P), from the solution. The organic layer was dried and evaporated giving 2.9 g. of crystalline product. Recrystallization of the above solid from 85 ml. of methyl ethyl ketone gave a first crop weighing 0.9 g., m.p. 188–194°; and a second crop weighing 0.33 g., m.p. 165–190°. The total crude yield of carbobenzyloxy-L-asparaginyl-L-tyrosine methyl ester was thus 1.23 g. (27%). The first crop was recrystallized from a mixture of 40 ml. of methyl ethyl ketone and 10 ml. isopropyl alcohol. This product, 479 mg., m.p. 197–199°, $[\alpha]_D^{25}$ 1.96° (c, 1.02 in methanol), was submitted for analysis.

Anal. Calcd. for $C_{22}H_{25}N_3O_7$: C, 59.58; H, 5.68; N, 9.48. Found: C, 59.48; H, 5.72; N, 9.40.

*Carbobenzyloxy-β-cyano-*L-*alanine.* A solution of 2.66 g. (10 mmoles) of carbobenzyloxy-L-asparagine in 27 ml. of dry dimethylformamide was added during 15 min. to an ice-cold magnetically stirred solution of 2.06 g. (10 mmoles) of *N,N'*-dicyclohexylcarbodiimide in 12 ml. of dry dimethylformamide. *N,N'*-dicyclohexylurea began precipitating within 10 min. After *ca.* 20 hr. at room temperature, a solution of 1.95 g. (10 mmoles) of L-tyrosine methyl ester[18] in 10 ml. of warm dimethylformamide was added to the reaction mixture in which solid dicyclohexylurea was present. After another 4 hr. at room temperature, the mixture was filtered giving 2.07 g. (92%) of dicyclohexylurea. The filtrate was evaporated to dryness and the residue was dissolved in 100 ml. of ethyl acetate. Extraction of this solution with two 25-ml. portions of half-saturated potassium bicarbonate solution removed 2.0 g. of acidic products. Further extraction with two 25-ml. portions of 2.5*N* hydrochloric acid removed 0.8 g. of L-tyrosine methyl ester, R_f^{BAm} 0.87 (P), from the solution. The remaining ethyl acetate solution was evaporated to dryness giving 0.5 g. of neutral material which showed R_f^{BAm} 0.95 (P) and gave some crystals, m.p. 200–210°, after solution in methanol. The neutral product may be impure carbobenzyloxy-L-asparaginyl-L-tyrosine methyl ester. The 2.0 g. of acidic products were crystallized from 25 ml. of ethylene dichloride. The product obtained weighed 1.1 g. (42%) and melted at 126–128°. Another crystallization from 60 ml. of ethylene dichloride gave 880 mg. of carbobenzyloxy-β-cyano-L-alanine, m.p. 126–128°,[20] $[\alpha]_D^{21}$ −19° (c, 1.26 in methanol). Its infrared spectrum showed a 4.43 μ band characteristic of a cyano function.

Anal. Calcd. for $C_{12}H_{12}N_2O_4$:C, 58.06; H, 4.87; N, 11.29. Found: C, 57.61; H, 4.91; N, 11.37.

*Carbobenzyloxy methylene-*L-*asparaginyl-nitro-*L-*arginine.* A solution of 22.2 g. (80 mmoles) of carbobenzyloxy methylene-L-asparagine (V) in 300 ml. of 1:1 tetrahydrofuran-dioxane mixture was stirred mechanically in a 200-ml. three-necked round bottomed flask immersed in an ice-methanol cooling bath. To this was added successively 12.3 ml. (80 mmoles) of triethylamine and a solution of 11.9 ml. (80 mmoles) of isobutylchlorocarbonate. Twenty minutes later, an ice-cold solution of 21.9 g. (100 mmoles) of nitro-L-arginine[16] and 15.1 g. (110 mmoles) of triethylamine in 300 ml. of water was added to the mixed anhydride solution over a 5-min. period. The reaction mixture was stirred for 4 hr., while the temperature was allowed to rise to 25°. The mixture was concentrated *in vacuo* to remove the organic solvents, and the resulting slurry was acidified with concentrated hydrochloric acid. This mixture was extracted with one 200-ml. and two 100-ml. portions of 1:1 butanol–ethyl acetate solution. These combined extracts were evaporated to dryness *in vacuo* and the residue was triturated with three portions of hot ethyl acetate. The dry crude carbobenzyloxy methylene-L-asparaginyl-nitro-L-arginine weighed 26.4 g., (60%), R_f^{BAm} 0.23, 0.35, 0.49 (UV).

Ten grams of the above crude product was dissolved in 75 ml. of hot 1:1 ethanol-water mixture. After 1 week at room temperature, the solution afforded 4.5 g. of crystalline carbobenzyloxy methylene-L-asparaginyl-nitro-L-arginine, m.p. 199–202°. Dilution of the mother liquor with water gave only an oily precipitate. A small sample, recrystallized for analysis from 3:7 ethanol-water, melted at 202–204° and showed R_f^{MPW} 0.82 (UV), R_f^{BAW} 0.70 (UV), R_f^{BAm} 0.20 (UV), $[\alpha]_D^{25}$ −27.5° (*c*, 2.18 in 0.1*N* sodium hydroxide).

Anal. Calcd. for $C_{19}H_{25}N_7O_8$: C, 47.59; H, 5.26; N, 20.45. Found: C, 47.72; H, 4.95; N, 20.75.

*Methylene-*L-*asparaginyl-*L-*arginine* (XII). A solution of 2.5 g. of carbobenzyloxy methylene-L-asparaginyl-nitro-L-

(19) M. Bergmann and L. Zervas, *Ber.*, **65**, 1192 (1932).

(20) The authors of reference 12 report m.p. 133–134°.

arginine (XI) in 60 ml. of warm 5:1 methanol-water mixture was cooled to room temperature and hydrogenated overnight at room temperature and 40 p.s.i. using 2.5 g. of 10% palladium-on-carbon catalyst. After removal of the catalyst, the solvent was evaporated *in vacuo* and the residue was dissolved in 50 ml. of water and the solution lyophilized. The residue, weighing 1.30 g., was dissolved in 12 ml. of hot methanol whereupon crystallization occurred. The crystalline methylene-L-asparaginyl-L-arginine·CH_3OH (XII) weighed 1.13 g. (72%) and showed m.p. 160–165° dec., R_f^{MPW} 0.29 (N). A 250-mg. sample of this product was dissolved in 1 ml. of water and diluted with 1 ml. of isopropyl alcohol. Seeding and addition of 3 ml. of methanol gave 177 mg. of crystalline material, m.p. 163–165°, $[\alpha]_D^{23}$ −31° (c, 1 in 0.1*N* hydrochloric acid). A sample was dried at 78° for 2 hr. at *ca.* 0.1 mm. over Drierite for analysis. NMR spectrum on this sample showed the presence of 1 mole of methanol.

Anal. Calcd. for $C_{12}H_{24}N_6O_5$: C, 43.36; H, 7.28; N, 25.29. Found: C, 43.16; H, 7.26; N, 25.40.

Attempted conversion of XII *to* L-*asparaginyl*-L-*arginine.* A solution of 600 mg. of dimedone was prepared in 50 ml. of hot water and a solution of 600 mg. of XII in *ca.* 3 ml. of water was added to it. The mixture was heated 1.5 hr. and put in the refrigerator. The dimedoneformaldehyde adduct, weighing 413 mg. (71%), was collected on a filter and the filtrate was lyophilized. The residue, after extraction with three 50-ml. portions of hot ethyl acetate, weighed 698 mg. and showed R_f^{MPW} 0.29–0.38 (N); L-arginine·HCl, R_f^{MPW} 0.32–0.48 (N). Further precipitations from methanol–ethyl acetate gave multicomponent products which were not further characterized.

Acknowledgment. The author expresses gratitude to Mr. R. N. Boos and associates for microanalyses and Mr. B. Arison for NMR spectra.

MERCK SHARP & DOHME RESEARCH LABORATORIES
DIVISION OF MERCK & CO., INC.
RAHWAY, N. J.

New Synthesis of 18-Hydroxy-17-methoxy-15,16,17,18,19,20-hexadehydroyohimbane Hydrochloride

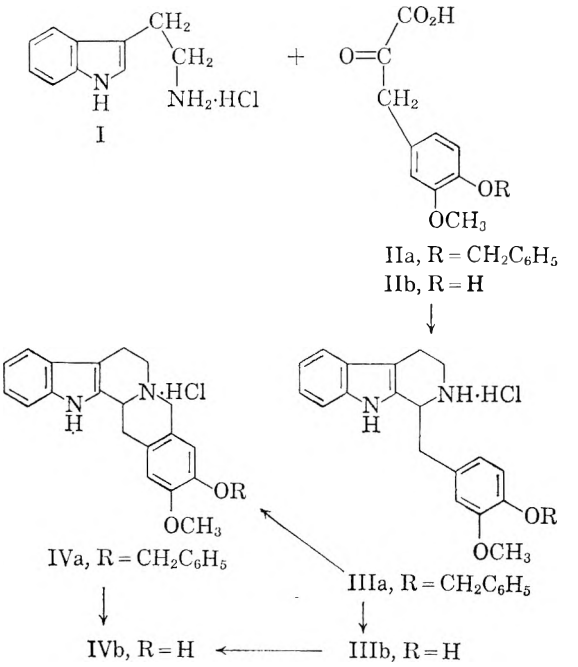
JAMES H. SHORT, MORRIS FREIFELDER, AND GEORGE R. STONE

Received November 28, 1960

Synthesis of 18-hydroxy-17-methoxy-15,16,17,-18,19,20-hexadehydroyohimbane hydrochloride (IVb), which contains the pentacyclic ring system of reserpine, deserpidine, and related compounds, was accomplished as early as 1938.[1] Since then, other investigators[2–4] have reported the preparation of this substance and related compounds.

Preparation of IVb is usually accomplished by condensing tryptamine (I) with 4-hydroxy-3-methoxyphenylpyruvic acid (IIb). The product, 1 - (4 - hydroxy - 3 - methoxybenzyl) - 1,2,3,4-tetrahydro-β-carboline hydrochloride (IIIb), is then cyclized with formaldehyde to obtain IVb. The preparation of IIIb by this method, while satisfactory on a small scale, did not lend itself to large scale work. The difficulty appeared to be the lack of stability of IIb. Douglas and Gulland[5] have previously commented on the instability of IIb.

As we desired a large quantity of IVb, it was necessary to find a suitable modification of this sequence. Covering the phenolic function with a group which could be removed later suggested itself, and it seemed likely that the benzyl group might satisfactorily serve this function.



Vanillin, therefore, was converted to its *O*-benzyl derivative, and then into an azlactone. Hydrolysis of the latter with barium hydroxide gave the desired 4-benzyloxy-3-methoxyphenylpyruvic acid (IIa).

Tryptamine (I) and IIa gave 1-(4-benzyloxy-3-methoxybenzyl) - 1,2,3,4 - tetrahydro - β - carboline hydrochloride (IIIa) in good yields, irrespective of the quantities used. Debenzylation of IIIa led to IIIb and the latter was cyclized to the desired IVb, or IIIa could first be cyclized to IVa, and then debenzylated to give IVb.

EXPERIMENTAL[6]

1-(4-Benzyloxy-3-methoxybenzyl)-1,2,3,4-tetrahydro-β-carboline hydrochloride (IIIa).[7] A mixture of 65.5 g. (0.33 mole) of tryptamine hydrochloride[8] and 100 g. (0.33 mole) of

(1) G. Hahn and A. Hansel, *Ber.*, **71**, 2195 (1938).
(2) W. Logemann *et al.*, *Ber.*, **88**, 1952 (1955); **89**, 1043 (1956).
(3) M. Onda and M. Kawanishi, *J. Pharm. Soc. Japan*, **76**, 966 (1956).
(4) T. Nogradi, *Monatsh. Chem.*, **88**, 1093 (1957).
(5) R. Douglas and J. Gulland, *J. Chem. Soc.*, **134**, 2893 (1931).
(6) Microanalyses were carried out by Mr. Elmer Shelberg and his staff of the Abbott Microanalytical Laboratory.
(7) The preferred Chemical Abstracts name for this substance is 1-(4-benzyloxy-3-methoxybenzyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole hydrochloride.
(8) M. Freifelder, *J. Am. Chem. Soc.*, **82**, 2386 (1960).

4-benzyloxy-3-methoxyphenylpyruvic acid[5] in 3.5 l. of 1-butanol was heated under reflux for 2 hr. The cooled solution was diluted with 2.0 l. of acetone and chilled. White fluffy needles precipitated and were collected. The product weighed 78 g. (55%) and melted at 223–226°. Recrystallization from glacial acetic acid, or from aqueous ethanol, raised the melting point to 226–227°.

Anal. Calcd. for $C_{26}H_{26}N_2O_2 \cdot HCl$: C, 71.79; H, 6.26; Cl, 8.15. Found: C, 71.76; H, 6.34; Cl, 8.27.

18-Benzyloxy-17-methoxy-15,16,17,18,19,20-hexadehydroyohimbane hydrochloride (IVa). A mixture of 43 g. (0.1 mole) of IIIa and 1.0 l. of 50% ethanol was heated on the steam bath until the solid dissolved. After adding 100 ml. of 36% formaldehyde, the solution was heated on the steam bath for 3 hr. The hot reaction mixture was filtered to remove a yellow solid which was washed with hot 50% ethanol. The product weighed 37 g. (83%) and melted at 265–268°.

Anal. Calcd. for $C_{27}H_{26}N_2O_2 \cdot HCl$: C, 72.55; H, 6.09; Cl, 7.93; N, 6.27; O, 7.16. Found: C, 72.34; H, 6.27; Cl, 7.68; N, 6.07; O, 7.26.

1-(4-Hydroxy-3-methoxybenzyl)-1,2,3,4-tetrahydro-β-carboline hydrochloride (IIIb). A suspension of 2.75 g. (0.005 mole) of IIIa and 0.3 g. 5% palladium on carbon in 100 ml. of 50% ethanol was hydrogenated at 1.7 atm. at 60°. Theoretical uptake occurred in 1 hr., and all of the solid was in solution. The catalyst was removed and the solution was chilled to obtain a solid, m.p. 254–255°. The filtrate was taken to dryness, and the residue was triturated with ether to obtain more product, m.p. 253–254°. The total yield was 1.45 g. (84%). The recorded melting point is 253–254°.[3]

On larger scale runs, it was necessary to extract the catalyst thoroughly with hot 75% ethanol to insure good yields. In a combined workup of four 16-g. (0.0368 mole) runs a 75% yield was obtained.

18-Hydroxy-17-methoxy-15,16,17,18,19,20-hexadehydroyohimbane hydrochloride (IVb).[9] A suspension of 44.7 g. (0.1 mole) of IVa and 7.5 g. of 5% palladium on carbon in 250 ml. of dimethylformamide was hydrogenated at 2 atm. at about 70°. When hydrogen uptake was complete (8–15 hours) product had begun to precipitate. The product was dissolved by heating to boiling with addition of 65 ml. of dimethylformamide and 360 ml. of water. The hot solution was filtered to remove the catalyst, and the filtrate chilled to obtain 26 g. (73%) of bright yellow solid melting at 277–279°. Recorded melting points are 254–256°,[1] 256–257°,[3] and 254–256°.[4]

Anal. Calcd. for $C_{20}H_{20}N_2O_2 \cdot HCl$: C, 67.31; H, 5.93; Cl, 9.93; N, 7.85; O, 8.96. Found: C, 67.27; H, 5.82; Cl, 10.00; N, 7.87; O, 9.27.

Consensation of IIIb with formaldehyde as described previously[1,3,4] gave a bright yellow solid, m.p. 277–279°, identical in every respect with the material described above. Although the melting point varied somewhat with the rate of heating, and also on whether an oil bath or metal block was used, pure material was never observed to melt below 270°.

DEPARTMENT OF ORGANIC CHEMISTRY
ABBOTT LABORATORIES
NORTH CHICAGO, ILL.

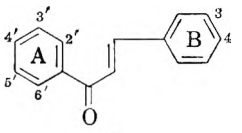
(9) The preferred *Chemical Abstracts* name for this compound is 5,7,8,13,13b,14-hexahydro-2-methoxybenz[g]-indolo[2,3-a]quinolizin-3-ol hydrochloride.

Spectral Studies on Flavonoid Compounds. III. Polyhydroxychalcones

LEONARD JURD[1a] AND ROBERT M. HOROWITZ[1b]

Received October 14, 1960

The ultraviolet spectra of most of the known, naturally occurring, hydroxylated chalcone (I) derivatives have been reported.[2] However, as an aid in the identification of new pigments, the spectra of a number of additional hydroxychalcones in neutral and in alkaline solutions are presented in this note.



I

The spectra of twenty-five hydroxychalcones are collected in Table I. These chalcones absorb strongly in the 300–400 mμ region and less strongly in the 220–270 mμ region. In alcoholic sodium ethylate solution the long wave-length band of those chalcones which contain a free hydroxyl group in the 4- position undergoes a bathochromic shift of 70–90 mμ and a considerable *increase* in its intensity (Table I; compounds I–II). This spectral shift is sufficiently characteristic of the 4-hydroxychalcones to be used as evidence for the the presence of this grouping in chalcones. The alkali spectrum of the natural chalcone, xanthohumol (II), reported by Verzele and his co-workers,[3] provides a good example of this shift.

Chalcones which contain a free 4′-hydroxyl *and* either a free 2′-hydroxyl or an alkylated or glycosidated 4-hydroxyl show a bathochromic shift of only 40–50 mμ in sodium ethylate (Table I; compounds 12–18). On the other hand, when the 2′- and 4- positions are unsubstituted, 4′-hydroxychalcones give a bathochromic shift of 65–70 mμ in sodium ethylate (Table I; compounds 19, 20). This shift is easily distinguished from that given by the 4-hydroxychalcones, however, since it is accompanied by a considerable *decrease* in the intensity of the long wave-length band. The difference is illustrated by the spectra of 4-hydroxychalcone and 4′-hydroxychalcone (Fig. 1). The influence of a 2′-hydroxy group on the alkali spectrum of a 4′-hydroxychalcone is probably to be attributed to chelation with the carbonyl group, while the influence of a 4-alkoxy group may be accounted for by assuming a cross-conjugation effect similar to that proposed by Geissman and Harborne[4] for hydroxyaurones.

(1) (a) Western Regional Research Laboratory, Albany, Calif.[1c]; (b) Fruit and Vegetable Chemistry Laboratory, Pasadena, Calif.[1c]; (c) Laboratories of the Western Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.

(2) For examples, see J. B. Harborne and T. A. Geissman, *J. Am. Chem. Soc.*, **78**, 829 (1956); T. A. Geissman, J. B. Harborne, and M. K. Seikel, *J. Amer. Chem. Soc.*, **78**, 825 (1956); T. A. Geissman, *Modern Methods of Plant Analysis*, Vol. 3, eds. K. Paech and M. V. Tracey, Springer-Verlag, 1955, p. 450.

(3) M. Verzele, J. Stockx, F. Fontijin, and M. Anteunis, *Bull Soc. Chim. Belg.*, **66**, 452 (1957).

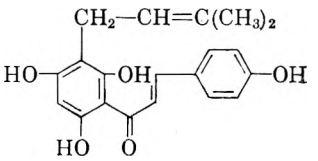
(4) T. A. Geissman and J. B. Harborne, *J. Am. Chem. Soc.*, **78**, 832 (1956).

TABLE I

SPECTRA OF CHALCONES IN ETHANOL AND IN SODIUM ETHOXIDE

Chalcone	C_2H_5OH λ_{max}, mμ	0.002*M* $NaOC_2H_5$ λ_{max}, mμ	Δλ[b]
1. 4-Hydroxy-	350, 248	438, 286	88
2. 4,4′-Dihydroxy-	348, 240	427, 250	79
3. 3,4-Dihydroxy-	367, 266	452, 267	85
4. 2′,4-Dihydroxy-3′-methoxy-	380, 267, 249	458, 273, 238	78
5. 2′,4-Dihydroxy-4′-methoxy-	370, 303, 242	441, 293, 250	71
6. 4-Hydroxy-2′,4′-dimethoxy-	350	423	73
7. 2′,3,4-Trihydroxy-	384, 320,[a] 271, 249	460, 280	76
8. 4,2′,4′-Trihydroxy-3-methoxy-	378, 307,[a] 260	451, 354, 280,[a] 253	73
9. Coreopsin[2]	385, 305,[a] 265, 245	450	65
10. 4-Hydroxy-2′,4′,3-trimethoxy-	360	440	80
11. Xanthohumol[3]	370	438	68
12. 2′,4′-Dihydroxy-	345,[a] 317, 267	394, 300, 279	49
13. 2′,4′-Dihydroxy-4-methoxy-	362, 307,[a] 237	400, 282, 234[a]	38
14. 4′-Hydroxy-2′,4-dimethoxy-	350	395	45
15. 4′,3-Dihydroxy-4-methoxy-	358, 314,[a] 262,[a] 235	404, 327,[a] 276, 250	46
16. 2′,4′-Dihydroxy-3,4-dimethoxy-	371, 310,[a] 259	407, 337,[a] 283, 258[a]	36
17. 4′-Hydroxy-2′,3,4-trimethoxy-	357	395	38
18. 4′-Hydroxy-2′,6′,3,4-	341, 320,[a] 252,[a] 239	389, 334, 250	48
19. 4′-Hydroxy-	320, 230	388, 297, 272[a]	68
20. 4′,3-Dihydroxy-	321, 242	385, 311, 267	64
21. 2′-Hydroxy-	366,[a] 316, 221	428, 303, 250	
22. 2′,3-Dihydroxy-	356, 316, 257	317, 273, 241	
23. 2′-Hydroxy-4′,6′-dimethoxy-	338, 236[a]	383, 295, 250	
24. 2′-Hydroxy-4,4′-dimethoxy-	362, 295,[a] 239	419, 321, 251	
25. 2′-Hydroxy-3,4-dimethoxy-	371, 316,[a] 264, 247	422, 341, 297,[a] 242	

[a] Inflection.
[b] $\Delta\lambda = \lambda_{max}$ (0.002*M* $NaOC_2H_5$) $= \lambda_{max}$ (EtOH) of the long wave-length band.
The most intense band in each spectrum is underlined.



II

TABLE II

SPECTRA OF ALUMINUM CHLORIDE-2′-HYDROXYCHALCONE COMPLEXES

Chalcone	C_2H_5OH λ_{max}, mμ	$AlCl_3$ λ_{max}, mμ	Δλ
2′-Hydroxy-	366[a]	425	59
2′,4′,4-Trihydroxy-	370	422	52
2′,4′-Dihydroxy-4-methoxy-	362	415	53
2′,3,4-Trihydroxy-	384	447	63
2′-Hydroxy-3,4-dimethoxy	371	437	66
2′,4′,3,4-Tetrahydroxy(coreopsin) (2)	385	450	50
2′,4′-Dihydroxy-3,4-methylenedioxy-	370	416	46
2′,3′,4′,3,4-Pentahydroxy-(okanin) (4)	381	420	39
Marein (4)	383	422	39
2′,3′,4′-Trihydroxy-	347	384	37

[a] Inflection.

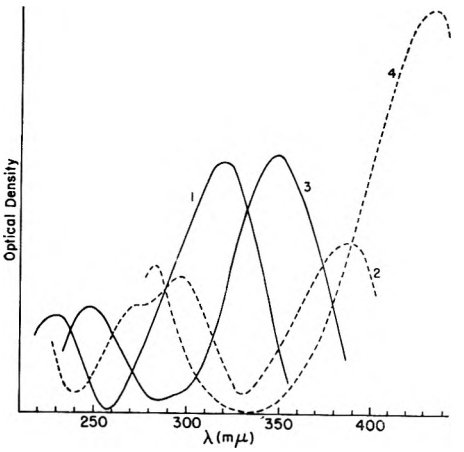


Fig. 1. Ultraviolet spectra of (1) 4′-hydroxychalcone in ethanol, (2) 4′-hydroxychalcone in 0.002*M* sodium ethoxide, (3) 4-hydroxychalcone in ethanol, (4) 4-hydroxychalcone in 0.002*M* sodium ethoxide

Chalcones whose only free hydroxyl group is in the 2′- position are readily distinguished by their characteristic spectral curves in sodium ethylate. The principal long wave-length band appears at a somewhat shorter wave length than in neutral solution, while the absorption in the short wave-

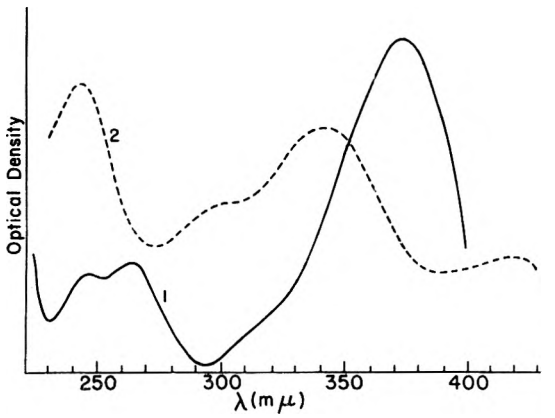


Fig. 2. Ultraviolet spectra of 2′-hydroxy-3,4-dimethoxychalcone in (1) ethanol, (2) 0.002*M* sodium ethoxide

length region undergoes a marked increase in intensity. A low intensity band may appear in the 400 mμ region (Fig. 2).

Spectral procedures for detecting *o*-dihydroxyl and 2′-hydroxyl groups in chalcones have been reported previously. Thus, chalcones which contain an *o*-dihydroxyl grouping in the B-ring give a characteristic bathochromic shift with boric acid–sodium acetate.[5] 2′-Hydroxychalcones form complexes with aluminum chloride in alcoholic solution,[2,6] the λ_{max} of the long wave-length band undergoing a bathochromic shift of 40–60 mμ (Table II). It is important that a large excess of aluminum chloride be employed in this test for a 2′-hydroxyl.[7] In Table II, it will be noted that 2′,3′,4′-trihydroxychalcone derivatives give a remarkably consistent bathochromic shift of only 37 mμ with aluminum chloride. This suggests that these compounds form aluminum complexes of a different type from those given by other 2′-hydroxychalcones.

Acknowledgment. The authors are indebted to Dr. T. A. Geissman for specimens of many of the chalcones used in this study.

(5) L. Jurd, *Arch. Biochem.*, **63**, 376 (1956).

(6) E. C. Bate-Smith and T. Swain, *J. Chem. Soc.*, 2185 (1953).

(7) L. Jurd and T. A. Geissman, *J. Org. Chem.*, **21**, 1395 (1956).

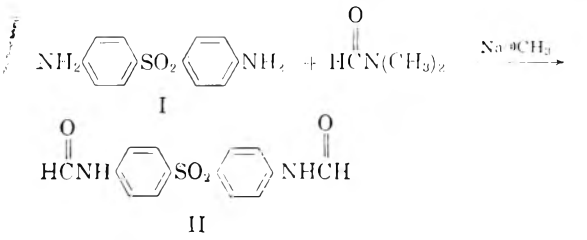
Potential Cancerocidal Agents. III. Formanilides[1,2]

George R. Pettit, Malda V. Kalnins, Thomas M. H. Liu, Evan G. Thomas, and Kevin Parent

Received October 27, 1960

As part of a study directed at defining the scope of a new procedure[3] for the preparation of formanilides it was considered of importance to submit several of these substances for evaluation as cancer chemotherapeutic agents.[4] One of the first compounds prepared was 2,5-dimethoxyformanilide (Table I) and this substance was subsequently found to inhibit growth of the Ehrlich Ascites tumor in preliminary screening studies.[5] Consequently, it appeared desirable to prepare a number of related formanilides.

Initial emphasis was placed on the preparation of alkylated, alkoxy, and halogenated derivatives of formanilide (Table I). In each case, the corresponding aniline was formylated (*cf.*, I → II) employing dimethylformamide in the presence of sodium methoxide.[3] Acylation was conveniently accomplished using excess dimethylformamide and



a 2:1 molar ratio of sodium methoxide to amine Generally the reaction was complete after fifteen to thirty minutes at reflux and was accompanied by evolution of dimethylamine. The structure of the first product, *p*-chloroformanilide (Table I), prepared by this new reaction was suggested on the basis of its infrared spectrum and elemental composition. Unequivocal evidence for this structure was obtained following comparison (infrared spectra and mixture melting point) with an authentic specimen of *p*-chloroformanilide.[6]

Although the substances illustrated in Table I

(1) Refer to G. R. Pettit and M. V. Kalnins, *J. Org. Chem.*, **25**, 1365 (1960) for the preceding contribution.

(2) This investigation was aided by Grant No. T-79A from the American Cancer Society and in part by a Frederick Gardner Cottrell grant from the Research Corporation.

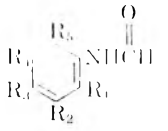
(3) Consult: G. R. Pettit and E. G. Thomas, *J. Org. Chem.*, **24**, 895 (1959) for a preliminary report of this reaction.

(4) The known inhibition of Sarcoma 180 by *N*-methylformamide emphasized the advisability of a concurrent biological investigation. An account of the tumor inhibitory activity of *N*-methylformamide has been prepared by D. A. Clarke, F. S. Philips, S. S. Sternberg, R. K. Barclay, and C. C. Stock, *Proc. Soc. Exptl. Biol. Med.*, **84**, 203 (1953). This substance has also been shown to prolong the survival time of mice with Leukemia L1210 and inhibit the growth of Adrenocarcinoma E0771; H. E. Skipper, F. M. Schable, V. Binns, J. R. Thomson, and G. P. Wheeler, *Cancer Research*, **15**, 143 (1955). An increase in the survival time of mice bearing Ehrlich Ascites tumor following treatment with *N*-methylformamide has been reported by A. Furst, W. C. Cutting, and H. Gross, *Cancer Research*, **15**, 294 (1955).

(5) Evaluation of 2,5-dimethoxyformanilide (NSC 30098) is being carried out by the Cancer Chemotherapy National Service Center, National Cancer Institute, Bethesda, Md.

(6) M. D. Farrow and C. K. Ingold, *J. Chem. Soc.*, **125**, 2552 (1924).

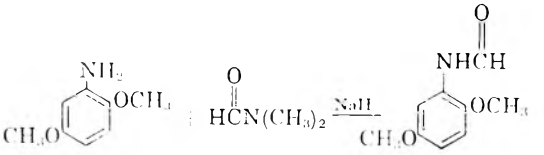
TABLE I



R_1	R_2	R_3	R_4	R_5	Yield, %[a]	Solvent[c]	M.P.[d]	Formula
CH_2CH_3					97	1	73.5–74.5 (70)[e]	$C_9H_{11}NO$
OCH_3					44[b]	1	84 (84)[f]	
		OCH_3			41		80–81 (80–81)[f]	
F					70	2	44	C_7H_6NOF
	F				35	2	63–64	C_7H_6NOF
		F			78	2	67–68 (66)[g]	
	CF_3				52	3	54–55	$C_8H_6F_3NO$
	Cl				48	4	56–57.5[h] (57–58)[i]	
		Cl			79	5	102–103.5[h] (100–102)[j]	
I					68	4	113–113.5	C_7H_6INO
CH_3	CH_3				62	6	103.5–104.5	$C_8H_{11}NO$
	CH_3	CH_3			51	2	68–69	$C_9H_{11}NO$
CH_3		OCH_3			63[b]	7	104–105	$C_9H_{11}NO_2$
OCH_3		OCH_3			35	8	140–141	$C_9H_{11}NO_3$
OCH_3			OCH_3		48	6	79–80	$C_9H_{11}NO_3$
OCH_2CH_3			OCH_2CH_3		36[b]	1	95.5–96	$C_{11}H_{15}NO_3$
	F	CH_3			53	2	68–69	C_8H_8FNO
	F			CH_3	56	2	88–89	C_8H_8FNO
		F		CH_3	41	2	91–92	C_8H_8FNO
	Cl	F			73	2	94–95	C_7H_5ClFNO
	CF_3		CF_3		54	1	124–125	$C_9H_5F_6NO$
	CF_3	Cl			58	2	108–109	$C_8H_5ClF_3NO$
Cl			CF_3		35[b]	8	110–111	$C_8H_5ClF_3NO$
	Cl	CH_3			68.5	4	97–97.5	C_8H_8ClNO
	Cl			CH_3	93	4	134–134.5	C_8H_8ClNO
Cl				CH_3	79[b]	7	167.5–168	C_8H_8ClNO
Cl	Cl				42[b]	1	151	$C_7H_5Cl_2NO$
	Cl	Cl			71	9	109.5–110 (110–112)[k]	
Cl			Cl		40[b]	1	148	$C_7H_5Cl_2NO$
	Cl		Cl		54	1	130	$C_7H_5Cl_2NO$
Br				Br	86	1	199.5–201	$C_7H_5Br_2NO$
	Br	Br			95	10	132–133	$C_7H_5Br_2NO$
OCH_3		Cl	OCH_3		96	7	108–109	$C_9H_{10}ClNO_3$
	CH_3O	Cl		OCH_3	89	1	103–104	$C_9H_{10}ClNO_3$
	Cl	OCH_3		OCH_3	76	8	184–185	$C_9H_{10}ClNO_3$
Cl		Cl	Cl		56[b]	7	169–169.5	$C_7H_4Cl_3NO$

[a] Yields are based on the crystalline product isolated following dilution of the reaction mixture with water unless otherwise noted. [b] The yield after one or more recrystallizations. [c] The formanilide was recrystallized from ethanol-water (1), benzene–petroleum ether (2), chloroform–petroleum ether (3), methanol (4), acetone (5), carbon tetrachloride (6), methanol-water (7), ethanol (8), benzene–carbon tetrachloride (9), or benzene (10). [d] Melting point of the analytical sample unless indicated otherwise. The melting point in parentheses has been previously reported. [e] R. B. Kelly, W. I. Taylor, and K.

were readily prepared by the dimethylformamide–sodium methoxide procedure, the reaction usually led to complex mixtures when applied to nitroanilines. The difficulty experienced with nitro compounds was attributed to additional reactions involving methoxide and was not further investigated. Attempts to formylate, for example, 3,4-dichloroaniline with dimethylformamide in the absence of sodium methoxide or by substituting sodium hydroxide for the alkoxide were unsuccessful. Heating at reflux for periods up to ninety hours resulted only in recovery of starting aniline. Formylation of 2,5-dimethoxyaniline with dimethylformamide using either sodium amide or hydride in place of sodium methoxide resulted in increased yield of formanilide III. These experiments served to approximately define the base requirements of



III

the reaction and were not pursued further in the present study.

The dimethylformamide–sodium methoxide formylation reaction was easily extended to the synthesis of *N*-phenyl-*p*-aminoformanilide, 4,4′-diformamidodiphenylsulfone (II), α-formamidonaphthalene, and 8-formamido-2-naphthol from the corresponding amines.

TABLE I (*Continued*)

Carbon		Hydrogen		Bromine		Chlorine		Fluorine		Nitrogen	
Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
72.46	72.35	7.43	7.49							9.93	9.36
60.42	59.99	4.35	4.30							10.07	10.27
60.42	60.37	4.35	4.29								
50.80	51.02	3.19	3.27					30.13	29.89	7.40	7.41
34.04	33.71	2.45	2.27							5.67	5.84
72.45	72.13	7.30	7.31							9.38	9.41
72.45	72.43	7.30	7.26							9.38	9.54
65.44	65.31	6.71	6.56							8.48	8.59
59.65	59.48	6.12	6.05							7.72	7.90
59.65	59.44	6.12	6.18							7.72	7.73
63.10	62.97	7.22	7.06							6.69	6.83
62.73	62.86	5.26	5.45					12.41	12.11	9.15	8.98
62.73	62.89	5.26	5.05					12.41	12.26	9.15	9.01
62.73	62.94	5.26	5.37							9.15	8.87
48.43	48.81	2.90	3.10					10.95	10.28	8.07	7.61
42.04	42.22	1.96	2.12							5.45	5.39
42.99	42.74	2.25	2.58							6.27	6.26
42.99	42.44	2.25	2.45							6.27	6.30
56.65	56.60	4.75	4.66							8.26	8.11
56.65	56.89	4.75	4.76							8.26	7.90
56.65	56.56	4.75	4.78							8.26	8.04
44.24	44.30	2.65	2.91							7.37	7.34
44.24	44.28	2.65	2.85			37.32	37.21			7.37	7.21
44.24	44.39	2.65	2.66							7.37	7.20
30.14	30.00	1.81	1.78	57.29	57.07					5.02	4.73
30.14	30.10	1.81	1.87	57.29	57.00					5.02	4.90
50.13	49.82	4.67	4.77							6.49	6.18
50.13	49.85	4.67	4.64			16.44	16.27			6.49	6.26
50.13	50.13	4.67	4.55			16.44	16.56			6.49	6.32
37.45	37.72	1.79	2.01							6.24	6.39

Wiesner, *J. Chem. Soc.*, 2094 (1953). [f] S. Sugasuwa and H. Shigehara, *Yakugaku Zasshi*, 62, 531 (1942); *Chem. Abstr.*, 45, 2861 (1951). [g] H. Rheinboldt and A. Levy, *Univ. Sao Paulo, Faculdade filosof., cienc. e letras, Bol. No. 129, Quimica* No. 3, 69 (1951); *Chem. Abstr.*, 46, 7552 (1952). [h] Melting point of the crude product. [i] O. C. M. Davis, *J. Chem. Soc.*, 95, 1397 (1909). [j] *Cf.* Ref. 6. [k] C. W. Huffman, *J. Org. Chem.*, 23, 727 (1958).

EXPERIMENTAL[7]

General formylation procedure. The following general procedure was employed for preparation of the formanilides described in Table I. Sodium methoxide[8] (0.3 mole) was added to the amine (0.15 mole), dissolved in 150 ml. of dimethylformamide[9] and the resulting mixture was heated at reflux for 30 min. Dimethylamine[10] was rapidly evolved during the first 15 to 20 min. The hot reaction mixture was diluted with 300 to 800 ml. of water, cooled and usually refrigerated overnight before collecting the product.[11]

(7) The infrared spectrum of each pure compound was recorded and found to be consistent with the assigned structure. Melting points were observed using open Kimble glass capillaries and are uncorrected. Microanalyses were provided by Dr. A. Bernhardt, Max-Planck Institut, Mülheim, Germany. Several of the fluorine-containing anilines were generously provided by L. F. Loutrel, Jr., Maumee Chemical Co.

(8) Dry sodium methoxide prepared in the laboratory was found to be the most reliable reagent. Several recently purchased, and previously unopened, commercial samples of sodium methoxide gave comparable results. The formylation reaction failed when poorer quality alkoxide was used.

(9) Commercial dimethylformamide was conveniently dried by allowing it to remain for 48 hr. in contact with Fischer Scientific Co. Molecular Sieve Type 4A. This procedure is based on unpublished experiments performed by Dr. J. L. Wolfhagen of this laboratory. Additional purification was found to be unnecessary.

(10) In several cases the amine was guided into dilute hydrochloric acid solution and identified as dimethylamine hydrochloride.

(11) The yield of several formanilides appreciably soluble in the aqueous mixture was improved by removing *ca.* half of the reaction solvent *in vacuo* before dilution. When carefully purified amine starting material was employed, the crude formamide was generally unaccompanied by a detectable (melting point determination) amount of impurity.

Formylation of 2,5-dimethoxyaniline in the presence of sodium hydride or sodium amide. To a solution of 2,5-dimethoxyaniline (12.1 g.) in 150 ml. of dimethylformamide (under nitrogen) was added 6.8 g. of a 53% dispersion of sodium hydride in oil.[12] The mixture was heated at reflux for 20 min., cooled (ice-bath) and then cautiously treated with water. After hydrolyzing the remaining sodium hydride, the mixture was diluted to *ca.* 1 l. with water and refrigerated for 16 hr. The crystalline 2,5-dimethoxyformanilide weighed 10.3 g. (62%), m.p. 78–79.5° (*cf.*, Table I).

When an equivalent quantity of commercial (Fisher Scientific Co.) sodium amide was substituted for sodium hydride and the reaction repeated exactly as described above, 8.7 g. (52%) of 2,5-dimethoxyformanilide, m.p. 79–80°, was isolated.

Each of the following formamides was prepared using the general sodium methoxide-dimethylformamide procedure. N-Phenyl-p-aminoformanilide. The crude product prepared from 27.6 g. of *p*-aminodiphenylamine recrystallized from methanol-water as purple crystals (18.7 g., 59%), m.p. 170–171°. Two additional recrystallizations from methanol-water (Norit-A) gave pure colorless leaflets melting at 174.5–175°.

Anal. Calcd. for $C_{13}H_{12}N_2O$: C, 73.56; H, 5.70; N, 13.20. Found: C, 73.66; H, 5.75; N, 13.12.

4,4′-Diformamidodiphenylsulfone (II). Conversion of 4,4′-diaminodiphenylsulfone (I, 40 g.) to the crude light brown diformyl derivative, m.p. 242–250° (48 g., 98%), was accomplished in the usual manner. Repeated recrystallization from methanol-water (Darco) led to a colorless crystalline analytical sample, m.p. 273–273.5° (lit.,[13] m.p. 260.5°).

Anal. Calcd. for $C_{14}H_{12}N_2O_4S$: C, 55.26; H, 3.97; N, 9.21; S, 10.53. Found: C, 55.22; H, 3.92; N, 9.10; S, 10.59.

α-Formamidonaphthalene. The crude formamide derivative prepared from 20 g. of α-naphthylamine weighed 19.7 g. (82.5%) and melted at 131–135°. Recrystallizing the reddish-brown product from benzene (Norit-A) gave colorless needles (19.0 g., 79.5%), m.p. 138.5–139.5° (lit.,[14] m.p. 138.5°).

8-Formamido-2-naphthol. Before collecting the formamide (8.8 g., 73%) derived from 10 g. of 8-amino-2-naphthol, the reaction mixture was cooled and adjusted to *p*H 5 with hydrochloric acid. Two recrystallizations from methanol-water (Darco) gave colorless needles melting at 205.5–207° dec. (lit.,[15] m.p. 205–207° dec.).

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF MAINE
ORONO, ME.

(12) Metal Hydrides, Inc.

(13) V. A. Zasosov, *Zhur. Obshchei Khim.*, **17**, 471 (1947); *Chem. Abstr.*, **42**, 534 (1948).

(14) G. Tobias, *Ber.*, **15**, 2447 (1882).

(15) H. E. Fierz-David and W. Kuster, *Helv. Chim. Acta.*, **22**, 82 (1939).

4-(4-Dimethylaminostyryl)quinolines with a Methyl Group on the Styryl Ring[1]

CARL TABB BAHNER, WILLIAM CHAPMAN, JR., HAROLD LYONS, AND LYDIA M. RIVES[1]

Received May 23, 1960

A series of 4-(4-dimethylaminostyryl)quinolines carrying a methyl group on the quinoline ring has been reported.[2] The series has been extended to include compounds carrying methyl groups on the ring in the styryl group. These compounds are of especial interest because of indications that the hydroxylation of certain positions of such compounds as *p*-aminodiphenyl *in vivo* is involved in their carcinogenetic effects.[3] It seemed that the methyl groups might modify the biological effects of the styrylquinolines by blocking or increasing hydroxylation at certain positions, or by steric effects. Melting points and analyses of the new compounds are shown in Table I.

The substituted 4-dimethylaminobenzaldehydes required were prepared from the corresponding substituted *N,N*-dimethylanilines by the method of Campaigne and Archer[4] or the method of Vilsmeier and Haack.[5] Attempts to prepare 4-dimethylamino-3,5-dimethylbenzaldehyde by these methods and by the method of Adams and Coleman[6] were unsuccessful.

The compounds have been tested against Walker 256 tumors by Professor Alexander Haddow and

(1) This research was supported in part by grants from the American Cancer Society and the National Institutes of Health. We are also grateful for the use of the laboratory facilities of the Chester Beatty Research Institute and for the assistance of Mr. David Hakim in the preparation of one of the compounds reported.

(2) C. T. Bahner, C. Cook, J. Dale, J. Fain, E. Franklin, J. C. Goan, W. Stump, and J. Wilson, *J. Org. Chem.*, **22**, 682 (1957).

(3) A. L. Walpole, M. H. C. Williams, and D. C. Roberts, *Brit. J. Ind. Med.*, **9**, 255–263 (1952).

(4) E. Campaigne and W. L. Archer, *Org. Syntheses*, **33**, 27 (1953).

(5) A. Vilsmeier and A. Haack, *Ber.*, **60**, 119 (1927).

(6) R. Adams and G. H. Coleman, *Org. Syntheses*, **2**, 17 (1922).

TABLE I

4-(4-DIMETHYLAMINOSTYRYL)QUINOLINES

Substituent	M.P.	Method	Reaction Time	Reaction Temp.	Yield, %	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
2′-Methyl-[a]	163.5–164.5	$ZnCl_2$[2]	30 hr.	120	20	83.29	6.99	9.71	83.2 83.1	6.6 6.8	9.60[b]
3′-Methyl-	191.0–193.0	Leese[7]	1 hr.	140–160	4	83.30	6.99	9.71	83.26 83.56	6.85 6.70	[c]
2′,6′-Dimethyl-	140.6–141.9	Leese	40 min.	155–165	50	83.40	7.33	9.26	83.27	7.29	9.03[b]
2′,6′-Dimethyl-3-methyl-	130	Leese	3 hr.	155–170		83.50	7.64	8.85	83.82	7.35	8.91[b]

[a] Positions marked by a (′) are on the benzene ring of the styryl group. [b] Analyses by Burroughs Wellcome Laboratories. [c] Analyses by Galbraith Laboratories.

his associates at the Chester Beatty Research Institute. Several of them exhibited antitumor activity. The effects of the different locations of the alkyl groups are to be discussed in a later paper.

CARSON-NEWMAN COLLEGE
JEFFERSON CITY, TENN.

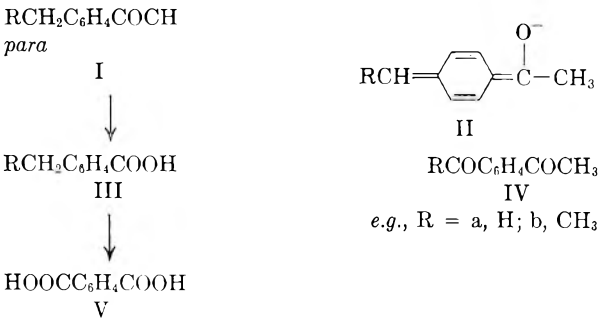
(7) C. T. Bahner, C. Cook, J. Dale, J. Fain, P. Smith, and J. Wilson, *J. Org. Chem.*, **23**, 1060 (1958).

Sodium Hypochlorite Oxidation of *p*-Methylacetophenone

JOSEPH P. FEIFER AND WILLIAM J. WELSTEAD, JR.

Received August 11, 1960

The recently proposed mechanism for sodium hypochlorite oxidations of *para*-methylene groups in acetophenone systems[1] (I), expressed in terms of the *a priori*-unlikely[2] enolization through the *para*-methylene group (e.g. II) and imputing a vital role to the acetyl group[1], is not supported by experimental evidence.



The experiment described below, under identical conditions, in which *p*-toluic acid (IIIa) was isolated in 77% yield after seven minutes, and was oxidized further to terephthalic acid (V) upon continuation of this treatment, demonstrates that in fact the vulnerable[2] acetyl group does not survive to give IV, and thus cannot participate in the oxidation of the aryl methyl or methylene group. The steps involved therefore are I → III → V, and the oxidation of the aryl methyl or methylene must be explained in terms of the effects of the first-formed carboxyl or carboxylate group.

EXPERIMENTAL

Oxidation of p-methylacetophenone (Ia). (A) A mixture of 5.0 g. of Ia and 800 ml. of commercial 5% sodium hypochlorite solution was refluxed gently under vigorous stirring and a nitrogen atmosphere.[1] After 7 min., a 100-ml. aliquot upon cooling and treatment with sodium bisulfite and acidification, precipitated 0.48 g. (77%) of pure *p*-toluic acid (m.p. 176–178°, identified as its amide and anilide). From the remainder of the reaction mixture after 28 hr., 2.9 g. of solid (m.p. >250°) was similarly obtained which upon washing with ether to remove *p*-toluic acid yielded 1.6 g. (30%) of pure terephthalic acid (V, subl. >300°, identified as its dimethyl and diethyl esters). Evaporation of the ether washings produced 1.3 g. (26%) of *p*-toluic acid containing chlorinated impurities (identified by infrared spectrum) which on oxidation under the above conditions gave only pure V (65% by weight).

(B) In a similar oxidation with added base (4.1 g. of sodium hydroxide), after 10 min., a 100-ml. aliquot yielded 0.62 g. (98%) of pure *p*-toluic acid, and the remainder of the reaction mixture after 44 hr. gave 1.26 g. (23%) of pure terephthalic acid and 2.34 g. (53%) of pure *p*-toluic acid.

Oxidation of p-toluic acid (IIIa, 4.3 g.) under the above conditions without adjusting for reagent changes entailed in the primary and rapid destruction of the acetyl group starting from Ia (24 hr.), gave 2.95 g. of solid (m.p. >240°) which was purified by washing with ether [1.65 g. (32%)] and identified as V by infrared spectrum. Evaporation of the ether washings produced 1.3 g. of impure IIIa.

Acknowledgment. The authors are grateful to Professor Robert E. Lutz for useful and stimulating discussions.

COBB CHEMICAL LABORATORY
UNIVERSITY OF VIRGINIA
CHARLOTTESVILLE, VA.

(1) D. D. Neiswender, Jr., W. B. Moniz, and J. A. Dixon, *J. Am. Chem. Soc.*, **82**, 2876 (1960).

(2) *Cf.* The first point of attack of hypohalite on *p*-alkylated acetophenones is the acetyl group. [A. M. Van Arendonk and M. E. Cupery, *J. Am. Chem. Soc.*, **53**, 3184 (1931); R. C. Fuson, *J. Am. Chem. Soc.*, **56**, 1417 (1934)].

Reactions of *N,N*-Dichloroamines

S. L. REID AND D. B. SHARP

Received August 23, 1960

N-Chlorinated derivatives of amines can be prepared by a number of methods involving hypochlorous acid or its derivatives.[1,2,3] *N*-Chloro-*prim*-alkylidenimines have been prepared by the reaction of aldehydes with chloroamine[4] and *N*-chloro-*sec*-alkylidenimines have been postulated as intermediates in the preparation of α-aminoketones from *N,N*-dichloro-*sec*-alkylamines.[3] The preparation of *N*-chlorocyclohexanimine has been claimed by the reaction of cyclohexanone with chloramine.[5]

We have found that *N*-chloro-*sec*-alkylidenimines can be prepared from *N,N*-dichloro-*sec*-alkylamines by the action of bases. For example, *N,N*-dichlorocyclohexylamine yields *N*-chlorocyclohexanimine.[6] Such widely different bases as tertiary amines and

(1) A. Berg, *Ann. chim. et phys.*, **3**, 289 (1894).

(2) G. F. Wright, L. K. Jackson, and G. N. R. Smart, *J. Am. Chem. Soc.*, **69**, 1539 (1947).

(3) (a) H. E. Baumgarten and F. A. Bower, *J. Am. Chem. Soc.*, **76**, 4561 (1954); (b) H. E. Baumgarten and J. M. Petersen, *J. Am. Chem. Soc.*, **82**, 459 (1960).

(4) C. R. Hauser, *J. Am. Chem. Soc.*, **52**, 1108 (1930).

(5) B. Rudner (to W. R. Grace & Co.), U. S. 2,894,028 (1959), "Cyclohexylideneimino Compounds."

potassium hydroxide in aqueous dioxane can be used successfully.

Certain aromatic *N*-chloroimines yield amides by a Beckmann rearrangement.[7] We were unsuccessful in attempts to obtain ϵ-caprolactam by treatment of *N*-chlorocyclohexanimine with such reagents as sulfuric acid, boron trifluoride, stannic chloride, and antimony pentachloride. Only cyclohexanone was isolated from the complexes after hydrolysis.

We have found that 2-aminocyclohexanone hydrochloride[3a] can be readily converted to 2-aminocyclohexanone oxime hydrochloride. A Beckmann rearrangement of this oxime should give either 2-oxo-7-aminohexamethylenimine or 2-oxo-3-aminohexamethylenimine. The latter could presumably be hydrolyzed to lysine. Paper chromatographic analysis of the products of an attempted Beckmann rearrangement of the oxime showed no ninhydrin-positive compounds, indicating that 2-oxo-7-aminohexamethylenimine was probably formed and was hydrolyzed to the *gem*-diamino derivative which would be expected to lose ammonia and be hydrolyzed to adipaldehydic acid. The presence of ammonia was noted during addition of base to the acid treated oxime. This direction of ring opening parallels the results of McLaren and Ungnade with 2-alkylcyclohexanone oximes.[8]

EXPERIMENTAL

Preparation of N-chloroimines. (a) *Triethylamine method.* To a solution of triethylamine in a solvent such as dry hexane or benzene was added an equimolar amount of the *N,N*-dichloroamine. The solution was stirred at room temperature for a short time and then at reflux temperature for 1–3 hr. The amine salt was filtered off and the filtrate was distilled at reduced pressure.

(b) *Potassium hydroxide method.* To a solution of potassium hydroxide in aqueous dioxane (0.1 mole per 120 cc. of water and 200 cc. of dioxane) was added an equimolar amount of the *N,N*-dichloroamine with vigorous stirring, maintaining the temperature below 35° during the addition and during a subsequent 15–30 min. reaction period. The solution was saturated with ammonium chloride and extracted thoroughly with ether. The combined extracts were dried and distilled from a water bath at reduced pressure.

N-Chlorocyclohexanimine. This compound was prepared in 52% yields by method (a) and 30% yields by method (b). It had b.p. 33–35°/1 mm., n_D^{25} 1.5053.

Anal. Calcd. for $C_6H_{10}ClN$: C, 54.76; H, 7.66; Cl, 26.95. Found: C, 54.09; H, 7.45; Cl, 26.42.

Its infrared absorption spectrum was consistent with an *N*-chloroimine structure and it could be hydrolyzed to cyclohexanone, identified as its 2,4-dinitrophenylhydrazone.

N-Chloroisopropylidenimine. This compound was prepared in 40% yields by method (a). It had b.p. 54–55°/100 mm.

Anal. Calcd. for C_3H_6ClN: C, 39.46; H, 6.61; Cl, 38.74; N, 15.31. Found: C, 39.59; H, 6.82; Cl, 38.41; N, 15.41.

Hydrolysis with dilute acid gave acetone, identified as its 2,4-dinitrophenylhydrazone.

2-Aminocyclohexanone oxime hydrochloride. 2-Aminocyclohexanone hydrochloride[3a] (9 g., 0.06 mole) in 15 cc. of water was added to 4.9 g. (0.07 mole) of hydroxylamine hydrochloride and 3.2 g. (0.03 mole) of sodium carbonate in 10 cc. of water. The solution was warmed on the steam bath 1.5 hr., cooled in ice, and filtered. The filtrate was concentrated and filtered again. The total solids were dissolved in methanol, treated with activated charcoal and filtered. Ether was added to the filtrate to precipitate the 2-aminocyclohexanone oxime hydrochloride, 7.1 g. A second crop of crystals was obtained by concentrating the mother liquor and adding ether. Total yield 7.9 g., 80%. An analytical sample was obtained by recrystallization from methanol-ether mixtures. It melted at 225° dec. Its infrared spectrum was consistent with an oxime structure.

Anal. Calcd. for $C_6H_{13}ClN_2O$: C, 43.75; H, 7.95; N, 17.01. Found: C, 43.94; H, 7.96; N, 17.16.

Beckmann rearrangement of 2-aminocyclohexanone oxime hydrochloride. One gram of the oxime was dissolved in 1 cc. of sulfuric acid containing one drop of water. After hydrogen chloride evolution ceased, the solution was heated to 120° for 2 min., cooled, diluted with 9 cc. of water, let stand several hours. Lysine hydrochloride (0.1 g.) was treated in the same way, as a control. The solutions were treated with saturated barium hydroxide solution at 80° to *p*H 10 ("pHydrion" test paper) and centrifuged. The *p*H was adjusted to 5 with dilute sulfuric acid and the solutions were chromatographed on Whatman No. 1 filter paper with a phenol solvent.[9] The chromatograms were dried, sprayed with ninhydrin solution, and developed in an oven at 35° for 1 hr. A well defined spot appeared for the lysine control but no spot appeared for the oxime rearrangement product.

In another experiment after the oxime had been heated with acid and diluted with water, cold potassium hydroxide solution was added until the solution was strongly basic. Ammonia was evolved as evidenced by its odor and reaction with moist indicator paper held above the solution.

RESEARCH AND ENGINEERING DIVISION
MONSANTO CHEMICAL CO.
DAYTON 7, OHIO

(6) *N*-Chlorocyclohexanimine was subsequently prepared independently by W. S. Knowles and G. Alt, *J. Org. Chem.*, **25**, 2047 (1960), and shown to be an intermediate in the transformation of *N,N*-dichlorocyclohexylamine to 2-aminocyclohexanone.

(7) W. Theilacker and H. Mohl, *Ann. der Chem.*, **563**, 99 (1949).

(8) A. D. McLaren and H. E. Ungnade, *J. Org. Chem.*, **10**, 29 (1945).

(9) R. J. Block, R. Le Strange, and G. Zweig, *Paper Chromatography*, N. Y. Academic Press, 1952, p. 53.

The Identity of Nottbohm's "C_6H_6O" with Sorbanilide

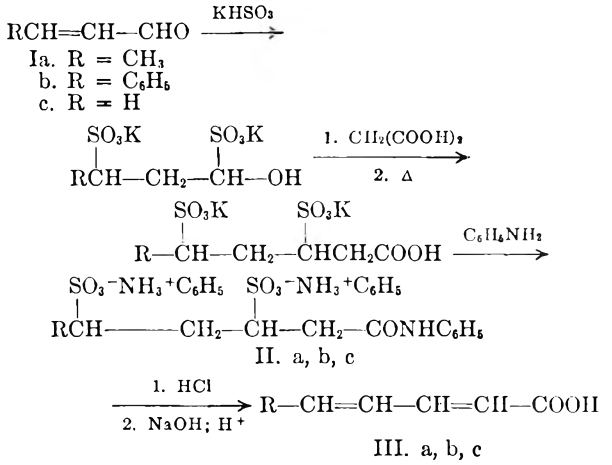
MORDECAI B. RUBIN AND M. F. HOOVER

Received September 6, 1960

In 1916 Nottbohm[1] reported a synthesis of dienoic acids by the sequence illustrated. The intermediate anilide dianilium sulfonates (II. a,b,c) were obtained in good yield as crystalline solids. Refluxing these with hydrochloric acid followed by refluxing with concentrated sodium hydroxide solution and acidification afforded the dienoic acids in good yield. However, if IIa or IIb were refluxed with concentrated sodium hydroxide

(1) O. Nottbohm, *Ann.*, **412**, 49 (1916).

omitting the hydrochloric acid treatment, crystalline solids were obtained upon dilution with water. Thus, for example, crotonaldehyde (Ia) led to the formation of a substance, m.p. 155–156°, which gave negative qualitative tests for sulfur and nitrogen and possessed an elementary analysis corresponding to the empirical formula C_6H_6O.



We have repeated this series of reactions starting with crotonaldehyde and obtained a substance with the same melting point and elementary analysis which gave at best doubtful qualitative tests for nitrogen. In view of (1) the difficulty of accommodating a transformation of IIa to $(C_6H_6O)_n$, (2) the similarity of the melting point with that reported for sorbanilide,[2] and (3) the very similar elemental analysis of C_6H_6O and sorbanilide ($C_{12}H_{13}NO$), we were led to compare the two substances in spite of the dubious tests for nitrogen. Mixture melting point and infrared spectral comparison with an authentic sample of sorbanilide[2] proved the identity of the two substances.

The explanation for the formation of sorbanilide presumably lies in the relative rates of elimination *vs.* amide hydrolysis and the fortuitous choice of reaction time by Nottbohm. Essentially all the material not converted to sorbanilide by refluxing IIa with sodium hydroxide solution was obtained as sorbic acid by acidification of the alkaline filtrate. Attempts to characterize the product formed from IIa with hydrochloric acid were not successful.

Nottbohm also reported formation of a substance, m.p. 188°, C_9H_8O, from cinnammaldehyde (Ib). This appears likely to be the unreported anilide of 5 - phenyl - 2,4 - pentadienoic acid. (*Anal.* Calcd. for $C_{17}H_{15}ON$: C, 81.9; H, 6.1; reported by Nottbohm[1]; C, 81.8, 81.7; H, 6.2, 6.1.)

CARNEGIE INSTITUTE OF TECHNOLOGY
SCHENLEY PARK
PITTSBURGH 13, PA.

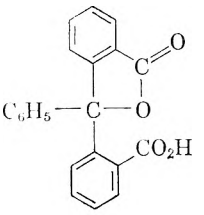
(2) O. Doebner and A. Wolf, *Ber.*, 34, 2221 (1901) report m.p. 154–156° for sorbanilide.

The Metalation of Diphenylferrocenylcarbinol[1]

ROBERT A. BENKESER, WALTER P. FITZGERALD, AND MARVIN S. MELZER

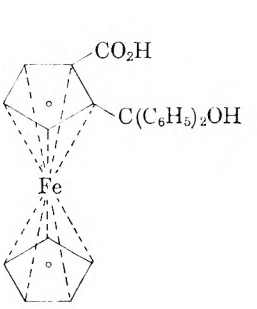
Received November 14, 1960

It is known that triphenylcarbinol can be metalated with *n*-butyllithium and then carbonated to form the lactone of triphenylcarbinol-2,2′-dicarboxylic acid[2] (I).

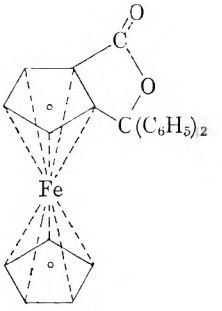


I

We are hereby reporting that a somewhat analogous reaction occurs with diphenylferrocenylcarbinol. Treatment of the latter compound with *n*-butyllithium, followed by carbonation with Dry Ice produced 2-carboxydiphenylferrocenylcarbinol (II) in 73% yield. When II was heated or treated with acid it readily converted to the lactone of 2-carboxydiphenylferrocenylcarbinol (III).



II



III

The structure of II was clearly indicated by its acidic nature and infrared spectrum which showed a strong carboxyl band at 5.95 μ and bands at 9 and 10 μ indicating an unsubstituted C_5 ferrocene ring. The ready conversion of II to III places the carboxyl group at the 2- rather than 3- position relative to the alcohol function.

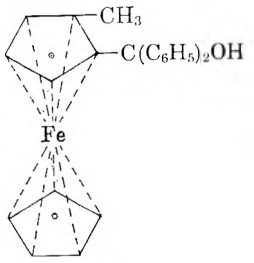
The structure of III was clearly indicated by its elemental analysis, molecular weight and infrared spectrum. The latter showed unambiguous five-

(1) This research was supported by the United States Air Force through the Air Force Office of Scientific Research of the Air Research and Development Command, under contract No. AF 49(638)-297. Reproduction in whole or in part is permitted for any purpose of the United States Government.

(2) (a) H. Gilman, G. E. Brown, F. J. Webb, and S. M Spatz, *J. Am. Chem. Soc.*, 62, 977 (1940); (b) H. Gilman and G. E. Brown, *J. Am. Chem. Soc.*, 62, 3208 (1940).

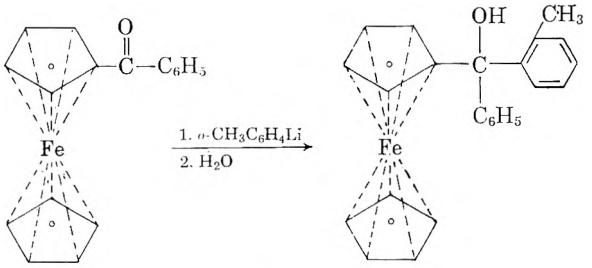
membered ring lactone absorption at 5.6 μ and ferrocene absorption at 9 and 10 μ. The spectrum was devoid of —OH absorption.

The metalated diphenylferrocenylcarbinol was found to react with methyl iodide producing a methylated compound, presumably with structure IV.



IV

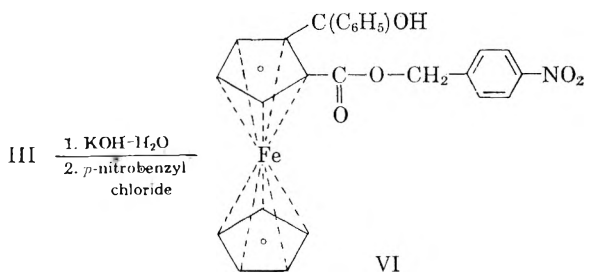
In order to prove that metalation of the diphenylferrocenylcarbinol had not occurred in one of the phenyl rings (paralleling the reaction with triphenylcarbinol) rather than in the ferrocene moiety, an authentic sample of ferrocenylphenyl-*o*-tolylcarbinol (V) was synthesized as shown below.



V

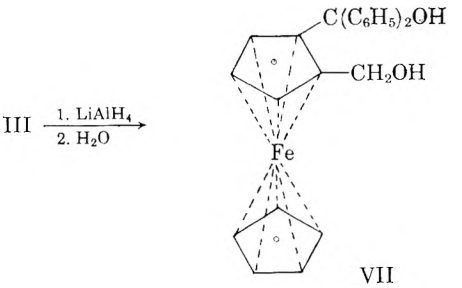
Compound V melted at 125° in contrast to 167° (the m.p. of IV) which clearly indicated that the site of metalation was in the ferrocene and not the phenyl ring.

Compound III exhibited reactions which are classical for lactones. When saponified with base and treated with *p*-nitrobenzyl chloride, an ester (VI) was produced.



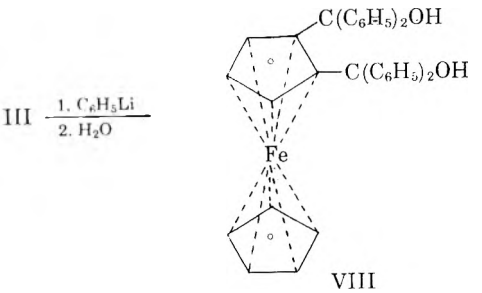
VI

When treated with lithium aluminum hydride, a diol (VII) was formed in quantitative yield.



VII

Similarly, treatment of the lactone with phenyllithium produced bis-1,2-(diphenylhydroxymethyl)-ferrocene (VIII) in 97% yield.



VIII

EXPERIMENTAL

Diphenylferrocenylcarbinol. Phenyllithium was prepared in dry diethyl ether under nitrogen from 5.0 g. (0.72 g.-atom) of lithium wire and 56.5 g. (0.36 mole) of bromobenzene. A solution of 33.1 g. (0.12 mole) of benzoylferrocene[3] in ether was added dropwise, and the mixture was refluxed for 24 hr. under nitrogen. Hydrolysis was effected with water, and the ether layer was separated and dried. Removal of the ether gave impure carbinol, which after crystallization from hexane melted at 130–131°. The yield was 76%.

Anal. Calcd. for $C_{23}H_{20}FeO$: C, 75.01; H, 5.47. Found: C, 75.29; H, 5.23.

2-Carboxydiphenylferrocenylcarbinol. n-Butyllithium (0.15 mole) in ether was added to 22.75 g. (0.062 mole) of diphenylferrocenylcarbinol also dissolved in ether. The dark yellow suspension was stirred under nitrogen at room temperature for 36 hr. and was then carbonated with Dry Ice. After the mixture had warmed to room temperature, water was added. Approximately 5 g. of the starting carbinol was recovered from the ether layer. The water layer was acidified (*p*H = 1) with hydrochloric acid and rapidly extracted with ether. The ether layer was washed extensively with water to remove the valeric acid and any residual hydrochloric acid. Evaporation of the ether yielded 13 g. (73%) of red crystals melting with effervescence at 137–139°. Recrystallization of this material from ether raised the melting point to 144–146° (effervescence).

Anal. Calcd. for $C_{24}H_{20}FeO_3$: C, 69.92; H, 4.89; Fe, 13.55; mol. wt. 395. Found: C, 69.34, 69.46; H, 5.65, 5.63; Fe, 13.16; mol. wt. (Rast), 418.

When heated above 146° the liquid melt resolidified and melted again at 203–204° (lactone). The acid could also be converted to the lactone by vigorous shaking with aqueous hydrochloric acid. It also reacted instantaneously with aqueous sodium bicarbonate or sodium hydroxide, forming an ether-insoluble yellow sodium salt. The free acid showed a sharp—OH band at 2.9 μ in the infrared, as well as a strong band at 5.95 μ (carboxyl) and the typical 9 and 10 μ bands of ferrocene.

(3) N. Weliky and E. S. Gould, *J. Am. Chem. Soc.*, 79, 2742 (1957).

Lactone of 2-Carboxydiphenylferrocenylcarbinol. If the carbonation product from above was allowed to remain in contact with the hydrochloric acid used to acidify the solution, brown crystals were obtained upon evaporation of the solvent. Crystallization from ether produced a solid (40% yield) which melted sharply at 200°.

Anal. Calcd. for $C_{24}H_{18}FeO_2$: C, 73.12; H, 4.57; Fe, 14.17. Found: C, 73.06; H, 4.51; Fe, 14.00.

The infrared spectrum of this product showed unambiguous five-membered ring lactone absorption at 5.6 μ, and 9,10 μ ferrocene absorption. The spectrum was devoid of —OH absorption.

2-Methyldiphenylferrocenylcarbinol. Diphenylferrocenylcarbinol (30 g.; 0.08 mole) was metalated with *n*-butyllithium as described above. To this product was added 118 g. (0.8 mole) of dry methyl iodide in ether. After spontaneous reflux subsided, the mixture was refluxed under nitrogen for 24 hr. Hydrolysis with water was followed by separation and drying of the ether layer. Evaporation of the solvent, yielded 21 g. (69%) of amber crystals, which, after crystallization from ether, melted sharply at 167°.

Anal. Calcd. for $C_{24}H_{22}FeO$: C, 75.39; H, 5.80; Fe, 14.61. Found: C, 75.11; H, 5.81; Fe, 14.53.

The infrared spectrum of this material showed a strong —OH band at 2.8 μ, ring methyl absorption at 7.2 μ (absent in the spectrum of the parent carbinol), as well as the ferrocene absorption at 9 and 10 μ.

Ferrocenylphenyl-o-tolylcarbinol. *o*-tolyllithium was prepared by adding 85.5 g. (0.5 mole) of *o*-bromotoluene in 60 ml. of ether to 7.8 g. (1.2 g.-atoms) of lithium wire in ether under nitrogen. An ethereal solution of 18 g. (0.062 mole) of benzoylferrocene was added at a dropwise rate to the *o*-tolyllithium at room temperature. The mixture was stirred at room temperature for 24 hr. and then refluxed an additional 4 hr. After hydrolysis with water, the ether layer was separated and dried. Removal of the solvent deposited 18.0 g. (80%) of a yellow solid melting at 124–127°. This material was placed on an alumina chromatogram column, developed with benzene and eluted with ether. The analytical sample melted at 124–125°.

Anal. Calcd. for $C_{24}H_{22}FeO$: C, 75.39; H, 5.80; Fe, 14.61. Found: C, 75.59; H, 5.71; Fe, 14.83.

An infrared spectrum of this compound showed an —OH stretch at 2.9 μ, methyl compression modes at 6.9 μ (sym.) and 7.24 μ (antisym.) as well as the 9 and 10 μ peaks characteristic of ferrocene.

2-Hydroxymethyldiphenylferrocenylcarbinol. A 0.6-g. sample (0.0025 mole) of the pure lactone in ether was treated with an ethereal solution of 0.5 g. (0.013 mole) of lithium aluminum hydride under nitrogen. The amber solution rapidly changed into a yellow suspension accompanied by spontaneous reflux. When the reflux subsided, the mixture was refluxed for 24 hr. The excess hydride was destroyed with ethyl acetate and water was added. The ether layer was separated, and the solvent was removed under vacuum. A yellow solid (0.6 g.) was deposited melting in the crude state at 145°. After recrystallization from ether, the yellow crystals melted at 146°. The yield was quantitative.

Anal. Calcd. for $C_{24}H_{22}FeO_2$: C, 72.30; H, 5.55. Found: C, 72.16; H, 5.80.

The infrared spectrum of this material showed strong —OH absorption at 2.9 μ and the characteristic 9 μ and 10 μ bands of ferrocene.

bis-1,2-(Diphenylhydroxymethyl)ferrocene. Approximately 0.1 mole of phenyllithium in ether was added dropwise to an ethereal solution of 1.0 g. (0.0025 mole) of the lactone under nitrogen. Spontaneous refluxing occurred, followed by the formation of a yellow suspension. The mixture was stirred for 4 hr. at room temperature and then refluxed an additional 20 hr. After hydrolysis with water, followed by the usual work-up procedure a yield of 1.35 g. (97%) of a yellow solid melting at 190–192° was obtained. Recrystallization from ether yielded a dark yellow crystalline solid melting at 195–196°.

Anal. Calcd. for $C_{36}H_{30}FeO_2$: C, 78.55; H, 5.49; Fe, 10.15. Found: C, 78.31; H, 5.72; Fe, 9.97.

The infrared spectrum showed —OH absorption at 2.8 μ as well as the 9 and 10 μ bands of ferrocene.

p-Nitrobenzyl ester of 2-carboxyferrocenyldiphenylcarbinol. A 2.0-g. sample of the lactone (0.005 mole) was refluxed for 40 hr. in 100 ml. of 20% aqueous potassium hydroxide whereupon a brick-red suspension formed. The alkaline solution was neutralized to a *p*H of 7 with hydrochloric acid. Then a slurry of 3.0 g. (0.0175 mole) of *p*-nitrobenzyl chloride in 200 ml. of ethanol was added. The mixture was now refluxed for 24 hr. under nitrogen during which time a tan suspension formed. The mixture was filtered and the precipitate recrystallized from a large volume of ethanol producing 2.5 g. (93%) of a tan solid. This solid was triturated with tetrahydrofuran and filtered. The filtrate was evaporated. The residue was washed several times with ether and then recrystallized from acetone. It melted at 246°.

Anal. Calcd. for $C_{31}H_{23}FeNO_5$: C, 68.03; H, 4.58; N, 2.56; Fe 10.21. Found: C, 67.63; H, 4.81; N, 2.54; Fe, 10.27.

The infrared spectrum of this compound showed OH— absorption at 2.8 μ, carbonyl absorption at 5.85 μ, conjugated —NO_2 group at 7.4 μ and the 9 and 10 μ bands of ferrocene.

The *p*-nitrobenzyl ester was also prepared by treating 3.5 g. (0.0175 mole) of the yellow solid carbonation salt formed from the metalated ferrocenyldiphenylcarbinol with 3.0 g. (0.0175 mole) of *p*-nitrobenzyl chloride in 125 ml. of anhydrous tetrahydrofuran. After 48 hr. reflux, the mixture was treated with water, causing a brown solid to precipitate. This solid was dried and washed several times with ether. After recrystallization from acetone, the orange crystals melted at 246°, in agreement with the previous value. This yield was 3.8 g. (89%).

DEPARTMENT OF CHEMISTRY
PURDUE UNIVERSITY
LAFAYETTE, IND.

The Enol Content of γ-Fluoro-β-keto Esters by Proton Magnetic Resonance

ROBERT FILLER AND SAIYID M. NAQVI

Received September 19, 1960

The enol contents of a number of perfluoroalkyl β-diketones have been determined by Park and co-workers[1] using the Kurt Meyer "indirect" method. In all cases examined, the % enol was over 90% and in fact, several values of 120% were obtained. Other workers[2,3] have reported anomalous values of 115–202% enol for β-diketones in various solvents.

In our studies of fluorine-containing β-keto esters, we were interested in determining the influence of γ-fluorine substitution on the enol content of ethyl acetoacetate (I), which has been shown to possess about 7.5% enol in the pure liquid and 6.9% in methanol at 0°.[4] The marked dependence of the

(1) J. D. Park, H. A. Brown, and J. R. Lacher, *J. Am. Chem. Soc.*, **75**, 4753 (1953).

(2) K. Meyer, *Ber.*, **45**, 2843, 2848, 2858 (1912).

(3) J. C. Reid and M. Calvin, *J. Am. Chem. Soc.*, **72**, 2952 (1950).

(4) J. B. Conant and A. F. Thompson, Jr., *J. Am. Chem. Soc.*, **54**, 4039 (1932).

TABLE I

Compound	% Enol K. Meyer (CH₃OH Solvent)	% Enol NMR[9] (Pure Liquid)
$CH_3COCH_2CO_2C_2H_5 \rightleftarrows CH_3\overset{OH}{\overset{\vert}{C}}=CHCO_2C_2H_5$	6.5	6.0[10]
$CH_2FCOCH_2CO_2C_2H_5 \rightleftarrows CH_2F\overset{OH}{\overset{\vert}{C}}=CHCO_2C_2H_5$	5.4	7.2 ± 0.2
$CHF_2COCH_2CO_2C_2H_5 \rightleftarrows CHF_2\overset{OH}{\overset{\vert}{C}}=CHCO_2C_2H_5$	—	53 ± 4
$CF_3COCH_2CO_2C_2H_5 \rightleftarrows CF_3\overset{OH}{\overset{\vert}{C}}=CHCO_2C_2H_5$	9.9–14.4	89

keto-enol ratio on solvent has been studied in detail.[4]

We therefore attempted to determine the % enol of ethyl 4,4,4,-trifluoroacetoacetate (II) by means of the Meyer technique. In contrast to I, it was observed that the rate of bromine addition to the double bond of the enol form of II was extremely slow, so that the short time interval between the addition of bromine and neutralization of excess bromine was insufficient for reaction with the total amount of enol present in the original sample. The unexpectedly low enol values obtained (10–14%) compared with those reported for the fluorinated β-diketones and the lack of reproducibility of our results, led us to seek a more reliable method for measuring the keto-enol ratio of II.

Since NMR spectra offer a sensitive means for detecting protons in different structural environments, we used this technique[5] to determine quantitatively the per cent enol in I and II, as well as in ethyl 4,4-difluoroacetoacetate[6] and ethyl 4-fluoroacetoacetate.[7] The results are shown in the table.

The spectral analyses were carried out on the pure liquids and were interpreted by comparing half the amplitude of the keto-CH_2 peak with the amplitude of the enol = CH peak. The NMR method is admirably suited for such determinations for it gives reproducible results, obviates the anomalies and problems mentioned earlier which are associated with the chemical method, and offers the further advantage of small sample requirements. However, this method fails to eliminate true solvent effects, since it is likely that the dielectric constants of the esters differ markedly and the dipole moments of the enol forms may also show considerable differences.[8]

In each of these compounds the enol form is stabilized by hydrogen bonding to the ester carbonyl oxygen atom. It will be noted, however, that the large change in enol content occurs after the introduction of the second fluorine atom. While it would be tempting to propose that O—H - - - -F bonding contributes to further stabilization of the enols, as suggested by Park,[1] the *discontinuity* in the observed per cent enol values disproves this explanation.

One may also postulate that enolization partially relieves the strong electrostatic repulsions between the carbonyl oxygen (of the keto form) and the neighboring fluorine atoms in compound II. However, the $—CHF_2$ and $—CH_2F$ groups possess group dipole moments which may point away from the carbonyl oxygen, thus avoiding O—F repulsions. If the variation in enol content were due to this factor, the discontinuity would occur between the $—CF_3$ and $—CHF_2$ analogs, rather than between $—CHF_2$ and $—CH_2F$, as observed.[8]

A consideration worth further examination is that the enols probably become increasingly acidic as the number of fluorine atoms increases. This should lead to increased proton donor capacity and to stronger hydrogen bonding to the ester carbonyl oxygen.

It is also of interest to note that the enol contents of ethyl 4-chloroacetoacetate and ethyl 4,4,4-trichloroacetoacetate have been reported[11] to be 10.9% and 40–50%, respectively (Kurt Meyer). Halogen substitution on the α- position of β-

(5) We wish to thank Dr. J. N. Shoolery and Mr. Le Roy Johnson of Varian Associates, Palo Alto, Calif., for running and interpreting the NMR spectra of the β-keto esters.

(6) E. T. McBee, O. R. Pierce, H. W. Kilbourne, and E. R. Wilson, *J. Am. Chem. Soc.*, 75, 3152 (1953).

(7) E. D. Bergmann, S. Cohen, and I. Shahak, *J. Chem. Soc.*, 3278 (1959).

(8) We wish to thank the referee for these important observations.

(9) The % enol shown here for ethyl acetoacctate and its trifluoro analog, as measured by NMR, was first reported as No. 43 in a series "This is NMR at Work," Varian Associates Technical Information Bulletin, Vol. 2, No. 2, 1958.

(10) Slightly different values for this compound have been found by the NMR method. Y. Masuda, Kobe University, Japan, private communication, reports 8%; J. D. Roberts, *"Nuclear Magnetic Resonance,"* McGraw-Hill, New York, 1959, p. 68, reports 10%.

(11) F. Arndt, L. Loewe, and L. Capuano, *Rev. faculté sci. univ. Istanbul*, 8A, 122 (1943).

ketoesters lowers the enol/keto ratio. Thus, ethyl α-bromoacetoacetate possesses 4% enol character.[12] It has also been shown[13] that α,γ-difluoroacetoacetate contains 5.2% enol.

Acknowledgment. The authors are grateful to the American Cancer Society for financial support of this work under grant No. T-60A.

DEPARTMENT OF CHEMISTRY
ILLINOIS INSTITUTE OF TECHNOLOGY
CHICAGO 16, ILL.

(12) K. H. Meyer, *Ann.*, 380, 241 (1911).
(13) I. Blank, J. Mager, and E. D. Bergmann, *J. Chem. Soc.*, 2190 (1955).

Methylenecyclopropane *via* Thermal Decomposition of Dimethylaminomethylcyclopropane *N*-Oxide[1,2]

A. T. BLOMQUIST AND DONALD J. CONNOLLY[3]

Received September 26, 1960

An earlier paper described the synthesis of bis(dimethylaminomethyl) derivatives of cyclopropane by methylenecyclopropane.[2] Their preparation was of interest as they could possibly serve as precursors for the hydrocarbons dimethylenecyclopropane and trimethylenecyclopropane, provided their deamination could be achieved *via* either the Hofmann elimination method or the thermal decomposition of their *N*-oxides. However, some initial studies in this Laboratory on the deamination of bis(dimethylaminomethyl)cyclopropane, by the above routes, to produce dimethylenecyclopropane, have not been encouraging. It seemed desirable, therefore, to examine carefully the usefulness of deamination procedures in the synthesis of the known simple hydrocarbon methylenecyclopropane (I). Such a study might provide some information pertinent to the optimum experimental conditions for effecting deamination to introduce *exo*-unsaturation in cyclopropane systems.

Demjanow prepared the hydrocarbon I by the Hofmann elimination method[4] and most recently I was obtained in high yield by the decomposition of cyclobutanone tosylhydrazone.[5] Prior to the latter discovery the most convenient route to I was cyclization, by a modified Freund method, of 3-chloro(2-chloromethyl)-1-propene.[6] The most complete account of the properties of I are given in the report by the Ohio State University workers.[6]

For the present study dimethylaminomethylcyclopropane *N*-oxide (II) was obtained smoothly from dimethylaminomethylcyclopropane (III) by the procedure described by Cope.[7] The tertiary amine III was prepared by lithium aluminum hydride reduction of *N,N*-dimethylcyclopropanecarboxamide (IV). Preparation of IV from cyclopropanecarboxylic acid (V)[8] was straightforward.

Thermal decomposition of the *N*-oxide II was effected, over a range of temperature between 135–275°, in a nitrogen atmosphere at 3–5 mm., by slow, dropwise addition of an aqueous sirup of II onto a heated column packed with glass beads. The products formed were trapped as described in the Experimental Section. All olefinic products were initially adsorbed on alumina, then eluted and analyzed by vapor phase chromatography and by determinations of infrared and mass spectra. Three olefins were found as products: the hydrocarbon I together with isobutylene and 1,3-butadiene. Decomposition of the *N*-oxide II to the tertiary amine III was not observed. The three stated olefins were produced in low conversion and in yields which varied from *ca.* 4–12% with changes in pyrolysis temperatures. At best, the hydrocarbon I was obtained in *ca.* 6.5% yield at 210°. At this temperature, the optimum one for obtaining I, isobutylene and 1,3-butadiene were each produced in *ca.* 3% yield.[9] It was shown by an independent experiment that authentic I did not give either isobutylene or 1,3-butadiene under the pyrolysis conditions.

In conclusion it should be pointed out that the thermal decomposition of the amine oxide II contrasts sharply with similar decompositions of amine oxide derivatives of higher ring systems, *i.e.*, those with four through seven ring members.[10,11,12] In these systems amine oxide decompositions generally give 60–80% yield of olefin product.

EXPERIMENTAL

Materials. 1,3-Butadiene and isobutylene, obtained from The Matheson Co., were C.P. grade. Methylenecyclopropane, prepared as described earlier,[6] was found by vapor phase chromatography (VPC) analysis to contain 14% isobutylene.

(1) This is the twelfth publication concerned with the chemistry of small carbon rings. For the preceding paper, see A. T. Blomquist and E. A. LaLancette, *J. Am. Chem. Soc.*, 83, 1387 (1961).
(2) For a closely related paper see A. T. Blomquist and D. T. Longone, *J. Am. Chem. Soc.*, 81, 2012 (1959).
(3) Supported by funds received from a Du Pont Grant-in-Aid, Summer, 1959; Dow Chemical Co. Fellow, Summer, 1960.
(4) N. J. Demjanow and M. Dojarenko, *Ber.*, 56, 2208 (1923).
(5) L. Friedman and H. Shechter, *J. Am. Chem. Soc.*, 82, 1002 (1960).
(6) J. T. Gragson, K. W. Greenlee, J. M. Derfer, and C. E. Boord, *J. Am. Chem. Soc.*, 75, 3344 (1953).
(7) A. C. Cope, N. A. LeBel, H.-H. Lee, and W. R. Moore, *J. Am. Chem. Soc.*, 79, 4720 (1957).
(8) C. M. McCloskey and G. H. Coleman, *Org. Syntheses*, Coll. Vol. III, 221 (1958).
(9) Under the pyrolysis conditions described *N,N*-dimethylbutylamine *N*-oxide gave consistently 90–95% pure 1-butene.
(10) H. E. Baumgarten, F. A. Bower, and T. T. Okamoto, *J. Am. Chem. Soc.*, 79, 3145 (1957).
(11) A. C. Cope, C. L. Bumgardner, and E. F. Schweizer, *J. Am. Chem. Soc.*, 79, 4729 (1957).

Cyclopropanecarbonyl chloride,[13] b.p. 46–48° (64 mm.) and n_D^{20} 1.4475, was prepared in a standard way by reaction of thionyl chloride with cyclopropanecarboxylic acid,[8] b.p. 64–65° (3.8 mm.) and n_D^{20} 1.4382, which had been prepared from γ-chlorobutyronitrile[14] of b.p. 104–107° (60–62 mm.).

N,N-Dimethylbutylamine,[15] b.p. 93–95° (745 mm.) and n_D^{20} 1.3970, was prepared from *n*-butylamine (Distillation Products Ind.) by a described methylation procedure.[16] The tertiary amine formed a picrate derivative of m.p. 95°,[15] a methiodide derivative of m.p. 230°,[17] and an *N*-oxide whose picrate had m.p. 107.5–108°.

Anal. Calcd. for $C_{12}H_{18}N_4O_8$: C, 41.62; H, 5.24. Found: C, 41.81; H, 5.42.

Instruments. Infrared spectra were determined with 10-cm. gas cells with potassium bromide windows and used in Perkin-Elmer Spectrophotometers, Models 21 and "Infracord." All VPC work was done at room temperature with a Perkin-Elmer Vapor Fractometer, Model 154 B, fitted with an aluminum column, 2 m. × 4 mm., packed with dinonyl phthalate (30% by weight) on "Chromasorb W" (Johns-Manville). Mass spectra were determined with a Consolidated Engineering Corp. Mass Spectrometer, Model No. 21-401, and with a spectrometer specially designed and built by Dr. Richard F. Porter of Cornell.

N,N-Dimethyl cyclopropanecarboxamide (IV). Anhydrous dimethylamine (The Matheson Co.) was passed with stirring, into a solution of 43.0 g. (0.42 mole) of cyclopropanecarbonyl chloride in 300 ml. of benzene, cooled with an ice bath, until precipitation of dimethylamine hydrochloride was complete. From the filtered, dried benzene solution there was obtained 36.5 g. (77%) of the amide IV; b.p. 55° (1.5 mm.), n_D^{20} 1.4640.

Anal. Calcd. for $C_6H_{11}NO$: C, 63.60; H, 9.78; N, 12.38; mol. wt. 113. Found: C, 63.58; H, 9.85; N, 12.42; mol. wt. 115.

Dimethylaminomethylcyclopropane (III). To 4.36 g. (0.12 mole) of lithium aluminum hydride in 60 ml. of anhydrous ether, which had been refluxed 3 hr. with stirring, 17.0 g. (0.15 mole) of the amide IV in 60 ml. of ether was added in 30 min. The mixture was refluxed 3 hr., cooled with an ice bath, and excess hydride decomposed by careful addition of 25 ml. of saturated ammonium chloride solution. From the filtered, dried ether solution there was obtained 9.12 g. (61%) of the amine III; b.p. 99–100° (750 mm.), n_D^{20} 1.4194.[4]

The *picrate and methiodide derivatives* of the amine III, m.p.'s 100–101°[4] and 180–181°,[4] respectively, were prepared by standard procedures. The *N-oxide derivative* of the amine III (II) was prepared by reaction of the amine, in two to three times its volume of methanol, with 50% excess 35% hydrogen peroxide. After this mixture had stood at room temperature for 24 hr. excess peroxide was destroyed by the portionwise addition of small amounts of platinum black.[7] The filtered solution of the *N*-oxide II, concentrated to a sirup under an air stream, was assayed by conversion of an aliquot to the *N*-oxide *picrate derivative*, m.p. 131–131.5°.

Anal. Calcd. for $C_{12}H_{16}N_4O_8$: C, 41.86; H, 4.69. Found: C, 41.96; H, 4.63.

Thermal decomposition of the N-oxide II. The procedure used was generally based on one described by Cope.[7] All experiments were done at temperatures which were varied from 135° to 275° and with sirups of the *N*-oxide which contained 0.01–0.07 mole of the compound II.

Apparatus. Thermal decompositions were done in a heated, vertical Pyrex tube (2 cm. O.D.) packed with 3-mm. glass beads over a 45 cm. length. Amine oxide solutions were introduced at the top of the tube through a fitted funnel whose stem extended 5–10 cm. into the column packing. Also attached to the top of the column was a nitrogen inlet line, fitted with a sulfuric acid bubbler to allow observation of rate of flow. Attached to the bottom of the pyrolysis tube was a series of six traps ultimately joined to a vacuum system. The six traps comprised the following: two traps at *ca.* −16° for the collection of nonolefinic liquid products; a U-tube at *ca.* −65° packed centrally with 40 g. of activated alumina (Alcoa F-20) and at each end with Drierite; a 2.5 × 30 cm., indented olefin trap cooled in liquid nitrogen; finally two additional traps cooled in liquid nitrogen.

Procedure. Prior to the addition of *N*-oxide solutions, the entire apparatus was evacuated to 3–5 mm. pressure while maintaining a constant nitrogen atmosphere, the pyrolysis tube was brought to the desired temperature for a particular experiment, and all traps were cooled. The entire apparatus was then kept at a constant state of readiness for 1 hr. Finally, before decomposition of the *N*-oxide of the amine was done, a check experiment was carried out on the decomposition of a known quantity of *N,N*-dimethylbutylamine *N*-oxide to make certain that the apparatus was in proper working order. In all such check experiments 90–98% of pure 1-butene was obtained, as indicated by VPC analysis.

The *N*-oxide of the amine, as a sirup, was then added dropwise to the evacuated heated column at a rate such that decomposition of each drop was complete before more material was added. This was ascertained by observation of the nitrogen flow rate. After addition of all material was complete, 0.5 to 1 hr., the column was kept at the prescribed temperature for one more hour. Then the vacuum system was disconnected and the apparatus brought to atmospheric pressure by the continued flow of nitrogen. With the flow of nitrogen through the system continued, the first two traps were allowed to warm to room temperature and the U-tube trap was heated to 70° for 6 hr. This procedure released the olefinic products which then condensed in the still cooled olefin trap.

The olefin trap was separated from the system and attached to a gas burett and the total volume of gaseous olefins determined. The mixture of gaseous olefins was then transferred to a 50-ml. flask for handling in subsequent analysis.

Product analysis. The gaseous olefinic products were analyzed by VPC and by the methods of infrared and mass spectrophotometry. Nonolefinic products which remained on the column and collected in the first two traps were analyzed by chemical methods.

Infrared analysis of the olefinic products, determined in samples at 100–200 mm. pressure in a gas cell, showed that the mixture comprised isobutylene, 1,3-butadiene, and methylenecyclopropane. VPC analysis confirmed this observation and also gave quantitative information about the relative amounts of the three hydrocarbons; the relative amounts varied depending upon the pyrolysis temperature. The VPC studies were confirmed by similar studies made with authentic specimens of the three hydrocarbons named. The mass spectra of pyrolysate samples, corrected for the known quantity of isobutylene and 1,3-butadiene present[18] as determined by VPC data, agreed at all a.m.u. (29–54) with the spectrum of authentic methylenecyclopropane. Finally, the infrared spectrum of methylenecyclopropane,[19] isolated by preparative VPC, was identical with that of an authentic specimen.

(12) (a) A. T. Blomquist and Y. C. Meinwald, *J. Am. Chem. Soc.*, **82**, 3619 (1960); (b) J. K. Williams and W. H. Sharkey, *J. Am. Chem. Soc.*, **81**, 4269 (1959).

(13) L. Henry, *Chem. Zentr.*, 1357 (1901).

(14) C. F. H. Allen, *Org. Syntheses*, Coll. Vol. I, 156 (1941).

(15) V. A. Engelhardt, *J. Am. Chem. Soc.*, **78**, 107 (1956).

(16) Ref. 8, p. 723.

(17) J. v. Braun, *Ann.*, **382**, 17 (1911).

(18) *Catalog of Mass Spectral Data*, Am. Pet. Inst. Research Project No. 44, Carnegie Inst. of Techn.

(19) We are indebted to Professor Richard F. Porter and E. E. Zeller for the mass spectra determinations.

Treatment with ethanolic picric acid of the nonolefinic material which collected in the first two traps gave no insoluble picrate derivatives characteristic of the tertiary amine III or its *N*-oxide II. From an ethanolic wash of the column itself, however, the picrate derivative of the original amine *N*-oxide II was obtained.

Thermal stability of methylenecyclopropane. A typical sample of olfinic pyrolysate was observed by VPC analysis to be unchanged in composition after standing at room temperature for two weeks. It was observed also, by VPC analysis, that authentic methylenecyclopropane underwent no change when passed through the complete pyrolysis apparatus at 210° as was done with the amine *N*-oxide II.

THE BAKER LABORATORY OF CHEMISTRY
CORNELL UNIVERSITY
ITHACA, N. Y.

Bicyclic Bases. I. 2-Hydroxymethyl-2-phenyl-3-pyrrolidinylmethyl-5-norbornene

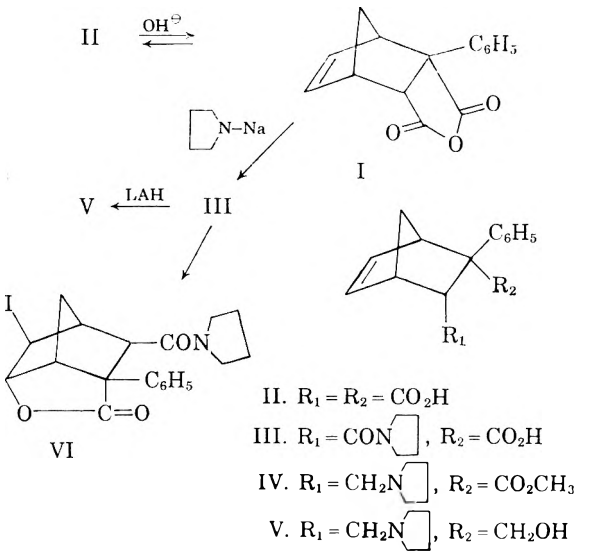
GEORGE I. POOS AND MARGARET M. LEHMAN

Received September 28, 1960

In considering structures that could have analgesic activity, we were attracted to the possibility that compounds such as the norbornene derivatives IV and V might be of interest. In addition to fulfilling the well known structural requirements for analgesic activity,[1] compounds such as IV and V might fit Beckett's proposed "analgesic receptor site"[2] although the "cavity" between the "flat place" and "anionic site" would have to be rather large to accommodate the bulk of the norbornene ring. Some advantage might be gained also by having functional groups fixed in space through their attachment to a rigid bicyclic system which would make any study of the relationship between conformation and pharmacological activity more precise.

Synthesis of these structures was approached through the cyclopentadiene-phenylmaleic anhydride[3] Diels-Alder adduct I. Anhydride I was first prepared by Miller and Mann[4] who characterized their product by saponification to the crystalline dicarboxylic acid II, which was obtained in 51.5% yield. No sterochemical assignment was made to this product. Subsequently, Winternitz, Mousseron, and Rouzier[5] reported that cyclopentadiene and phenylmaleic anhydride reacted to give a noncrystalline product which upon hydrolysis gave 55% of a crystalline mixture of diacids. The French workers concluded on the basis of the isolation of a bromo acid lactone after bromination of their diacid that their crystalline diacid was 70% *cis-exo* and 30% *cis-endo* (II).

In our hands, the reaction of cyclopentadiene and phenylmaleic anhydride under conditions very similar to those reported[4,5] led directly to 69% of pure crystalline *endo*-anhydride I, m.p. 69–70°. We first obtained the crystalline anhydride by saponification of the crude adduct to the pure acid II (66% yield, m.p. 171–172°) followed by cyclization with acetyl chloride to the pure anhydride (87% yield). Proof for the *endo*-configuration of I is given below.



II. $R_1 = R_2 = CO_2H$

III. $R_1 = CON$, $R_2 = CO_2H$

IV. $R_1 = CH_2N$, $R_2 = CO_2CH_3$

V. $R_1 = CH_2N$, $R_2 = CH_2OH$

Opening the anhydride ring of I with secondary amines proved to be surprisingly difficult. In 25% aqueous dimethylamine at 55° for many hours as well as in anhydrous dimethylamine in a sealed tube at 60°, I was uneffected and recovered unchanged. The anhydride was also returned in good recovery after heating eighteen hours under reflux in pyrrolidine. However, by dissolving three equivalents of sodium hydride in a large excess of pyrrolidine and allowing the anhydride to stir in the resulting suspension of pyrrolidine salt at room temperature, the desired amide acid was obtained in 87% yield. Structure III is most probable for this product. The *endo*-sterochemistry of the carboxyl group was proved by conversion to an iodolactone VI. This iodolactonization also proves the *endo*-configuration for anhydride function and carboxyl groups of I and II. The position of the amide function in III is inferred from the expected attack of the pyrrolidine amide anion at the less hindered carbonyl group attached to the 3- position of the norbornene ring. Only one sharp-melting amide acid was obtained, indicating definite selectivity. Support for this assignment of the acid and amide functions in III is gained by analogy with the reaction of phenylsuccinic anhydride with ammonia and

(1) N. B. Eddy, *Chemistry & Industry*, 1462 (1959).

(2) A. H. Beckett and A. F. Casy, *J. Pharm. & Pharmacol.*, **6**, 986 (1954).

(3) (a) L. E. Miller, H. B. Staley, and D. J. Mann, *J. Am. Chem. Soc.*, **71**, 374 (1949); see also (b) C. S. Rondesvedt and A. H. Filbey, *J. Org. Chem.*, **19**, 119 (1954), note 2.

(4) L. E. Miller and D. J. Mann, *J. Am. Chem. Soc.*, **72**, 1484 (1950).

(5) F. Winternitz, M. Mousseron, and G. Rouzier, *Bull. soc. chim. France*, 170 (1955).

amines which gives exclusively the succinamic acid with the phenyl and carboxyl group on the same carbon atom.[6] Since the anhydride I is opened in strong alkali to give the *endo-cis* diacid II without any appreciable isomerization to a *trans*-diacid, the *endo*-configuration for the amide group in III is most likely.

The reduction of amide acid III with excess lithium aluminum hydride in tetrahydrofuran led to amino alcohol V in good yield. This basic product was characterized as the fumarate. In pharmacological tests, V showed no analgesic activity.[7] Although in a preliminary experiment, selective reduction of III as the sodium salt in tetrahydrofuran with lithium aluminum hydride to the amino acid followed by esterification with diazomethane to the amino ester IV appeared to proceed in low yield, it was not pursued further due to the lack of analgesic activity for compound V.

EXPERIMENTAL[8]

Phenylmaleic anhydride. Phenylmaleic anhydride was prepared by the method of Miller and Mann.[3a] From 51.7 g. (0.294 mole) of phenylsuccinic anhydride and 105 g. (0.588 mole) of *N*-bromosuccinimide, there was obtained 34.2 g. (67%) of the anhydride, m.p. 121–123°. As reported by Rondesvedt and Filbey,[3b] the use of a nichrome wire stirrer was found to be essential to the success of this reaction.

exo-2-Phenyl-endo-5-norbornene-2,3-dicarboxylic acid anhydride (I). A solution of 34 g. (0.195 mole) of phenylmaleic anhydride and 2.58 g. (0.390 mole) of freshly distilled cyclopentadiene in 150 ml. of benzene was stirred under nitrogen at room temperature for 22 hr. and at 50° for 5 hr. The solvent was removed under reduced pressure on the steam cone. The oily residue crystallized from ether–petroleum ether (b.p. 30–60°).The yield in three crops was 36.2 g. (77%) of anhydride (I) m.p. 65–70°.

From an ether–petroleum ether recrystallization of 0.17 g. of the anhydride (I), m.p. 69–70°, there was obtained 0.09 g., m.p. 69–70°; λ_{max}^{KBr} 5.41, 5.61 μ (anhydride C=O).

Anal. Calcd. for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found: C, 75.00; H, 5.22.

In the initial experiment, the total noncrystalline product was saponified by the method of Miller and Mann[3a] to give recrystallized II, m.p. 171–172°, in 65% yield. A sample of the diacid II was cyclized to the crystalline anhydride I, m.p. 68–69° by refluxing in acetyl chloride. Thereafter the anhydride I was crystallized directly from the Diels-Alder preparations.

exo-2-Phenyl-endo-3-pyrrolidinecarbonyl-5-norbornene-endo-2-carboxylic acid (III). Thirty-five milliliters of pyrrolidine was reacted with 3.75 g. (0.081 mole) of 53% sodium hydride–mineral oil. The suspension was stirred for 1 hr. at room temperature. A total of 6.50 g. (0.027 mole) of anhydride I was added in portions. The suspension was stirred for 1 hr. and allowed to stand overnight at room temperature. The pyrrolidine was removed under vacuum and the residue was dissolved in water. On acidification, a white solid precipitated which did not dissolve when ether was added. The solid was collected by filtration, washed with water and ether, and air-dried. The crude solid, m.p. 150–151°, was recrystallized from methylene chloride–ether in three crops, all melting at 150–151.5°, totaling 7.29 g. (87%) of amide III.

A recrystallization of 0.25 g. of III, m.p. 150–151.5°, from methylene chloride–ether, gave 0.14 g., m.p. 150.5–151.5°; λ_{max} 5.78 (carboxyl C=O), 6.24 μ (amide C=O).

Anal. Calcd. for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.16; H, 6.83; N, 4.44.

Iodolactonization of III *to give* VI. A solution of 0.1 g. of III in 3 ml. of 0.5*N* sodium bicarbonate was combined with a solution of 0.25 g. of iodine and 0.5 g. of potassium iodide in 1.5 ml. of water. The mixture was allowed to stand at room temperature overnight. The dark gummy precipitate was washed with water and dissolved in a mixture of methylene chloride and aqueous sodium thiosulfate. The organic layer was dried over magnesium sulfate and the solvent was removed under vacuum. The oily product crystallized from acetone—ether. One recrystallization from acetone—ether gave 0.03 g. of VI, m.p. 222–225°; λ_{max} 5.59, 5.85 (lactone C=O), 6.22 (amide C=O), 6.30 μ (aromatic C=C).

Anal. Calcd. for $C_{19}H_{20}NO_3I$: C, 52.19; H, 4.61; N, 3.20. Found: C, 52.20; H, 4.70; N, 3.41.

1-(endo-2-Hydroxymethyl-exo-2-phenyl-5-norbornene-3-ylmethyl)pyrrolidine (V). A suspension of 7.5 g. (0.198 mole) of lithium aluminum hydride in 250 ml. of dry tetrahydrofuran was stirred at room temperature for 2 hr. and then was heated to reflux and a solution of 15.09 g. (0.0485 mole) of III in 750 ml. of hot tetrahydrofuran was rapidly added. The mixture was heated under reflux for 66 hr. While stirring, the mixture was cooled and carefully decomposed with 22.5 ml. of water. After stirring for 2 hr. the inorganics were removed by filtration and washed with ether. Concentration of the ethereal filtrate gave 12.97 g. of viscous yellow oil, V; $\lambda_{max}^{CHCl_3}$ 3.0 (br., —OH), 6.24, and 6.67 μ (aromatic).

The hydrogen fumarate was prepared from 1.59 g. (0.00563 mole) of V and 0.66 g. (0.00563 mole) of fumaric acid in isopropyl alcohol. The 1.51 g. of fumarate, m.p. 197–200° (67%), was recrystallized from methanol–isopropyl alcohol to give 1.33 g., m.p. 203–205°; λ_{max} 3.0–4.0 (br., carboxyl —OH), 5.90 (carboxyl C=O), 6.08 (C=C), 6.24 (aromatic C=C), 6.32 μ (carboxylate C=O).

Anal. Calcd. for $C_{19}H_{25}NO \cdot C_4H_4O_4$: C, 69.15; H, 7.32; N, 3.51. Found: C, 69.30; H, 7.43; N, 3.46.

McNeil Laboratories, Inc.
Fort Washington 32, Pa.

(6) R. Anschutz, *Ann.*, 354, 117 (1907).

(7) We are indebted to W. M. Govier, M.D., and our Department of Pharmacology for these results.

(8) Melting points were determined with a Kofler microhotstage. Infrared spectra were obtained in Nujol mull with a Perkin-Elmer Model 21 Spectrometer unless otherwise noted.

Bicyclic Bases. II. 3-Aminomethyl-2-norbornenearylmethanols

George I. Poos and Margaret M. Lehman

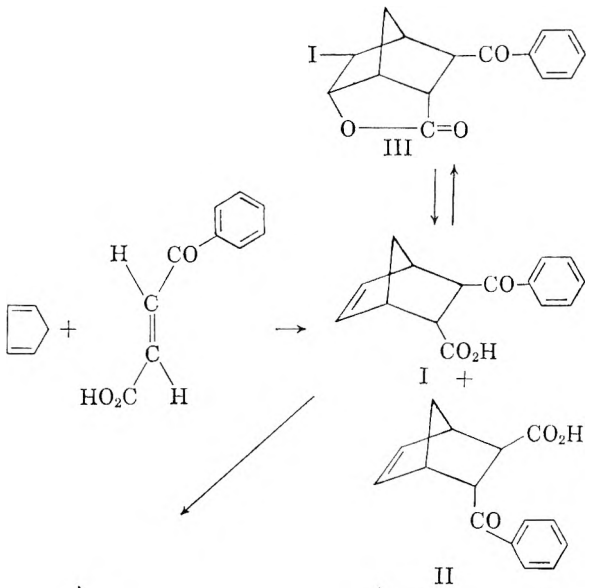
Received September 28, 1960

This note describes an exploratory attempt to find interesting pharmacological activity within a series of basically substituted norbornenearylmethanols.

Our investigation started with the reaction product of *trans*-benzoylacrylic acid and cyclopentadiene which was reported by Winternitz, Mousseron and Rouzier[1] to be a crystalline mixture containing 60% of the *exo-trans*-isomer II and 40% of the *endo-trans*-isomer I. The French workers separated the mixture by a laborious process

(1) F. Winternitz, M. Mousseron, and G. Rouzier, *Bull. soc. chim. France*, 170 (1955).

involving twenty recrystallizations and assigned structures based on bromolactone and hydroxylactone formation from I but not from II. We obtained the mixture of adducts as reported[1] and separated by iodolactonization. The pure crystalline iodolactone III was obtained in a yield of 48%. From the iodolactonization, an acidic fraction was obtained which afforded a crystalline mixture in 39% yield. This crystalline acidic product was largely an iodohydrin mixture (IV) based on analysis and spectra. Reduction of the iodolactone III with zinc in ethanol gave an excellent yield of the pure *endo*-acid I. With the impure iodohydrin mixture, a longer reduction time was required and a 75% yield of pure *exo*-acid II was obtained.



	R_1	R_2
V.	$-COC_6H_5$	$-CON(CH_3)_2$
VI.	$-CHOHC_6H_5$	$-CH_2N(CH_3)_2$
VII.	$-COC_6H_5$	$-CH_2N(CH_3)_2$
VIII.	$-COH(C_6H_5)_2$	$-CH_2N(CH_3)_2$
XI.	$-C(OH)(o\text{-tolyl})-C_6H_5$	$-CH_2N(CH_3)_2$
IX.	$-COH(C_6H_5)_2$	$-CH_2N(CH_3)_2$
X.	$=C(C_6H_5)_2$	$-CH_2N(CH_3)_2$

Because of the greater abundance of I from the reduction step, subsequent reactions were carried out with this isomer.

By the mixed anhydride technique,[2] the acid I was converted to its dimethylamide (V) in 60% yield. Attempts to improve this yield by varying the quality and quantity of the reagents employed were fruitless; however, in all cases the balance of material was recovered as pure starting acid I. Reduction of ketoamide V with excess lithium aluminum hydride in tetrahydrofuran afforded the amino alcohol VI in good yield as a mixture of steroisomers. More than half of this mixture was a single isomer melting at 125°.

Oxidation of amino alcohol VI which was largely one largely one steroisomer with chromic anhydride-pyridine[3] gave the amino ketone VII as a gum, characterized as the fumarate salt. The yield of crude base was about 60% and of the pure salt about 45%. Similar oxidation of the crude base VI or of lower melting or non-crystalline fractions gave VII-fumarate but in lower yields. The major difficulty in this oxidation was a low material balance. Exhaustive extraction of the reaction mixtures or reduction of the chromium salts followed by extraction on the alkaline side never gave a recovery of organic material better than 65%. Alternate methods of oxidation failed—*e.g.*, the Oppenauer oxidation (aluminum isopropoxide–cyclohexanone in benzene), chromic acid in acetic acid, chromic acid in acetic acid with sulfuric acid and platinum catalyzed air oxidation all gave recovered starting material. An oxidation with chromic acid in aqueous pyridine proceeded but in low yield (33%).

Treatment of amino ketone VII with excess phenyllithium led to the aminomethylnorbornyldiphenylmethanol VIII as a noncrystalline product which was characterized as the hydrogen fumarate. Several attempts to dehydrate VIII to the corresponding diphenylmethylene derivative were unsuccessful. Because of the possible interference of the isolated double bond, amino alcohol VIII was hydrogenated to the norbornane derivative IX. In polyphosphoric acid at 100° for several hours, IX appeared to dehydrate to the extent of at least 50% as judged by the ultraviolet maximum at 245 mμ and the lack of —OH absorption in the infrared of the basic product. However, all attempts to obtain a crystalline salt of the gummy product X failed, possibly due to the presence of mixtures resulting from the rearrangement of the norbornane skeleton.

Amino ketone VII failed to react with *o*-tolylmagnesium bromide but was converted smoothly to the phenyl-*o*-tolylcarbinol XI with *o*-tolyllithium. Compound XI was noncrystalline and gave a mixture of fumarate salts, probably because of the introduction of a new asymmetric center in the molecule. Several recrystallizations served to separate a single, sharply melting salt from the mixture.

Compounds V, VI, VIII, and XI were examined for pharmacological activity, both as to gross behavioral effects and more detailed pharmacodynamic actions.[4] Behaviorally they may be

(2) D. S. Tarbell, *J. Org. Chem.*, **22**, 248 (1957).

(3) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 422 (1953).

(4) We are indebted to W. M. Govier, M.D., and the Department of Pharmacology for the testing results.

best classified as weak convulsants having lethal doses in the range of 100 to 300 mg./kg., i.p. Compounds VII, VIII and probably V demonstrated multiple actions such as ganglionic blockade, antihistamine, anticholinergic, and antiserotonin activities. As compound IX produced mydriasis at low doses in behavioral testing, it probably also has autonomic activity although insufficient compound was available for accurate determinations. No analgesic or anti-inflammatory action was found in the series.

EXPERIMENTAL[5]

exo-3-Benzoyl-5-norbornene-endo-2-carboxylic acid (I) *and endo-3-benzoyl-5-norbornene-exo-2-carboxylic acid* (II). By the method of Winternitz *et al.*[1] 248.1 g. (1.41 moles) of β-benzoylacrylic acid was dissolved in 1.2 l. of benzene with warming, and 103 g. (1.55 moles) of freshly distilled cyclopentadiene was added while stirring. The reaction mixture was stirred overnight at room temperature and then concentrated to dryness. The product was crystallized from ether-petroleum ether (b.p. 30–60°) in four crops, totaling 331.7 g. (97%) of the crystalline mixture of the *trans*-acids I and II, m.p. 102–134°; λ_{max}^{Nujol} 3.25–3.85 (—OH), 5.90 (carboxyl C=O), 5.96 (ketone C=O), 6.24 μ (aromatic C=C).

The mixture of acids was separated by iodolactonization. A solution of 27.44 g. (0.113 mole) of total crystalline product from a small Diels Alder reaction in 686 ml. (0.343 mole) of 0.5*N* sodium bicarbonate was combined with 59.3 g. of iodine (0.468 eq.) in 115 g. of potassium iodide in 345 ml. of water and stored overnight at room temperature in the dark. The mixture was extracted three times with methylene chloride, which was washed with sodium thiosulfate solution and water and dried over magnesium sulfate. Removal of the solvent left 22.3 g. of brown solid, which, after decolorizing carbon treatment, was crystallized from methylene chloride–ether in two crops. The yield of iodolactone III was 20.0 g. (48%) m.p. 154–156°; λ_{max}^{Nujol} 5.62 (lactone C=O), 5.97 (ketone C=O), 6.25 μ (aromatic C=C). A 0.12-g. sample was recrystallized to give 0.09 g., m.p. 155.5-156°.

Anal. Calcd. for $C_{15}H_{13}IO_3$: C, 48.93; H, 3.56; Found: C, 48.95; H, 3.74.

The above sodium bicarbonate layer, containing the iodohydrin, was decolorized with sodium thiosulfate and acidified with 2*N* hydrochloric acid. The gummy precipitate was extracted with methylene chloride, which after drying over magnesium sulfate gave 22.7 g. of a buff-colored solid. This was crystallized from methylene chloride-petroleum ether in three crops, totaling 17.02 g. (39%) m.p. 169–182° dec.; λ_{max}^{Nujol} 3.74–.83 (—OH), 5.86 μ (ketone and carboxyl C=O). A 0.19-g. sample was recrystallized to give 0.09 g., m.p. 177–182° dec.

Anal. Calcd. for $C_{15}H_{15}IO_3$: C, 46.65; H, 3.92. Found: C, 49.63; H, 4.71.

Reduction of the iodolactone III back to the *endo*-acid I was accomplished by heating a mixture of 88.9 g. (0.241 mole) of III and 157 g. (2.41 moles) of zinc dust in 2 l. of ethanol under reflux for 2 hr. while stirring. The zinc dust was removed by filtration and the solvent was removed under vacuum. The residue was taken up in ether and washed well with 2*N* hydrochloric acid and water. The ether layer was dried over magnesium sulfate and the solvent was removed under vacuum. After decolorization, the 59-g. residue crystallized from methylene chloride–ether–petroleum ether in three crops, totaling 52.1 g. (90%) of I, m.p. 138.5–142.5°. Spectra were taken on a sample, m.p. 142.5–143.5°; λ_{max}^{Nujol} 3.25–4.50 (—OH), 5.90 (carboxyl (C=O), 5.97 (ketone C=O), 6.25 μ (aromatic C=C). Lit.[1] m.p. 136–137° for I.

Reduction of 2.0 g. (0.0052 mole) of impure iodohydrin (IV) by reflux with 3.60 g. (0.055 mole) of zinc dust in 40 ml. of ethanol was complete in 4 hr. The crystalline *exo*-acid II was isolated as above in 75.5% yield, 0.95 g., m.p. 127–128°; λ_{max}^{Nujol} 3.75 (—OH), 5.92, Shl. 6.00–.15 (ketone and carboxyl C=O), 6.25 μ (aromatic C=C). Lit.[1] m.p. 123–124° for II.

exo-3-Benzoyl-N,N-dimethyl-5-norbornene-endo-2-carboxamide (V). A suspension of 47.4 g. (0.1955 mole) of I in 300 ml. of dry toluene was cooled to −5°, and 21.8 g. (0.216 mole) of triethylamine was added. To the resulting solution, 23.4 g. (0.216 mole) of ethyl chloroformate in 100 ml. of dry toluene was added dropwise over 30 min. with stirring at −5° to 0°. The suspension was stirred at 0° for 2.25 hr. A solution of 9.75 g. (0.216 mole) of dimethylamine in cold toluene was added rapidly. The suspension was stirred at room temperature for 18 hr., and the organic layer was washed with water, 2*N* hydrochloric acid, water, 5% sodium bicarbonate, and water. The aqueous washes, at *p*H 8, were back-extracted with ether and similarly washed. The combined ethereal extracts were dried and concentrated, and the product was crystallized from ether–petroleum ether in two crops giving a total of 26.3 g. (50%) of V, m.p. 91–95°. A sample, m.p. 94–95°, was characterized; λ_{max}^{Nujol} 5.97 (ketone C=O), 6.11 (amide C=O), 6.25 μ (aromatic C=C).

Anal. Calcd. for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 76.08; H, 7.36; N, 5.26, 5.27 (Kjeldahl).

In a later preparation of amide V, from 16.25 g. (0.0672 mole) of I, using the above conditions, a 60.3% yield of V was isolated, m.p. 108.5–109°; λ_{max}^{Nujol} 6.00 (ketone C=O), 6.14 (amide C=O), 6.26 μ (aromatic C=C).

Anal. Calcd. for $C_{17}H_{19}NO_2$: N, 5.20. Found: N, 5.32, 4.93.

Infrared solution spectra of the two different melting amides were identical, although the solid state spectra differed in the finger-print region. A mixed m.p. of 94–95° and 108.5–109° amides melted at the higher temperature. A sample of V, m.p. 94–95°, was converted to V, m.p. 107.5–108.5°, by seeding an ether solution of the former with the latter. All of the evidence indicates that the two substances are isomorphic forms of V.

In the first amide V preparation above, the aqueous washes were acidified, and the precipitate was extracted into ether, which was dried over magnesium sulfate. The 13.43 g. (28.4%) of crude acidic material crystallized from methylene chloride-ether-petroleum ether to give 10.30 g. (21.7%) of recovered I, m.p. 143–144°.

endo-3-Dimethylaminomethyl-α-phenyl-5-norbornene-exo-2-methanol (VI). A solution of 23.7 g. (0.0881 mole) of V in 100 ml. of dry tetrahydrofuran was added slowly to a suspension of 10.0 g. (0.264 mole) of lithium aluminum hydride in 300 ml. of dry tetrahydrofuran. The mixture was refluxed for 20 hr., cooled in an ice bath, and decomposed slowly with 30 ml. of water. The mixture was stirred for 4.5 hr. at room temperature, and the precipitate was removed by filtration. The filtrate was concentrated and the residue crystallized from methylene chloride–ether–petroleum ether to give, in three crops, 13.1 g. (58%) of VI, m.p. 118–125°. A sample of VI, m.p. 124–124.5°, λ_{max}^{Nujol} 3.20, 3.29 μ (—OH), was characterized as the acid fumarate, which was obtained from isopropyl alcohol, m.p. 190°; λ_{max}^{Nujol} 3.0 (—OH), 5.80 (carboxyl C=O), 6.04 (C=C), 6.36 μ (carboxylate C=O).

Anal. Calcd. for $C_{21}H_{27}NO_5$: C, 67.54; H, 7.29; N, 3.75. Found: C, 67.38; H, 7.63; N, 3.89, 3.85 (Kjeldahl).

A fourth crop of VI, 3.00 g. (total yield 71.3%), was crystallized from ether-petroleum ether, m.p. 78–90°. Recrystallization gave 0.56 g., m.p. 78–90°; λ_{max}^{Nujol} 3.20 (—OH), 6.24 and 6.68 μ (aromatic).

(5) Melting points were taken on a Kofler block; infrared spectra were determined with a Perkin-Elmer Model 21 Spectrometer and ultraviolet spectra with a Cary Model 11 Spectrometer in methanol solution unless otherwise noted.

Anal. Calcd. for $C_{17}H_{23}NO$: C, 79.33; H, 9.01; N, 5.44. Found: C, 79.44; H, 9.24; N, 5.54.

endo-3-Dimethylaminomethyl-5-norbornen-2-yl exo-phenyl ketone (VII). Pyridine, 200 ml., was cooled in an ice bath and 13.3 g. of chromic oxide was added in portions with thorough mixing. To the resulting complex was added a solution of 13.32 g. of aminoalcohol VI in 80 ml. of pyridine. The resulting dark mixture was allowed to stand at room temperature for 22 hr. and then was treated with 280 ml. of water. This mixture was extracted three times with ether, washing each ether extract with a small portion of water, which was added to the pyridine-water reaction mixture. The combined ethereal extracts were dried over magnesium sulfate and concentrated to dryness, finally with pumping under high vacuum, to give 8.39 g. (63%) of crude VII as a dark oil; λ_{max}^{neat} 5.96 μ (ketone C=O), 6.25 μ (aromatic C=C).

The hydrogen fumarate prepared from 3.39 g. (0.0133 mole) of VII and 1.54 g. (0.0133 mole) of fumaric acid in isopropyl alcohol–ether amounted to 3.67 g. (over-all 47%) melting at 144–146°; λ_{max}^{Nujol} 3.0 (broad, —OH), 5.78 (carboxyl C=O), 5.92 (ketone C=O), 6.03 (C=C), 6.35 μ (carboxylate C=O); λ_{max} 244 mμ (ϵ 16,500).

Anal. Calcd. for $C_{17}H_{21}NO \cdot C_4H_4O_4$: N, 3.77. Found: N, 3.97, 3.89 (Kjeldahl).

endo-3-Dimethylaminomethyl-α,α-diphenyl-5-norbornene-exo-2-methanol (VIII). A solution of phenyllithium was prepared by adding in portions under nitrogen 2.88 g. (0.146 g.-atom) of lithium wire to a solution of 32.8 g. (0.208 mole) of bromobenzene in 100 ml. of anhydrous ether. The mixture was stirred with a Hershberg stirrer until the reaction was complete. At the same time, the pure amino ketone VII was isolated by dissolving its fumarate in water, making the solution strongly basic with sodium hydroxide, extraction with ether, washing, drying, and concentration. A solution of 26.6 g. (0.104 mole) of *endo*-3-dimethylaminomethyl-5-norbornen-2-yl *exo*-phenyl ketone (VII) in 100 ml. of anhydrous ether was then added to the phenyllithium solution at a rate to maintain reflux (15 min.). The resulting reaction mixture was stirred at room temperature overnight and hydrolyzed by adding 33 ml. of water dropwise. When all of the solid had dissolved, the layers were separated and the aqueous part was extracted with ether. The combined ethereal solutions were washed with water, treated with charcoal, concentrated to dryness and the residue dried by distilling benzene from it. The product was 33.4 g. of VIII a brown gum; $\lambda_{max}^{CCl_4}$ 3.30 (—OH), 5.98 (very weak C=O), 6.26 μ (aromatic C=C).

Combination of 10.12 g. (0.034 mole) of this product with 3.54 g. (0.034 mole) of fumaric acid in isopropyl alcohol led to 9.13 g. (over-all 74%) of the fumarate, m.p. 212–214°. A sample of this salt, washed with hot ethanol, showed a m.p. of 214–215.5°; λ_{max}^{KBr} 3.25, 3.33, 4.14 (—OH), 6.28 μ (aromatic C=C). There was only benzene ring absorption in the ultraviolet spectrum above 210 mμ.

Anal. Calcd. for $(C_{23}H_{27}NO)_2 \cdot C_4H_4O_4$: C, 76.69; H, 7.47; N, 3.58. Found: C, 76.33, 76.41; H, 7.38, 7.66; N, 3.25, 3.51.

endo-3-Dimethylaminomethyl-α,α-diphenylnorbornane-exo-2-methanol (IX). A solution of 5.67 g. of the crude amino alcohol VIII from the previous experiment in 50 ml. of methanol was shaken under 3 atm. of hydrogen with 0.2 g. of 10% palladium-on-carbon for 3.5 hr. The catalyst was removed by filtration and the filtrate was concentrated to dryness under vacuum. The residue was dissolved in ether and extracted into dilute hydrochloric acid; the aqueous layer was made basic and extracted with ether. After drying over magnesium sulfate, the ether solution was treated with decolorizing carbon, filtered, and concentrated to dryness to give IX as a yellow gum (5.13 g.). From 0.26 g. of this base and 0.090 g. of fumaric acid in isopropyl alcohol–ether, there was obtained 0.26 g. of the hydrogen fumarate, m.p. 185–192°. Recrystallization from methanol-isopropyl alcohol–ether gave pure IX hydrogen fumarate, m.p. 191–192°; ultraviolet and infrared spectra consistent with structure.

Anal. Calcd. for $C_{23}H_{29}NO \cdot C_4H_4O_4$: C, 71.81; H, 7.37; N, 3.10. Found: C, 71.70; H, 7.52; N, 3.14.

endo-3-Dimethylaminomethyl-α-phenyl-α-o-tolyl-5-norbornene-exo-2-methanol (XI). A solution of *o*-tolyllithium was prepared from 6.45 g. (0.0375 mole) of *o*-bromotoluene and 0.52 g. (0.075 g.-atom) of lithium in 20 ml. of ether. This was treated with a solution of 4.78 g. (0.0187 mole) of amino ketone VII in 20 ml. of ether and worked up as described under the preparation of VIII. The product was 5.94 g. of a yellow oil; λ_{max}^{neat} 2.85, 3.29 (—OH), 6.25 μ (aromatic C=C).

From 3.16 g. of this product and 1.06 g. of fumaric acid in isopropyl alcohol–ether, there was obtained 2.37 g. (56%) of XI hydrogen fumarate melting at 174–189°; ultraviolet and infrared spectra consistent with structure.

A recrystallization of this material from isopropyl alcohol–ether gave a sample of XI hydrogen fumarate melting at 190.5–192.5° in about 50% recovery.

Anal. Calcd. for $C_{24}H_{29}NO \cdot C_4H_4O_4$: C, 72.54; H, 7.18; N, 3.02. Found: C, 72.28; H, 7.42; N, 3.07, 2.81.

McNeil Laboratories, Inc.
Fort Washington, Pa.

Carbamoylation of Some Cyclic 1,3-Dicarbonyl Compounds with Urea

Homer C. Scarborough

Received October 3, 1960

The general class of tricarbonylmethane compounds contains examples with a wide variety of physiological actions as antifungal, anthelmintic, and antibacterial.[1] However, only the tetracycline incorporate a carbamoyl moiety as part of the tricarbonylmethane system. We wish to report a method of preparing 2-carbamoyl derivatives of some cyclic 1,3-dicarbonyl compounds through the use of readily accessible intermediates, *i.e.*, cyclic 1,3-dicarbonyl compounds and urea. The interest of others in such compounds has been disclosed using acetyl cyanate as an intermediate.[2]

Urea has found application as a source of the elements of cyanic acid as in the preparation of urethanes by reactions with alcohols and in the preparation of substituted ureas by reaction with amines.[3] The zinc chloride catalyzed carbamoylation of resorcinol under Friedel-Crafts conditions by means of urea has been reported.[4] Since organic acids catalyze the decomposition of urea, presumably *via* cyanic acid,[5] it was hoped that compounds

(1) C. H. Hassel, *Experimentia*, **6**, 642 (1950); C. H. Hassel in J. W. Cook, *Progress in Organic Chemistry*, vol. 4, 115, Academic Press, New York, 1958.

(2) M. M. Shemyakin, *et al.*, *Zhur. Obshchei Khim.*, **30**, 542 (1960).

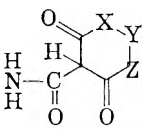
(3) R. B. Wagner and H. D. Zook, *Synthetic Organic Chemistry*, John Wiley & Sons, Inc., New York, 1953, p. 645.

(4) J. J. Roemer and W. M. Degnan, *J. Am. Chem. Soc.*, **63**, 103 (1941). According to these workers, the zinc chloride-urea method of carbamoylation is restricted to resorcinol.

(5) S. Ozaki, T. Mukaiyama, and K. Uno, *J. Am. Chem. Soc.*, **79**, 4358 (1947). T. Mukaiyama and T. Matsunaga, *J. Am. Chem. Soc.*, **75**, 6209 (1953).

such as 5,5-dimethyl-1,3-cyclohexanedione might furnish a proton for the catalytic decomposition of urea, with concurrent reaction of the anion with the cyanic acid to yield the carbamoyl derivative. The reaction of the anions of 1,3-diketones with alkyl or aryl isocyanates and isothiocyanates to furnish their 2-*N*-substituted carbamoyl and thiocarbamoyl derivatives has been reported.[6] The use of cyanic acid for the preparation of the desired primary amides did not appear attractive in view of its instability. Further, simple neutralization might occur in the reaction of 1,3-diketo salts with cyanic acid. When no basic catalyst was employed, 5,5-dimethyl-1,3-cyclohexanedione furnished the enolic carbamate with phenyl isocyanate.[6a]

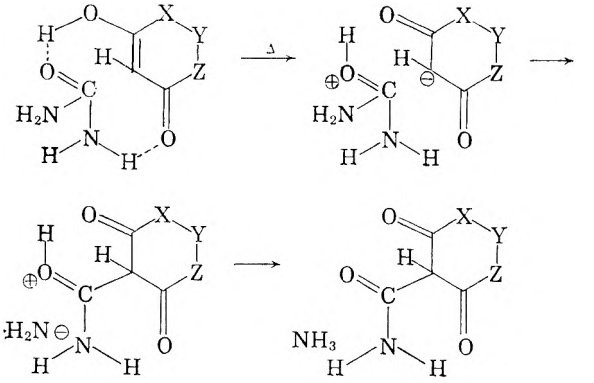
In the present work, urea was heated with 5,5-dimethyl - 1,3 - cyclohexanedione, 1,2 - diphenyl-3,5-pyrazolidinedione,[7] and 1 - phenyl - 3,5 - pyrazolidinedione[8] to furnish their carbamoyl derivatives (I, II, and III). All of the carbamoyl compounds were soluble in 0.1*N* sodium hydroxide and gave colored crystalline derivatives with cupric acetate. The pale blue copper derivative of I was stable to cold dilute sulfuric acid, but could be hydrolyzed to I at room temperature.[9]



Compound	X	Y	Z
I	CH_2	$(CH_3)_2C$	CH_2
II	C_6H_5N	C_6H_5N	—
III	C_6H_5N	HN	—

It is not necessary to postulate the existence of free cyanic acid at the elevated reaction temperatures which are required if the reaction is envisioned as proceeding through cyclic resonance stabilized transition states. We are investigating these possibilities further, using 2-substituted cyclic 1,3-dicarbonyl compounds and substituted ureas as intermediates.

Additional applications of the reaction are currently being investigated. The reaction is apparently limited to cyclic 1,3-dicarbonyl compounds since the urea adduct of 4,6-dimethyl-2-pyrimidol[10] was obtained by refluxing an aqueous



solution of acetylacetone and urea. The pyrimidine was characterized by conversion to the nitrate.[11]

EXPERIMENTAL[12]

2-Carbamoyl-5,5-dimethyl-1,3-cyclohexanedione (I). A mixture of 20 g. (0.15 mole) of 5,5-dimethyl-1,3-cyclohexanedione and 18 g. (0.3 mole) of urea was heated at 137° for 20 min. The cooled mixture was dissolved in 150 ml. of hot methanol, the solution treated with Nuchar brand activated charcoal, and 250 ml. of 0.1*N* hydrochloric acid added. Cooling gave 9 g. (33%) of white crystalline solid, m.p. 139–143°. Recrystallizations from methanol and from ethyl acetate furnished 8 g. (30%), m.p. 145–146°. A solution in 0.1*N* sodium hydroxide exhibited maxima in mμ in the ultraviolet at 272 (ϵ = 14,120); in 0.1*N* hydrochloric acid at 260 (ϵ = 15,790).

Anal. Calcd. for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 58.82; H, 7.11; N, 7.47.

The pale blue *copper salt* was obtained by the addition of methanolic cupric acetate to a solution of I in methanol. The copper salt did not melt and was insoluble in organic solvents. The salt could be hydrolyzed by stirring with 10% sulfuric acid and ether at room temperature for 2 hr. The ether was separated and the aqueous phase washed with ether. The combined ethereal solutions were washed with water, dried with magnesium sulfate and concentrated to yield I, m.p. 145–146°.

4-Carbamoyl-1,2-diphenyl-3,5-pyrazolidinedione (II). A mixture of 16 g. (0.064 mole) of 1,2-diphenyl-3,5-pyrazolidinedione[4] and 7.6 g. (0.126 mole) of urea contained in a 100-ml. round bottom flask was heated in an oil bath at 150° for 10 min. and at 145° for an additional 10 min. with intermittent hand stirring. The glass obtained upon cooling was dissolved with heat in 50 ml. of methanol and then 300 ml. of water was added. The solution was concentrated to about two-thirds volume and then diluted to 300 ml. with water. After washing with two 40-ml. portions of ethyl acetate the solution was acidified to *p*H 2 with hydrochloric acid. The precipitated product was collected, dried, and suspended in 120 ml. of butanone. The insoluble portion was separated and the liquor concentrated to 30 ml. The solution was diluted with heptane to 220 ml. and chilled to furnish 13 g., m.p. 144–147°. Recrystallization from 60 ml. of methanol gave 11 g. (59%), m.p. 154–156°; in 0.1*N* sodium hydroxide, λ_{max} 243 mμ (ϵ = 31,200). In 50% aqueous ethanol, the half neutralization point was at *p*H 3.0.

Anal. Calcd. for $C_{16}H_{13}N_3O_3$: C, 65.08; H, 4.44; N, 14.23. Found: C, 65.29; H, 4.46; N, 13.93.

4-Carbamoyl-1-phenyl-3,5-pyrazolidinedione (III). A mixture of 3.5 g. (0.02 mole) of 1-phenyl-3,5-pyrazolidinedione[4]

(6) (a) W. Dieckmann, J. Hoppe, and R. Stein, *Ber.*, **37**, 4635 (1904). (b) S. Ruhemann, *J. Chem. Soc.*, **93**, 621 (1908). (c) D. E. Worall, *J. Am. Chem. Soc.*, **50**, 1456 (1928); *J. Am. Chem. Soc.*, **42**, 1055 (1920).

(7) H. Ruhkopf, *Ber.*, **73**, 820 (1940).

(8) M. Conrad and A. Zart, *Ber.*, **39**, 2283 (1906).

(9) The pale blue copper salt of C-acetyldimedon is hydrolyzed in dilute sulfuric acid at 0°. See W. Dieckmann and R. Stein, *Ber.*, **37**, 3370 (1904).

(10) S. Birtwell, *J. Chem. Soc.*, 1725 (1953).

(11) T. deHoan, *Rec. trav. chim.*, **27**, 162 (1908); *J. Chem. Soc.*, **94i**, 577 (1908).

(12) All melting points are uncorrected. Microanalyses by Spang Microanalytical Laboratory, Ann Arbor, Mich.

and 2.4 g. (0.04 mole) of urea was heated at 150° for 12 min. to yield a glass which was boiled with 50 ml. of water. Cooling gave a gelatinous material which was discarded. The liquor, *p*H 4, was acidified to *p*H 1 with hydrochloric acid to precipitate a heavy solid which was collected and then stirred with 150 ml. of methanol for 1.5 hr. After separation of a small amount of insoluble material, the methanol solution was concentrated to dryness and the residue suspended in butanone. A little insoluble material was removed and the liquor diluted with heptane to furnish a solid which was collected, dried and recrystallized from water and from butanone to furnish 1 g. (23%), m.p. 186–191°. The melting point varied with the rate of heat; however, the product showed good depression with 1-phenyl-3,5-pyrazolidinedione; in 0.1*N* sodium hydroxide, λ_{max} 290 (shoulder) and 256 mμ (ϵ = 4710 and 12,600).

Anal. Calcd. for $C_{10}H_9N_3O_3$: C, 54.79; H, 4.14; N, 19.17. Found: C, 54.46; H, 4.16; N, 19.20.

Acknowledgment. The author is indebted to Dr. Coy W. Waller for his assistance in the initiation of this work and to Dr. Richard T. Arnold for his suggestions regarding to mechanism proposed.

DEPARTMENT OF SYNTHETIC ORGANIC CHEMISTRY
MEAD JOHNSON AND CO.
EVANSVILLE 21, IND.

Adducts of Halogenated Cyclopentadienes with Halogenated Quinones[1,2]

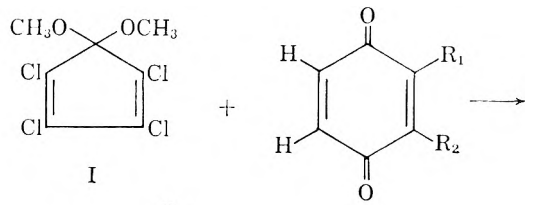
HENRY RAKOFF AND BRAD H. MILES[3]

Received October 26, 1960

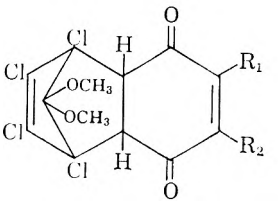
The use of tetrachloro-substituted, conjugated, alicyclic dienes as reactants in the Diels-Alder Reaction has been known for some time. 1,2,3,4-Tetrachloro-1,3-cyclopentadiene,[4] tetrachlorocyclopentadienone,[5] and 5,5-dimethoxy-1,2,3,4-tetrachloro-1,3-cyclopentadiene (I)[6] are all known to undergo this reaction.

McBee, Diveley, and Burch[6] describe a method for preparing aromatic compounds by a sequence of reactions involving hydrolysis of the ketal and removal of the carbonyl bridge from adducts between I and various dienophiles. It was hoped that this sequence could be applied to the synthesis of chlorinated naphthoquinones. While this desire was not realized, some novel information on the chemical behavior of the adducts between I and chlorinated quinones was obtained.

The diene (I) was treated with *p*-benzoquinone, monochloroquinone, and 2,3-dichloroquinone to yield the expected adducts (II–IV). Attempts to react I with 2,5-dichloroquinone or with chloranil were unsuccessful.

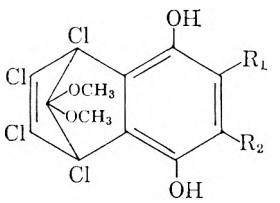


I



II. $R_1 = R_2 = H$
III. $R_1 = H$; $R_2 = Cl$
IV. $R_1 = R_2 = Cl$

Attempts to hydrolyze the adducts to the carbonyl bridge compounds with sulfuric acid gave either no reaction or highly colored, pasty materials depending upon the concentration of the acid employed. Attempted hydrolysis of II with an acetic acid-hydrochloric acid mixture converted it to its enol isomer (V). Adducts III and IV were isomerized to their enol isomers, VI and VII, by refluxing the respective adducts in methyl alcohol containing pyridine.[7]



V. $R_1 = R_2 = H$
VI. $R_1 = H$; $R_2 = Cl$
VII. $R_1 = R_2 = Cl$

The diacetates and dibenzoates of enol isomers V, VI, and VII and the diethyl ethers of V and VI were prepared according to standard procedures.

The reaction of II with stannous chloride and hydrochloric acid resulted in reduction of the double bond in the quinone portion of the molecule. The carbonyl groups were not reduced, but the yellow color of the quinone was lost leaving the white compound VIII. The infrared spectrum of this compound is consistent with the presence of carbonyl groups and the absence of hydroxy groups. In addition, VIII reacted with 2,4-dinitrophenylhydrazine to form a bright yellow, bis-2,4-dinitrophenylhydrazone. The reduction of III or IV with

(1) A portion of this work is taken from the M.S. thesis of Brad H. Miles.

(2) A portion of this work was presented before the Southwest Regional Meeting of the American Chemical Society. San Antonio, Tex., Dec., 1958.

(3) Present address: Dow Chemical Company, Freeport, Tex.

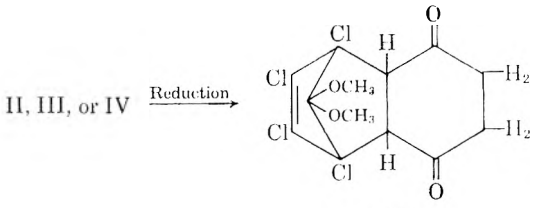
(4) E. T. McBee, R. K. Meyers, and C. F. Baranauckas, *J. Am. Chem. Soc.*, **77**, 86 (1955).

(5) J. S. Newcomer and E. T. McBee, *J. Am. Chem. Soc.*, **71**, 948 (1949).

(6) E. T. McBee, W. R. Diveley, and J. E. Burch, *J. Am. Chem. Soc.*, **77**, 385 (1955).

(7) E. Segel, R. E. Lidov, and J. Hyman, U. S. Pat. **2,584,140** (Feb. 5, 1952); *Chem. Abstr.*, **46**, 9591i (1952).

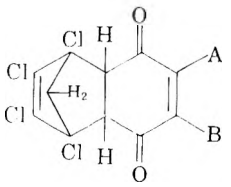
iron and acetic acid also yielded VIII. The method of mixed melting points, elemental analyses, formation of the same bis-2,4-dinitrophenylhydrazone, and comparison of infrared spectra all testify to the fact that the same compound VIII is produced by reduction of the three different adducts.



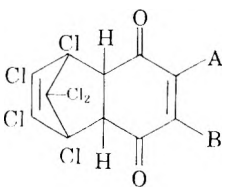
VIII

Reduction of II to the dione (VIII) is straight forward. Reduction of III or IV to VIII, however, requires replacement of chlorine by hydrogen. A similar type of replacement has been reported.[8] 3-Chloro-5-hydroxynaphthoquinone (3-chlorojuglone) is converted to 1,2,3,4-tetrahydro-5-hydroxy-1,4-naphthalenedione (β-hydrojuglone) by acidic stannous chloride.

The non-reactivity of diene I with 2,5-dichloroquinone and with chloranil led to a study of the reaction of hexachlorocyclopentadiene, 1,2,3,4-tetrachlorocyclopentadiene, and cyclopentadiene with these and the other chlorinated quinones employed. It was found that both hexachlorocyclopentadiene[9] and tetrachlorocyclopentadiene would form adducts with chloroquinone and with 2,3-dichloroquinone (IX-XII) but not with 2,5-dichloroquinone nor with chloranil. These observations are in accord with previous results[10] obtained when hexachlorocyclopentadiene was permitted to react with halogenated olefins. It was found then that hexachlorocyclopentadiene would not form an adduct with a halogenated olefin unless that olefin had at least one hydrogen on each of the doubly bonded carbon atoms. This observation lends support to the structures presented for the monochloro- and the 2,3-dichloroquinone adducts as against the alternative possibility in which the diene adds to the double bond holding the halogen.



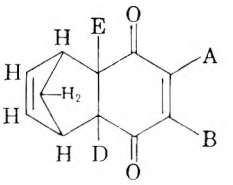
IX. A = Cl; B = H
X. A = B = Cl



XI. A = Cl; B = H
XII. A = B = Cl

It would appear at first though that the two allylic chlorines in hexachlorocyclopentadiene or the two allylic methoxy groups in dimethoxytetrachlorocyclopentadiene, which are not in the plane of the ring, would interact sterically with the chlorine on the double bonds of 2,5-dichloroquinone and chloranil. As tetrachlorocyclopentadiene also fails to react with these two quinones, however, it appears that the groups on the allylic position of the diene do not make possible nor inhibit this reaction.

The adducts of cyclopentadiene with quinone[11] and with chloranil,[11,12,13] are recorded in the literature while the adducts with chloroquinone (XIII) and with 2,3-dichloroquinone (XIV) have not been reported previously. An unsuccessful attempt to prepare the adducts between cyclopentadiene and 2,5-dichloroquinone (XV) or 2,6-dichloroquinone (XVI), has been reported by Gaertner.[13]



	A	B	D	E
XIII.	Cl	H	H	H
XIV.	Cl	Cl	H	H
XV.	Cl	H	Cl	H
XVI.	Cl	H	H	Cl

EXPERIMENTAL[14]

Hexachlorocyclopentadiene was donated by the Hooker Chemical Corporation while the Velsicol Chemical Corporation supplied the dicyclopentadiene. 2,5-Dichloroquinone and chloranil were purchased from Eastman Organic Chemicals. 1,2,3,4-Tetrachlorocyclopentadiene,[4] 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene,[5] 2-chloroquinone,[15] 2,3-dichloroquinone,[16] 2,6-dichloroquinone,[17] and adduct II[6] were prepared by published procedures.

III. Between 2,5-dichloroquinone and cyclopentadiene. Freshly cracked cyclopentadiene (1.8 g.; 0.026 mole) and 2,5-dichloroquinone (4 g.; 0.02 mole) were mixed in benzene solution (25 ml.) and heated at the reflux temperature for 2 hr. The cool solution was diluted with petroleum ether (b.p. 60–70°) (100 ml.) and a pale yellow solid (1.75 g., m.p. 113–114°) was obtained by filtration. A second crop (3.35 g., m.p. 113–114°) was obtained by evaporating the filtrate almost to

(8) D. B. Bruce and R. H. Thomson, *J. Chem. Soc.*, 2759 (1952).

(9) R. E. Lidov, J. Hyman, and E. Segel, U. S. Pat. **2,584,139** (Feb. 5, 1952) claim the preparation of XI and XII but give no physical constants nor elemental analyses.

(10) E. T. McBee, H. Rakoff, and R. K. Meyers, *J. Am. Chem. Soc.*, **77**, 4427 (1955).

(11) E. C. Ladd, Canadian Pat. **501,628** (Apr. 20, 1954); *Chem. Abstr.*, **50**, 8126e (1956).

(12) J. Hyman, U. S. Pat. **2,507,207** (May 9, 1950); *Chem. Abstr.*, **44**, 9617f (1950).

(13) R. Gaertner, *J. Am. Chem. Soc.*, **76**, 6150 (1954).

(14) All melting points are uncorrected. Carbon and hydrogen determinations were run by Weiler and Strauss Microanalytical Laboratory, Oxford, England, and by the Galbraith Microanalytical Laboratory, Knoxville, Tenn. Chlorine determinations were run by the authors and by the State Chemist's Laboratory.

(15) L. F. Fieser, *Experiments in Organic Chemistry*, 2nd Ed., D. C. Heath and Co., New York, 1941, p. 228.

(16) J. B. Conant and L. F. Fieser, *J. Am. Chem. Soc.*, **45**, 2204 (1923).

(17) F. Kehrmann and W. Tiesler, *J. prakt. chem.* [2], **40**, 481 (1889).

TABLE I

PREPARATION OF ADDUCTS

Diene	Adduct	Reaction			Rextn.			% Cl	
		Solvent	Temp.	Time	Solvent	M.P.	Conv.	Calcd.	Found
				I. Between Chloroquinone and					
Cyclopentadiene	XIII	Skelly B[a]	R.T.	3 min.	Skelly B	63–64°	77%	16.99	16.96; 16.85
Tetrachlorocyclopentadiene	IX	Benzene	Reflux	8 hr.	Ethanol	148.5–149°	99%	51.18	50.87; 51.00
Hexachlorocyclopentadiene	XI	None	Heated to 160°		Skelly B	177–178°	69%	59.76	59.64; 59.65
Dimethoxytetrachlorocyclopentadiene	III	Toluene	Reflux	16 hr.	Ethanol	155.5–157°	81%	43.62	43.89[b]
				II. Between 2,3-Dichloroquinone and					
Cyclopentadiene	XIV	Benzene	R.T.	16 hr.	Skelly B	109–110°	74%	29.17	28.90; 28.93
Tetrachlorocyclopentadiene	X	Benzene	R.T.	16 hr.	Skelly B	168–169°	69%	55.86	55.44; 55.52
Hexachlorocyclopentadiene	XII	None	Heated to 138°		Skelly B	177–179°	88%	63.07	62.46; 62.50
Dimethoxytetrachlorocyclopentadiene	IV	Toluene	Reflux	42 hr.	Ethanol	204–205.5°	54%	48.25	47.83[c]

[a] Petroleum ether (b.p. 60–70°). [b] C and H analysis; Calcd.: C, 38.41; H, 2.23. Found: C, 38.92, 38.94; H, 2.50, 2.52. [c] C and H analysis: Calcd.: C, 35.41; H, 1.83. Found: C, 35.58, 35.60; H, 2.29, 2.04.

dryness and diluting with petroleum ether (50 ml.). The analytical sample, XV, m.p. 113–114°, was prepared by recrystallizing the crude material twice from petroleum ether (once with Darco); yield (crude), 93%.

Anal. Calcd. for $C_{11}H_8Cl_2O_2$: C, 54.35; H, 3.32; Cl, 29.17. Found: C, 54.55, 54.60; H, 3.11, 3.09; Cl, 29.39, 29.05.

With these same two reagents Gaertner[13] reported the preparation of a compound, m.p. 113.5–115.5° for which good analytical data could not be obtained.

IV. *Between 2,6-dichloroquinone and cyclopentadiene.* Freshly cracked cyclopentadiene (0.85 g. 0.012 mole) and 2,6-dichloroquinone (2.2 g.; 0.012 mole) were mixed in benzene (5 ml.) and an exothermic reaction ensued. About an hour later the solution was diluted with petroleum ether (20 ml.) and cooled in a Dry Ice–acetone bath. A pale yellow solid (2.7 g.) was filtered, m.p. 70.5–72°. The analytical sample, XVI, m.p. 72.5–73.5°, was prepared by recrystallizing this material twice from petroleum ether (once with Darco); yield (crude), 93%.

Anal. Calcd. for $C_{11}H_8Cl_2O_2$: C, 54.35; H, 3.32; Cl, 29.17. Found: C, 54.35, 54.48; H, 3.14, 3.37; Cl, 29.28, 29.08.

With these same two reagents, Gaertner[13] obtained a compound, m.p. 138–140°, which decomposed rapidly on standing and for which good analytical data could not be obtained. Our product, m.p. 72.5–73.5°, whose analysis checked well with the calculated values, decomposed slowly; after two weeks the melting point had dropped to 64–65°. The difference in the products obtained may be due to the difference in reaction time employed and to the fact that Gaertner took cyclopentadiene and 2,6-dichloroquinone in a 1.5:1 ratio while we took them in a 1:1 ratio.

Preparation of enol isomers. A. *Of Adduct* III. *Preparation of compound* VI. *Typical Preparation.* A mixture of adduct III (5 g.; 0.012 mole), methanol (50 ml.), and pyridine (15 drops) was heated under reflux for 12 hr. The solution was neutralized with sulfuric acid and reduced to about one-fourth the original volume by boiling at atmospheric pressure. Water was added to precipitate the product which was extracted into boiling petroleum ether. This extract was filtered, reduced in volume by boiling, and cooled in an ice bath. The reddish-white precipitate which formed was recrystallized from petroleum ether (Darco added) and yielded the enol isomer, VI, m.p. 132–134°; conversion was 48%.

Anal. Calcd. for $C_{13}H_6Cl_6O_4$: C, 38.41; H, 2.23; Cl, 43.62. Found: C, 38.50, 38.71; H, 2.65, 2.56; Cl, 43.13.

B. *Of adduct IV. Preparation of compound* VII. M.p. 154.5–156°; conversion; 70%.

Anal. Calcd. for $C_{13}H_8Cl_6O_4$: C, 35.41; H, 1.83; Cl, 48.25. Found: C, 35.86, 36.09; H, 1.79, 1.54; Cl, 47.95.

C. *Of adduct* II. *Preparation of compound* V. M.P. 203–204°; conversion, 90%.

Anal. Calcd. for $C_{13}H_{10}Cl_4O_4$: C 41.97; H, 2.71; Cl, 38.12. Found: C, 41.78, 41.93; H, 3.03, 3.15; Cl, 38.19, 38.38.

Preparation of derivatives of the enol isomers. A. *Benzoates.* The dibenzoates were prepared by treating 0.5-g. quantities of the enol isomers with dry pyridine (3 ml.) and benzoyl chloride (2 ml.). After the exothermic reaction had subsided, concentrated hydrochloric acid was added. An oil separated from the solution but it solidified on stirring with a glass rod. The crystals were filtered, washed with 5% sodium carbonate solution, and recrystallized from methanol. Conversions of 90% were realized.

Dibenzoate of enol isomer V. M.p. 228–230°.

Anal. Calcd. for $C_{27}H_{18}Cl_4O_6$: C, 55.88; H, 3.13; Cl, 24.44. Found: C, 55.83, 55.61; H, 3.23, 3.34; Cl, 24.44, 24.17.

Dibenzoate of enol isomer VI. M.p. 204.5–206°.

Anal. Calcd. for $C_{27}H_{17}Cl_5O_6$: C, 52.75; H, 2.79; Cl, 28.84. Found: C, 52.93, 53.12; H, 2.72, 2.80; Cl, 28.96.

Dibenzoate of enol isomer VII. M.p. 230°.

Anal. Calcd for $C_{27}H_{16}Cl_6O_6$: C, 49.96; H, 2.48; Cl, 32.44. Found: C, 50.58, 50.03; H, 2.61, 2.60; Cl, 32.77.

B. *Acetates.* The diacetates were prepared by treating 2-g. quantities of the enol isomers with 2 ml. of acetic anhydride and 1 drop of concentrated sulfuric acid. After the exothermic reaction had subsided, water was added to precipitate the product and to hydrolyze excess acetic anhydride. The product was filtered, washed with water, and recrystallized from petroleum ether. Conversions ranged from 83 to 98%.

Diacetate of enol isomer V. M.p. 161–163°.

Anal. Calcd. for $C_{17}H_{14}Cl_4O_6$: C, 44.76; H, 3.09; Cl, 31.09. Found: C, 44.85, 45.08; H, 3.37, 3.12; Cl, 31.01, 31.30.

Diacetate of enol isomer VI. M.p. 165–166°.

Anal. Calcd. for $C_{17}H_{13}Cl_5O_6$: C, 41.62; H, 2.67; Cl, 36.13. Found: C, 40.62, 40.74; H 3.06, 3.06; Cl, 35.68.

Diacetate of enol isomer VII. M.p. 160–161°.

Anal. Calcd. for $C_{17}H_{12}Cl_6O_6$: C, 38.89; H, 2.30; Cl, 40.52. Found: C, 39.06, 39.02; H, 2.35, 2.10; Cl, 40.20.

C. *Ethers.* The diethers of enol isomers V and VI were prepared by treating the enol isomer in acetone solution with ethyl bromide and potassium carbonate according to the method described in Hickinbottom.[18]

Diethyl ether of enol isomer V. M.p. 153–154°; conversion 85%.

Anal. Calcd. for $C_{17}H_{18}Cl_4O_4$: C, 47.96; H, 4.23; Cl, 33.12. Found: C, 47.87, 47.84; H, 4.32, 4.41; Cl, 32.54, 33.18.

Diethyl ether of enol isomer VI. M.p. 99–101°.

Anal. Calcd. for $C_{17}H_{17}Cl_5O_4$: C, 44.14; H, 3.70; Cl, 38.32. Found: C, 44.29, 44.02; H, 3.72, 4.13; Cl, 38.17.

Preparation of 5,6,7,8-tetrachloro-9,9-dimethoxy-2,3,4a,5,8,-8a-hexahydro-5,8-methanonaphthalene-1,4-dione. VIII. A. *From adduct* II. A solution containing adduct II (5 g.; 0.013 mole), methanol (200 ml.), stannous chloride dihydrate (30 g.; 0.13 mole), and hydrochloric acid (40 ml.) was shaken until the color disappeared. Water was added and the white solid which formed was recrystallized from methanol to give VIII (4.9 g.; 98%), m.p. 128–129°.

Anal. Calcd. for $C_{13}H_{12}Cl_4O_4$: C, 41.74; H, 3.23; Cl, 37.92. Found: C, 42.38, 41.91; H, 3.15, 2.87; Cl, 38.28.

B. *From adduct* III. A solution of adduct III (5 g.; 0.012 mole), iron (by reduction) (15 g.; 0.27 mole), and acetic acid (100 ml.) was refluxed for 1.5 hr. The solution was filtered while hot, and water was added to precipitate the product. The mixture was allowed to stand overnight before it was filtered and the product which was obtained was recrystallized twice from methanol-water to give VIII in 80% conversion; m.p. 129–131.°

Anal. Calcd. for $C_{13}H_{12}Cl_4O_4$: C, 41.74; H, 3.23; Cl, 37.92. Found: C, 42.23, 42.20; H, 3.61, 3.64; Cl, 37.82.

C. *From adduct* IV. Compound VIII was prepared from adduct IV in a manner similar to that described for the preparation from adduct III. It was obtained in 72% conversion, m.p. 129–132°.

Anal. Calcd. for $C_{13}H_{12}Cl_4O_4$: C, 41.74, H, 3.23; Cl, 37.92. Found: C, 41.18, 41.89; H, 3.31, 2.97; Cl, 37.82.

Preparation of the bis-2,4-dinitrophenylhydrazone of VIII. An excess of specially prepared[19] 2,4-dinitrophenylhydrazine reagent was added to a solution of VIII in ethanol (25 ml.). The bright yellow precipitate was filtered and washed with water. It was then recrystallized once from xylene, twice from acetic acid, and once more from xylene to give the bright yellow derivative in 30% conversion. Decomposition temperature, 234°.

Anal. Calcd. for $C_{25}H_{20}Cl_4N_8O_{10}$: Cl, 19.31; Found, Cl, 19.27.

Department of Chemistry
Agricultural and Mechanical College of Texas
College Station, Tex.

(18) W. J. Hickinbottom, *Reactions of Organic Compounds*, 2nd Ed., Longmans, Green and Co., London, 1948, p. 92.

(19) G. D. Johnson, *J. Am. Chem. Soc.*, **73**, 5888 (1951).

Condensation Reactions of Phthalaldehydic Acid. II

Vaughn W. Floutz

Received November 1, 1960

Many of the reactions of phthalaldehydic acid can best be accounted for by using the tautomeric closed-ring structure. That such a structure actually exists has been verified recently through infrared absorption studies.[1] A previous paper by this writer[2] reported a number of condensation reactions of phthalaldehydic acid with aromatic hydrocarbons and with aryl halides which involve the reactive 3- position in the 3-hydroxy form of the acid.[3] Sulfuric acid in various concentrations was employed as the condensing agent. In all of the substituted phthalides which were synthesized in this manner, the carbon at the 3- position became linked directly to carbon in the aromatic ring.

The investigations reported in this paper show that this same general method can be used for condensing phthalaldehydic acid with phenols, phenolic ethers, and ring halogenated phenols and phenolic ethers. Bistrzycki[4,5] and his associates have reported success in preparing 3-(*p*-methoxyphenyl)phthalide by this approach, but they failed in attempts to similarly synthesize 3-(*p*-ethoxyphenyl)phthalide. In a series of papers Adams,[6] *et al.* describe condensations of opianic acid with a number of phenolic compounds, and suggest a similar behavior for phthalaldehydic acid.

The structures of certain phthalides which are formed in condensations of this type can be established with reasonable certainty on the basis of the relative directive strengths of the substituent groups. Thus, the condensation product to be expected from the reaction of phthalaldehydic acid with *p*-chloroanisole is 3-(5-chloro-2-methoxyphenyl)phthalide, and not the isomeric 3-(2-chloro-5-methoxyphenyl)phthalide. That this is a correct conclusion was proved unequivocally by converting this phthalide into 5-chloro-2-methoxyaniline and *o*-phthalic acid. To this end the phthalide was first oxidized with alkaline permanganate to produce the corresponding substituted *o*-benzoylbenzoic acid. From this compound there was prepared the oxime, isolated as an oxime anhydride. Heating the oxime with concentrated hydrochloric acid brought about a Beckmann rearrangement, and subsequent hydrolysis. Two products were isolated from the reaction mixture and identified as 5-chloro-2-methoxyaniline and *o*-phthalic acid.

Infrared absorption spectra were obtained for 3-phenylphthalide, a compound previously reported,[2] and also for 3-(5-chloro-2-methoxyphenyl)-phthalide and 3-(5-methyl-2-methoxyphenyl)-

(1) D. D. Wheeler, D. C. Young, and D. S. Erley, *J. Org. Chem.*, **22**, 556 (1957).

(2) Part I appeared in *J. Org. Chem.*, **25**, 643 (1960).

(3) It is to be noted that prior to 1937 *Chemical Abstracts* used the notation 2-substituted phthalides instead of 3-substituted phthalides.

(4) A. Bistrzycki and G. Oehlert, *Ber.*, **27**, 2632 (1894).

(5) A. Bistrzycki and S. Zen-Ruffinen, *Helv. Chim. Acta*, **3**, 369 (1920).

(6) M. M. Brubaker and R. Adams, *J. Am. Chem. Soc.*, **49**, 2279 (1927).

phthalide. These spectra show intense absorption at 5.73 μ, 5.68 μ, and 5.70 μ respectively, attributed to C=O stretch as affected by five-membered ring strain. Intense bands also occur at 9.33 μ, 9.48 μ, and 9.40 μ, respectively, and are assigned to asymmetric C—O—C stretch. For 3-phenylphthalide and 3-(5-methyl-2-methoxyphenyl)phthalide strong absorption occurs at 10.35 μ and 10.25 μ, respectively, due to symmetric C—O—C stretch. No pronounced absorption is evident in this region for 3-(5-chloro-2-methoxyphenyl)phthalide; the symmetric C—O—C stretch is particularly sensitive to the group attached at the 3- position. Wheeler, Young, and Erley[1] have noted these same three absorption bands for a number of 3-substituted phthalides in which the carbon at this position is linked to an element other than carbon. Their suggestion that these bands have value in the identification of phthalide derivatives is strengthened by the infrared data cited here

With the exception of 3-(*p*-methoxyphenyl)-phthalide, the phthalides whose syntheses are reported here are believed to be new compounds.

EXPERIMENTAL

The phthalaldehydic acid used in this study was supplied by the Dow Chemical Co.; it was purified as previously described.[2] The ratios of acid to water, and of acid to acid, are on a volume basis.

3-(p-Methoxyphenyl)phthalide. One and one-half grams (0.01 mole) of phthaladehydic acid was dissolved in 24 ml. of 3:1 concd. sulfuric acid–water. This solution was cooled in an ice water bath and 1.08 g. (0.01 mole) of anisole was added. The cold mixture was mechanically stirred to disperse the anisole. After about 1 hr. the mixture became light red in color and homogeneous. Stirring was continued for an additional 0.5 hr. to insure complete reaction. Upon pouring the reaction mixture into about ten times its volume of cold water a soft, yellow solid separated; this soon became sufficiently hard to crumble. Thorough washing and air-drying gave 2.4 g. (100%) of crude product. This was recrystallized from glacial acetic acid, and washed on the filter with a small volume of ice-cold ethanol. The nearly white crystalline product melted at 116–117° and weighed 1.85 g. (77%), lit.[7] m.p. 116–117°.

Anal.[8] Calcd. for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found: C, 75.14; H, 5.23.

3-(p-Ethoxyphenyl)phthalide. One and one-half grams (0.01 mole) of phthalaldehydic acid was dissolved in 18 ml. of 2:1 concd. sulfuric acid–water, and the solution cooled in an ice water bath. To this was added 1.22 g. (0.01 mole) of phenetole, and the cold mixture was then mechanically stirred. After 2 hr. soft, white, bead-like curds separated. The mixture was kept cold and stirred for an additional 3 hr. The crude product was isolated as described for 3-(*p*-methoxyphenyl)phthalide; it weighed 2.2 g. (87%). Recrystallization from ethanol gave 1.7 g. (67%) of white crystals, m.p. 110–111°.

Anal. Calcd. for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 75.69; H, 5.42.

3-(5-Chloro-2-methoxyphenyl)phthalide. The reaction mixture was prepared by dissolving 1.5 g. (0.01 mole) of phthalaldehydic acid in 25 ml. of 4:1 concd. sulfuric acid–water, then adding 1.42 g. (0.01 mole) of *p*-chloroanisole. This was stirred mechanically at room temperature for a period of 6 hr., and then poured into a large volume of cold water. The crude phthalide separated at once as a pale yellow solid. Crushing, washing with cold water, and air-drying gave 2.52 g. (92%) of crude product. Recrystallization from ethanol yielded 1.95 g. (71%) of white needle-like crystals, m.p. 126–127°.

Anal. Calcd. for $C_{15}H_{11}O_3Cl$: C, 65.58; H, 4.04; Cl, 12.91. Found: C, 65.88; H, 3.92; Cl, 13.03.

o-Phthalic acid and 5-chloro-2-methoxyaniline from 3-(5-chloro-2-methoxyphenyl)phthalide. That the condensation of phthalaldehydic acid with *p*-chloroanisole, which conceivably could lead to the formation of one or both of two possible isomers, gave 3-(5-chloro-2-methoxyphenyl)phthalide as the only isolated product was proved as follows. One gram of this phthalide was oxidized by use of alkaline permanganate solution in the usual manner. The crude oxidation product was recrystallized from aqueous ethanol; this gave 0.87 g. of a white solid, m.p. 141–141.5°. Neut. equiv. Calcd. for $C_{14}H_{10}O_2Cl$-COOH: 290.7. Found: 291.2.

The oxidation product was converted into the corresponding oxime anhydride by following essentially a procedure outlined by Thorpe.[9] Recrystallization of the crude oxime anhydride from ethanol gave 0.7 g. of white fibrous needles, m.p. 174–175°. A successful Beckmann rearrangement, followed by hydrolytic splitting, was carried out by suspending 0.2 g. of the oxime anhydride in 10 ml. of concd. hydrochloric acid. This mixture was sealed in a glass tube and heated for a total of 6 hr. in an oil bath maintained at 125–130°; during this time the suspended solid gradually disappeared. After standing undisturbed for 24 hr. a crystalline solid separated upon shaking the tube. This proved to be *o*-phthalic acid. Following removal of the *o*-phthalic acid the solution was carefully neutralized with sodium hydroxide solution. Fine glistening plates, somewhat dark in color, separated. Recrystallization from aqueous ethanol gave plates of pronounced aniline-like odor, m.p. 82–83°. The accepted melting point for 5-chloro-2-methoxyaniline is 82–83.5.° A mixed melting point with an authentic sample showed no depression. A small quantity of the picrate of this compound was prepared; it gave a melting point of 194–195°; lit. m.p. 194°.

3-(5-Chloro-2-ethoxyphenyl)phthalide. One and one-half grams (0.01 mole) of phthalaldehydic acid was dissolved in 25 ml. of 4:1 concd. sulfuric acid–water solution. To this was added 1.57 g. (0.01 mole) of *p*-chlorophenetole, and the mixture then mechanically stirred at room temperature to disperse the *p*-chlorophenetole. After a period of 6 hr. the mixture was milky with fine particles of solid in evidence. This was then poured into about ten times its volume of cold water; granules of pink solid separated at once. The 2.47 g. (85%) of crude product, when recrystallized from glacial acetic acid, afforded 2.1 g. (73%) of a granular, crystalline, white solid. An analytical sample melted at 164.5–165.5°.

Anal. Calcd. for $C_{16}H_{13}O_3Cl$: C, 66.56; H, 4.54; Cl, 12.28. Found: C, 67.04; H, 4.38; Cl, 12.19.

3-(5-Bromo-2-ethoxyphenyl)phthalide. The reaction mixture consisted of 1.5 g. (0.01 mole) of phthalaldehydic acid dissolved in 25 ml. of 4:1 concd. sulfuric acid–water, with 2.0 g. (0.01 mole) of added *p*-bromophenetole. Following essentially the same procedure as outlined above for the chloro analog, there was obtained 3.1 g. (93%) of crude phthalide, yellow in color. Crystallization from glacial

(7) A. Bistrzycki and Yessel de Schepper, *Ber.*, 31, 2790 (1898).

(8) The majority of the elementary analyses reported here were performed by the Tiedcke Laboratory of Microchemistry.

(9) F. Thorpe, *Ber.*, 26, 1261, 1795 (1893).

acetic acid gave 2.35 g. (71%) of fine white crystals, m.p. 175–176°.

Anal. Calcd. for $C_{16}H_{13}O_3Br$: C, 57.67; H, 3.94; Br, 23.98. Found: C, 57.91; H, 3.83; Br, 23.82.

3-(5-Chloro-2-hydroxyphenyl)phthalide. One and one-half grams (0.01 mole) of phthalaldehydic acid was dissolved in 18 ml. of 3:1 concd. sulfuric acid–water. This solution was cooled in an ice-water bath, and 1.28 g. (0.01 mole) of *p*-chlorophenol was added. After mechanically stirring the mixture for 2 hr. the cooling bath was removed and stirring was continued for an additional 2 hr. At this point the thick, milky emulsion was brought into a large volume of cold water, with vigorous stirring. A voluminous white solid separated and gradually settled out. The crude product was removed, washed thoroughly with cold water, and permitted to dry overnight. This gave a white powdery solid weighing 2.3 g. (88%). Recrystallization from ethanol yielded 1.83 g. (70%) of soft, glistening needles. An analytical sample melted at 163.5–164°.

Anal. Calcd. for $C_{14}H_9O_3Cl$: C, 64.51; H, 3.48; Cl, 13.60. Found: C, 64.64; H, 3.29; Cl, 13.73.

3-(5-Methyl-2-methoxyphenyl)phthalide. A solution of 1.5 g. (0.01 mole) of phthalaldehydic acid in 24 ml. of 3:1 concd. sulfuric acid–water was prepared. This was cooled by immersion in an ice-water bath, and 1.22 g. (0.01 mole) of *p*-methylanisole was then added. The mixture was mechanically stirred; after 3 hr. testing showed that the brown oil which had separated as a top layer would solidify in water. The entire reaction mixture was poured with stirring into a large volume of cold water. The gum which separated soon hardened to a yellow solid; when firm it was removed and thoroughly washed with cold water. Drying gave as crude product 2.55 g. (100%) of light yellow solid. Recrystallization from ethanol yielded 2.03 g. (80%) of white crystals, m.p. 120.5–121.5°.

Anal. Calcd. for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 75.34; H, 5.71.

3-(5-Methyl-2-ethoxyphenyl)phthalide. This phthalide was synthesized by using 1.5 g. (0.01 mole) of phthalaldehydic acid and 1.34 g. (0.01 mole) of *p*-methylphenetole with 24 ml. of 3:1 concd. sulfuric acid–water as the condensing agent. The procedure followed was essentially the same as outlined for 3-(5-methyl-2-methoxyphenyl)phthalide. The crude reaction product weighed 2.42 g. (91%). Recrystallization from ethanol gave 1.98 g. (74%) of white needles. An analytical sample melted at 151–151.5°.

Anal. Calcd. for $C_{17}H_{16}O_3$: C, 76.09; H, 6.01. Found: C, 76.21; H, 5.92.

3-(2,4,6-Trichloro-3-hydroxyphenyl)phthalide. One and one-half grams (0.01 mole) of phthalaldehydic acid was dissolved in 20 ml. of 1:1 concd. sulfuric acid–20% fuming sulfuric acid. To this solution at room temperature was added 1.98 g. (0.01 mole) of 2,4,6-trichlorophenol, and the mixture mechanically stirred. The dispersed phenol reacted over a period of 3 hr. to give a yellow solution. The reaction vessel was then immersed in a water bath maintained at 60–70°, and stirring was continued for an additional 2 hr. The reaction mixture was poured into a large volume of cold water. The gum which separated hardened very slowly, but became brittle after standing overnight. The crude product, nearly white in color, weighed 3.0 g. (90%). Recrystallization from glacial acetic acid gave 2.6 g. (80%) of nearly white cubic crystals, m.p. 164.5–165°.

Anal. Calcd. for $C_{14}H_7O_3Cl_3$: C, 51.02; H, 2.14; Cl, 32.27. Found: C, 51.10; H, 1.98; Cl, 32.41.

Acknowledgment. Appreciation is expressed to William V. Floutz, Wyandotte Chemicals Corp., for the infrared data, and its interpretation.

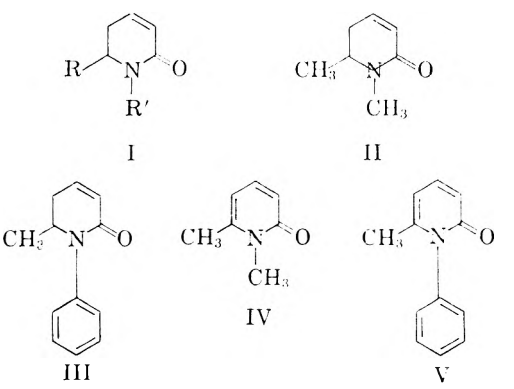
KNIGHT CHEMICAL LABORATORY
UNIVERSITY OF AKRON
AKRON 4, OHIO

Unsaturated Lactams. II.[1] The Catalytic Dehydrogenation of α,β-Unsaturated Valerolactams to Pyridones[2]

MAURICE SHAMMA AND PAUL D. ROSENSTOCK

Received November 2, 1960

The fact that α,β-unsaturated lactams of type (I) are now readily available[1] induced us to extend the method used by Spath and Galinovsky for the synthesis of pyridones. These two workers found that six-membered saturated lactams could be smoothly dehydrogenated to the corresponding pyridones by treatment with palladium. In the present work, the unsaturated lactams (II) and (III) were dehydrogenated to the pyridones (IV) and (V), respectively.



As indicated in Table I, the dehydrogenation reactions were found to be temperature dependent.

TABLE I

DEHYDROGENATION OF α,β-UNSATURATED VALEROLACTAMS TO PYRIDONES WITH 5% PALLADIUM ON CARBON

Solvent	B.P.	% Yield of IV	% Yield of V
Benzene	80°	30	—
Xylene	140°	40	28
p-(*n*-Propyl)anisole	247°	—	49

Catalytic dehydrogenation of α,β-unsaturated lactams can provide a route, therefore, to a variety of substituted pyridones which would be difficult to prepare by other routes.

EXPERIMENTAL[3]

1,6-Dimethyl-2-pyridone (IV). *Method A.* A well stirred suspension of 2 g. of 5% palladium on carbon, 50 ml. of xylene, and 10 g. (0.08 mole) of 1,6-dimethyl-5,6-dihydro-2-

(1) For paper I see Maurice Shamma and Paul D. Rosenstock, *J. Org. Chem.*, 26, 718 (1961).

(2) This research was supported in part by grant NSF-G10032 from the National Science Foundation.

(3) Elemental analyses were carried out by A. Bernhardt, Mulheim, Germany.

pyridone (II) was heated under reflux for 2 days. At the end of this period the reaction mixture was filtered, the catalyst washed well with benzene, and the solvent removed on a steam bath under a stream of nitrogen. The residue was distilled *in vacuo* to yield 5.4 g. (52%) fraction of a colorless liquid boiling at 60–64° at less than 0.5 mm. and a 4.2 g. (40%) fraction of colorless liquid that crystallized in the receiver; b.p. 80–88° at less than 0.5 mm. The former fraction was shown, on the basis of its infrared spectrum, to be starting material and the latter fraction was the desired 1,6-dimethyl-2-pyridone (IV).

The solid distillate was purified by recrystallization from dry ether to yield 3.7 g. (94% recovery) of hygroscopic, white crystalline solid; m.p. 54–56° in air or 55–57° in a sealed tube; reported[4], b.p. 110° at 2 mm.

Method B. If the identical reaction were run employing benzene as a solvent, the yield of 1,6-dimethyl-2-pyridone (IV) was only 30%.

1,6-Dimethyl-2-pyridone hydrochloride. A solution of 1.87 g. (0.015 mole) of 1,6-dimethyl-2-pyridone (IV) in 10 ml. of dry ether was saturated with dry hydrogen chloride gas. The precipitate was filtered, washed well with ether, and dried. The yield of white solid was 2.25 g. (97%); m.p. 138–168°. The product was recrystallized from methanol-ether to yield 2.21 g. (96%) of white crystalline solid; m.p. 198–201° in a sealed tube; reported[4] m.p. 202–203°.

1-Phenyl-6-methyl-2-pyridone (V). *Method A.* A well stirred suspension of 1.3 g. of 5% palladium on carbon, 50 ml. of *p*-(*n*-propyl)anisole and 12 g. (0.064 mole) of 1-phenyl-6-methyl-5,6-dihydro-2-pyridone (III) was heated under reflux for 2 days. At the end of this period the reaction mixture was filtered and the catalyst washed well with benzene. The filtrate was then extracted with three 200-ml. portions of 10% hydrochloric acid. The combined acid extracts were washed twice with 100 ml. of chloroform, made basic with 50% sodium hydroxide solution, and the resulting basic solution extracted three times with 200 ml. of ether. The combined ether extracts were dried over anhydrous sodium sulfate, filtered, and the ether solution evaporated to 70 ml. on a steam bath. The solution was cooled to room temperature and filtered to yield 5.8 g. (49%) of white rhombic crystals; m.p. 136–139° in a sealed tube. Two additional recrystallizations from ether netted an analytic sample that exhibited a melting point of 136–139° in a sealed tube.

Anal. Calcd. for $C_{12}H_{11}ON$: C, 77.81; H, 5.99; N, 7.56. Found: C, 78.21; H, 5.59; N, 7.82.

Method B. If an identical reaction were run according to Method A employing xylene as the solvent, the yield of 1-phenyl-6-methyl-2-pyridone (V) was only 28%.

1-Phenyl-6-methyl-2-pyridone hydrochloride. A solution of 1 g. (0.0054 mole) of 1-phenyl-6-methyl-2-pyridone (V) in 1 ml. of dry methanol and 10 ml. of dry ether was saturated with dry hydrogen chloride gas. Twenty milliliters of ether was added to the solution which was then cooled for 2 hr. in an ice bath. The solution was filtered, the precipitate washed with ether, and dried to yield 1.17 g. (98%) of white crystalline solid; m.p. 172–179° in a sealed tube. The product was recrystallized from methanol-ether to give 1.06 g. (90%) of white crystals; m.p. 198–201° in a sealed tube. Three additional recrystallizations from the same solvent combination gave an analytic sample that exhibited a melting point of 201–204° in a sealed tube.

Anal. Calcd. for $C_{12}H_{12}NOCl$: C, 65.01; H, 5.46; N, 6.32; Cl, 15.99. Found: C, 65.37; H, 5.78; N, 6.04; Cl, 15.46.

DEPARTMENT OF CHEMISTRY
THE PENNSYLVANIA STATE UNIVERSITY
UNIVERSITY PARK, PA.

(4) S. Susawa and M. Kirisawa, *Pharm. Bull. (Japan)*, **3**, 187 (1955).

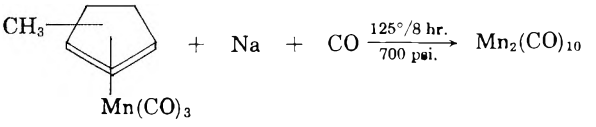
Reductive Carbonylation Synthesis of Metal Carbonyls. V. Synthesis of Manganese Carbonyl from π-Methylcyclopentadienylmanganese Tricarbonyl[1]

HAROLD E. PODALL[2] AND ALBERT P. GIRAITIS

Received November 3, 1960

Only two satisfactory methods have thus far been reported for the preparation of manganese carbonyl. One involves the use of the sodium benzophenone ketyl for forming a metastable manganese intermediate for carbonylation,[3] while the other involves the use of an alkylaluminum compound as a selective reducing agent for the manganese salt in the presence of carbon monoxide.[4,5] The latter reaction has been named reductive-carbonylation.[4] This paper deals with a third method which is much more convenient for preparing manganese carbonyl, based on reductive carbonylation with metallic sodium.

We have found that manganese carbonyl can be readily prepared in 45–50% yields by reductively carbonylating π-methylcyclopentadienylmanganese tricarbonyl (I) with sodium in diethylene glycol dimethyl ether (diglyme) solvent at about 125°. Highest yields were obtained when employ-



I

ing three gram-atoms of sodium per mole of I in diglyme. Use of smaller quantities of sodium resulted in decreased yields, while a 50% increase in sodium resulted in an uncontrollable reaction which set in at 122° and ruptured the safety disk of the reactor. The reaction was found to be considerably slower in benzene, requiring a temperature of about 200°, and gave only a 15% yield of manganese carbonyl. In diglyme, on the other hand, under comparable conditions, carbonylation set in at 100° or lower and resulted in a 50% yield. It appears therefore that diglyme plays a very important role in this reaction. One possibility here is that the diglyme serves to stabilize a manganese carbonyl moiety such as $Mn(CO)_3$ for carbonylation.

Use of other manganese salts in place of I resulted in decreased yields due to the formation of

(1) For paper IV, see H. Podall, H. B. Prestridge, and H. Shapiro, *J. Am. Chem. Soc.*, **83**, 2057 (1961).

(2) Present address: Melpar, Inc., Physical Sciences Laboratory, Falls Church, Va. To whom all inquiries should be addressed.

(3) R. D. Closson, L. R. Buzbee, and G. G. Ecke, *J. Am. Chem. Soc.*, **80**, 6167 (1958).

(4) H. Podall, *J. Am. Chem. Soc.*, **80**, 5575 (1958).

(5) H. Podall, J. H. Dunn, and H. Shapiro, *J. Am. Chem. Soc.*, **82**, 1325 (1960).

metallic manganese. It appears therefore that the methylcyclopentadienyl group serves to moderate the reactivity of the manganese atom toward reduction.[6]

An investigation of the stoichiometry of the reaction indicated that five sodium atoms and three carbon monoxide molecules are consumed per $Mn(CO)_5$ formed regardless of the solvent and temperature up to 200°. The reaction mixture generally contained a brown viscous oil which was insoluble in petroleum ether and did not appear to contain free manganese carbonyl prior to hydrolysis. Unchanged I was generally evident, and methylcyclopentadiene could not be detected before or after hydrolysis. Sodium did not appear to react with carbon monoxide to any significant extent under the conditions employed. Accordingly, it appears that the large excess of sodium required may be due solely to its reaction with the cyclopentadienyl group, and that the sodium methylcyclopentadienide which may be formed reacts further with carbon monoxide. It is suggested that the brown oil contains the sodium salt of manganese carbonyl, probably as a diglyme complex, $(diglyme)_2 Na^+ Mn(CO)_5^-$, and that the manganese carbonyl arises by oxidative-hydrolysis of the latter. Further work is required to define the various products of the evidently complex reaction involving I, sodium, and carbon monoxide.

EXPERIMENTAL

To a 1-l. Parr autoclave were added 80 ml. (0.50 mole) of π-methylcyclopentadienylmanganese carbonyl (Ethyl Corp.), 300 ml. of dry diglyme, and 100 ml. of a 40% dispersion (1.48 g.-atoms) of sodium in Nujol (Plough, Inc.). The autoclave was then pressurized with 700 p.s.i. of c.p. carbon monoxide and the mixture was heated with stirring to 125° for 8 hr. with intermittent repressurizing to speed up the reaction. The reaction mixture was then carefully quenched with about 500 ml. of water at 0° (or 25–65° under 500 p.s.i. of carbon monoxide) and steam distilled. The yield of manganese carbonyl was 45.7 g. (48%), m.p. 151–153° (uncorrected).

Acknowledgment. The authors wish to thank Mr. H. Shapiro for helpful advice.

RESEARCH AND DEVELOPMENT DEPARTMENT
ETHYL CORPORATION
BATON ROUGE, LA.

(6) The oxidation state of manganese in I can be considered formally as +1.

Acylation, Bromination and Oxidation of 4-Pyrones and Pyronones[1]

L. L. WOODS AND P. A. DIX

Received Nov. 7, 1960

A review of pertinent literature[2-4] on the chemistry of 6-methyl-2-pyrononc fails to show that the compound when treated with acetic anhydride or acetyl chloride regenerates dehydroacetic acid. We have found this to be a very easy transformation to accomplish in the presence of trifluoroacetic acid, further the acid does not degrade dehydroacetic acid to any appreciable degree when refluxed in its presence for as long as twenty-four hours.

Since the acetylation proved to be so facile it was decided to prepare a series of pyrononc compounds similar to 3-acetyl-6-methyl-2-pyrononc (dehydroacetic acid) by changing the acyl group in position 3.

It was found that not only would different acyl halides place different groups in position 3, but when two equivalents of the acyl halide were used, a second acyl radical was placed on the nucleus without destruction of the ring structure, presumably at position 5 since it is very unlikely that a second acyl group could be put on position 3 without rupture of the ring. The pyrononcs synthesized are listed as the I_{A-F} series in Table I.

Pyrononc when treated in the presence of three equivalents of an acyl halide such as *m*-nitrobenzoyl chloride gave 2-(*m*-nitrophenyl)-3,5-di(*m*-nitrobenzoyl)-6-methyl-4-pyrone (II).

A verification of the structure of the compounds in the I_{A-F} series was obtained by using compounds I_A and $_B$ as models. Carbon dioxide was eliminated from them by the usual hydrochloric acid method and the method of Light and Hauser[6] to form the 2-aryl-4-pyrones described in the experimental portion of this report as compounds III and IV respectively.

One of the objectives of our study of the pyrones was to devise methods of oxidizing the various mononuclear 4-pyrones without rupture of the ring. A method to effect this oxidation has been found using chloranil as the oxidant. The product of such an oxidation appears to be a 6,6′-bipyrone as indicated by the figure adjacent to Table II in which the substances formed by the oxidation are listed as compounds V_{A-D}. Infrared spectra run on the substances with a Beckman IR-5 failed to show more than an intensification of the absorption bands of the starting materials; however, ultraviolet absorption spectra do show an unmistakable difference.

The absorption maxima for the two model compounds V_A and V_B are slightly but definitely different from the substances from which they are derived, kojic acid and α-chloro-α-deoxy-kojic acid respectively.

The bromination studies included in this report consists of an inelegant generalized method for

(1) The investigations reported here were supported by the Robert A. Welch Foundation.
(2) F. Arndt and B. Eistert, *Berichte*, **69**, 2373 (1936).
(3) F. Feist, *Ann.*, **257**, 253 (1890).
(4) J. D. BúLock and H. G. Smith, *J. Chcm. Soc.*, **103**, 502 (1960).

TABLE I

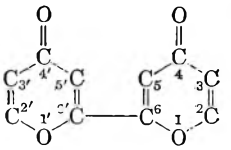
3-ACYL-6-METHYL-2-PYRONONES FROM 6-METHYL-2-PYRANONE

	Acyl Halide Used	Equivalents of Acyl Halide	M.P.	Yield, %	Empirical Formula	Calcd. (Found) Carbon	Hydrogen	Nitrogen
I_A	Benzoyl chloride	1	70–71	73	$C_{13}H_{10}O_4$	77.40 (77.69)	5.4[illegible] (5.27)	
I_B	Benzoyl chloride	2	68–69	100	$C_{20}H_{14}O_5$	71.85 (71.49)	4.22 (4.40)	
I_C	*m*-Nitrobenzoyl chloride	1	148–150	99	$C_{13}H_9NO_6$	56.73 (56.84)	3.29 (2.8[illegible])	5.08 (4.94)
I_D	Phenylacetyl chloride	1	151–152	87	$C_{14}H_{12}O_4$	68.87 (69.08)	4.95 (5.02)	
I_E	Phenylacetyl chloride	2	110–111	91	$C_{22}H_{18}O_5$	72.91 (72.64)	5.00 (4.82)	
I_F	*p*-Nitrobenzoyl chloride	1	208–209	88	$C_{13}H_9NO_6$	56.73 (56.75)	3.2[illegible] (3.3[illegible])	5.08 (5.05)

I_A = 3-Benzoyl-6-methyl-2-pyronone. I_B = 3,5-Di-benzoyl-6-methyl-2-pyronone. I_C = 3-(*m*-Nitrobenzoyl)-6-methyl-2-pyronone. I_D = 3-Phenylacetyl-6-methyl-2-pyronone. I_E = 3,5-Diphenylacetyl-6-methyl-2-pyronone. I_F = 3-(*p*-Nitrophenylacetyl)-6-methyl-2-pyronone.

TABLE II

BIPYRONES



No.	Pyrone Used	M.P.	Crude Yield, %	Empirical Formula	Calcd. (Found) Carbon	Hydrogen	Chlorine
V_A	Kojic acid	156–156.5	100	$C_{12}H_{10}O_8$	51.72 (51.44)	3.57 (3.35)	
V_B	α-Deoxy-α-chlorokojic acid	168.5	58	$C_{12}H_8Cl_2O_6$	45.16 (44.94)	2.52 (2.77)	22.22 (22.09)
V_C	2-Hydroxymethyl-5-methoxy-4-pyrone	163–164	74	$C_{14}H_{14}O_8$	54.19 (53.89)	4.54 (4.29)	
V_D	2-Chloromethyl-5-methoxy-4-pyrone	119–120	27	$C_{14}H_{12}Cl_2O_6$	48.43 (48.62)	3.48 (3.57)	20.42 (20.30)

V_A = 2,2′-Di(hydroxymethyl)-5,5′-di-hydroxy-6,6′-bi(4-pyrone). V_B = 2,2′-Di(chloromethyl)-5,5′-di-hydroxy-6,6′-bi(4-pyrone). V_C = 2,2′-Di(hydroxymethyl)-5,5′-di-methoxy-6,6′-bi(4-pyrone). V_D = 2,2′-Di(chloromethyl)-5,5′-di-methoxy-6,6′-bi(4-pyrone).

TABLE III

BISBROMO DERIVATIVES OF 4-PYRONES

No.	Pyrone Used	M.P.	Crude Yield, %	Empirical Formula	Bromine Calcd.	Found
VI_A	Kojic acid	Softens above 135 Melts 143–144	23	$C_6H_4Br_2O_4$	53.28	53.01
VI_B	2,6-Dimethyl-4-pyrone	152	59	$C_7H_6Br_2O_2$	56.68	56.47
VI_C	2-Methyl-4-pyrone[a]	148–149	58	$C_6H_4Br_2O_2$	59.65	59.41
VI_D	6-Methyl-2-pyronone	174–176	73	$C_6H_4Br_2O_3$	56.29	55.87

[a] Furnished as a concentrate by the courtesy of Monsanto Chemical Corp. VI_A = 2-Hydroxymethyl-3,6-dibromo-5-hydroxy-4-pyrone. VI_B = 2,6-Dimethyl-3,5-dibromo-4-pyrone. VI_C = 2-Methyl-3,6-dibromo-4-pyrone. VI_D = 3,5-Dibromo-6-methyl-2-pyronone.

placing two bromine atoms on a pyrone nucleus. The method does produce, for the first time, the compounds sought, but in low yields from tacky semi-solids that often contained considerable tar.

The only common denominator among the pyrones used as starting materials was the fact that position 3 in all of them was unoccupied and was one of the sites of halogenation in every case.

The di-bromo pyrones produced in the reaction are given as compounds VI_{A-D} in Table III.

EXPERIMENTAL[5]

Preparation of compounds of I_{A-F} Series. A mixture consisting of 0.1 mole of 6-methyl-2-pyronone (11.4 g.), 0.1 mole of the acyl halide and 20 ml. of trifluoroacetic acid was refluxed in an all-glass assembly until hydrogen chloride vapors ceased to be evolved. This usually required between 90 min. and 2 hr. At the end of the reaction period the mixture was poured into 100 ml. of water and chilled. Those compounds which remained as oils or semi-solids such as II_A and $_B$ were taken up in alcohol and reprecipitated with water; chilling at this stage produced soft crystals which could be dried in air and weighed, as were the higher melting compounds.

The analytical samples were obtained by recrystallizing the compound several times from boiling heptane.

Those compounds in which the pyronone had been bisacylated were prepared by using 0.2 mole of the acyl halide. All other conditions for the preparation and purification of the compounds were the same.

Synthesis of 2-(m-nitrophenyl)-3,5-di(m-nitrobenzoyl-6-methyl-4-pyrone (II). To 20 ml. of trifluoroacetic acid was added 0.05 mole (6.2 g.) 6-methyl-2-pyronone followed by 0.15 of mole (27.9) of *m*-nitrobenzoyl chloride. This mixture was refluxed in an all-glass assembly over a glass heating mantle for 4 hr., and then diluted while hot with 100 ml. of water. The precipitate was filtered off, dried in air to give 32.1 g. of the crude compound, which was then recrystallized twice from ethanol. An 8 g. sample of the partially purified substance was refluxed with 70 ml. of concd. hydrochloric acid for 3 hr., diluted with water and chilled to give 6.2 g. of the air-dried compound. The purified material was recrystallized once from heptane to give a melting point of 143–144°.

Anal. Calcd. for $C_{26}H_{15}N_3O_{10}$: C, 58.98; H, 2.85; N, 7.93. Found: C, 58.79; H, 2.74; N, 7.67.

Synthesis of 2-phenyl-6-methyl-4-pyrone (III). A 5 g. sample of I_A was heated for 30 min. at 155–160° in a Fisher constant temperature oil bath. The resulting melt was poured into 100 ml. of water and chilled to give 4.5 g. of an air-dried sample.

Refluxing 5 g. of I_A with 70 ml. of concd. hydrochloric acid for 2 hr. gave a similar yield.

The crude III was recrystallized once from heptane, m.p. 84–85° which is in good agreement with the results of Light and Hauser[6] and in fair agreement with those of Ruhemann.[7]

Anal. Calcd. for $C_{12}H_{10}O_2$: C, 77.40; H, 5.41. Found: C, 77.69; H, 5.27.

Synthesis of 2-phenyl-5-benzoyl-6-methyl-4-pyrone (IV). Ten grams of I_B was refluxed in 60 ml. of concd. hydrochloric acid for 3 hr., diluted with 100 ml. of water and then chilled to produce 7.5 g. of crude IV. The compound was crystallized once from heptane to give the analytical sample, m.p. 124–125°.

Anal. Calcd. for $C_{19}H_{14}O_3$: C, 78.60; H, 4.86. Found: C, 78.29; H, 4.69.

Preparation of compounds of V_{A-D} Series. One tenth of a mole of the pyrone along with 0.05 mole of chloranil was vigorously refluxed for 3 hr. in 100 ml. of absolute ethanol. The brown solution was filtered while hot and placed in the freezing compartment of the refrigerator overnight. The precipitate was filtered off, dried in air and the analytical sample prepared by recrystallizing it three times from absolute ethanol.

Ultraviolet absorption spectra of V_A and $_B$ were taken on a Bausch and Lomb Spectronic-505 and compared with spectra of the pyrones from which they were prepared. The spectra were made in the wave length range of 222–372 mμ in spectro grade methanol:

Substance	Maxima
Kojic acid	264 mμ
V_A	269.5 mμ
α-Chloro-α-deoxy kojic acid	272 mμ
V_B	277 mμ

Preparation of dibromopyrones (VI_{A-D}). A mixture consisting of 0.1 mole of the pyrone, 20 ml. of trifluoroacetic acid and 32 g. of bromine was placed in the hood in an all glass assembly with two standard taper 300 mm. condensers fitted in tandem and gently refluxed for a period of 2 hr. The reaction mixture was poured into water, thoroughly chilled, filtered and dried in air.

Samples of the tarry materials were recrystallized twice from heptane to give the analytical sample.

DEPARTMENT OF CHEMISTRY
TEXAS SOUTHERN UNIVERSITY
HOUSTON 4, TEX.

(5) All analyses were performed by Dr. Carl Tiedcke, Teaneck, N. J., and all melting points were determined on a Fisher-Johns Melting Point Assembly.

(6) R. J. Light and C. R. Hauser, *J. Org. Chem.*, 25, 538 (1960).

(7) S. Ruhemann, *J. Chem. Soc.*, 93, 431 (1908).

Behavior of α-Substituted Chalcones on Attempted Friedel-Crafts Arylation

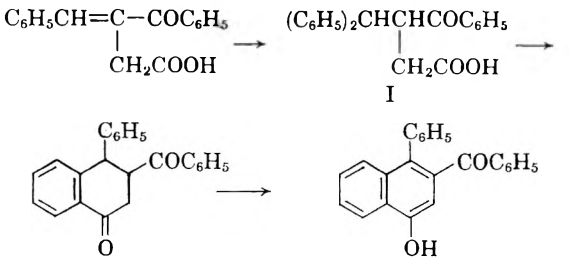
C. F. KOELSCH

Received November 7, 1960

Addition of an aromatic nucleus to an α,β-unsaturated compound under the influence of aluminum chloride is a well known process;[1] for example, benzene and chalcone yield β,β-diphenylpropiophenone.[2]

$$C_6H_6 + C_6H_5CH{=}CHCOC_6H_5 \longrightarrow (C_6H_5)_2CH{-}CH_2COC_6H_5$$

It was thought that this reaction could be applied in a synthesis of 3-benzoyl-4-phenyl-1-naphthol (II)[3] in the following way.



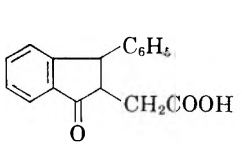
However the expected keto acid (I) was not formed, and further processing gave a compound

(1) Vorlander and Friedberg, *Ber.*, 56, 1144 (1923); R. C. Fuson and H. G. Cooke, *J. Am. Chem. Soc.*, 73, 3515 (1951) and previous papers by Fuson and co-workers; J. F. J. Dippy and A. L. L●Palluel, J. Chem. Soc., 1415 (1951).

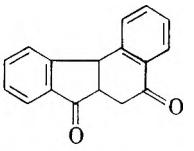
(2) P. R. Shildneck, *Org. Syntheses*, Coll. Vol. II, 236 (1943).

(3) C. F. Koelsch, *J. Org. Chem.*, 26, 1003 (1961).

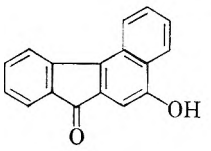
which was not the substituted naphthol desired (II). The keto acid was found to be III, the intermediate diketone was IV, and the end product was V.



III

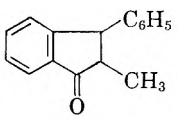


IV

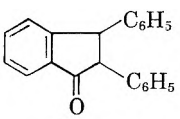


V

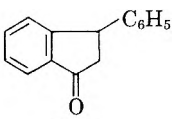
Formation of III appeared anomalous, and therefore a simpler compound, α-methylchalcone, was treated with aluminum chloride in benzene. Here too, a similar reaction occurred, forming VI in 93% yield. Also α-phenylchalcone yielded VII. Careful examination of the products from interaction of chalcone itself with aluminum chloride in benzene allowed isolation of 0.3% of VIII in addition to 90% of β,β-diphenylpropiophenone, the normal product.



VI



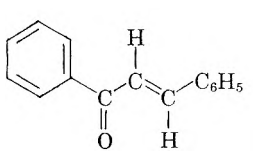
VII



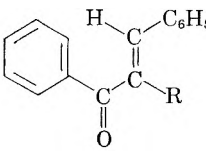
VIII

It was apparent from these results that an α-substituent in a chalcone caused the main reaction to involve addition of the benzoyl nucleus to the α,β-double bond. At first it was thought that the results might be explained by an electronic effect, but Professor R. M. Dodson, with whom the matter was discussed, held strongly to the belief that a steric effect was responsible. Investigation of the behaviors of α-bromo- and α-carbethoxychalcone then supported this belief completely. The α-substituents here are entirely different electronically from methyl, etc., and yet the compounds gave hydrindones and not phenylation products.

Thus, it was concluded that a nearly flat chalcone has configuation IX only when hydrogen is in its α-position and is crowded into configuration X when a larger group is present, and orientation about the C—CO bond (*s-cis* or *s-trans*) controls reaction type.



IX



X

If the configurations were exactly as in IX and X, the latter compounds should show stronger O=C—C=C absorption, corresponding to their linear structures and consequent greater oscillator strength, as contrasted with the folded system in IX. However, this is not the case: chalcone has ϵ_{307} = 24,300, whereas α-methylchalcone has ϵ_{290} = 17,400 and α-bromochalcone has ϵ_{305} = 15,400.[4] It is probable that the anomaly is caused by incomplete planarity in X, a result of interference between β-H and *o*-H.

The present reaction is analogous to Fuson's hydrindone synthesis,[5] where α-substituted acrylophenones and β-hydroxypropiophenones are used. However in that synthesis, the reaction medium is sulfuric acid, and no question of competition between cyclization and phenylation arises.

EXPERIMENTAL

3-Phenylhydrindone-2-acetic acid (III). Addition of 10 g. of 3-benzoyl-4-phenyl-3-pentenoic acid[6] to a suspension of 12 g. of aluminum chloride in 50 ml. of benzene gave an orange gum which dissolved during 15-min. boiling, forming a deep orange-red solution. Decomposition with iced hydrochloric acid and extraction with dilute sodium carbonate then gave 9.4 g. of acidic product that crystallized completely when it was rubbed with ether. It formed colorless plates from dilute acetic acid, m.p. 131–133°.

Anal. Calcd. for $C_{17}H_{14}O_3$: C, 76.7; H, 5.27; Found: C, 76.5; H, 5.39.

Addition of 0.06 g. of bromine to a solution of 0.1 g. of III in 1 ml. of acetic acid, followed by gentle warming led to rapid evolution of hydrogen bromide. Evaporation gave a crystalline residue, completely soluble in cold 2% sodium carbonate. When it was boiled, this solution became deep yellow and deposited 25 mg. of waxy material. Acidification and crystallization from dilute acetic acid gave 50 mg. of 3-phenylindone-2-acetic acid, m.p. 165–167° alone or mixed with an authentic sample.[7]

3,4-Benzo-1,2,4a,9a-tetrahydro-2,9-fluorenedione (IV). A mixture of 1.2 g. of III and 6 ml. of sulfuric acid was heated 4 min. on a water bath, then poured on ice, giving 0.6 g. of pink crystals. Recrystallization from alcohol furnished 0.4 g. of long colorless needles, m.p. 165–167°.

Anal. Calcd. for $C_{17}H_{12}O_2$: C, 82.2; H, 4.85. Found: C, 82.0; H, 4.93.

3,4-Benzo-2-oxy-9-fluorenone (V). Addition of 0.4 g. of bromine to a suspension of 0.8 g. of IV in 5 ml. of acetic acid caused rapid evolution of hydrogen bromide and separation of dark purple crystals. Recrystallization from 75 ml. of acetic acid gave 0.55 g. of flat red-purple needles, m.p. above 235°.

Anal. Calcd. for $C_{17}H_{10}O_2$: C, 82.9; H, 4.09. Found: C, 82.3; H, 4.18.

When 0.2 g. of V was boiled with 5 ml. of 2% sodium hydroxide, it gave a deep blue solution, which deposited purple-gray needles on cooling. Addition of a little methanol caused the salt to dissolve, and the resulting solution was treated alternately with methyl sulfate and sodium hydroxide until the latter no longer developed a blue color. The precipitate was then removed and crystallized from ethyl acetate–ligroin, giving 0.2 g. of *2-methoxy-3,4-benzo-9-fluorenone*, deep red needles, m.p. 155–156°.

(4) W. B. Black and R. E. Lutz, *J. Am. Chem. Soc.*, **77**, 5134 (1955).

(5) J. H. Burckhalter and R. C. Fuson, *J. Am. Chem. Soc.*, **70**, 7184 (1948), and previous papers. J. Colonge and G. Weinstein, *Bull. Soc. Chim.*, 462 (1952).

(6) W. Borsche, *Ber.*, **47**, 1108 (1914).

(7) C. F. Koelsch and H. J. Richter, *J. Am. Chem. Soc.*, **57**, 2010 (1935).

Anal. Calcd. for $C_{18}H_{12}O_2$: C, 83.0; H, 4.65. Found: C, 82.8; H, 4.71.

The same compound (0.35 g.) (mixed melting point and infrared spectrum) was obtained when 0.5 g. of 4-methoxy-1-phenyl-2-naphthoic acid[8] was boiled for 15 min. with thionyl chloride, and the resulting oily acid chloride was treated with 0.4 g. of aluminum chloride in 5 ml. of benzene.

Chalcone and aluminum chloride in benzene. When a suspension of 70 g. of aluminum chloride in 300 ml. of benzene was treated with 100 g. of chalcone, a smooth exothermic reaction took place during 15 min., forming a bright yellow solid complex. Boiling for 15 min. more gave an orange-red solution, and this was hydrolyzed with iced hydrochloric acid. Most of the benzene was then distilled and replaced with 60–70° ligroin, giving 97 g. of nearly pure β,β-diphenylpropiophenone. The mother liquor was concentrated and treated again with ligroin, giving 21 g. more of the same ketone. The material (17.4 g.) remaining in the second mother liquor was separated by fractional distillation and chromatography into 6.4 g. of β,β-diphenylpropiophenone, 2 g. of diphenylmethane, and 0.29 g. of 3-phenylhydrindone, m.p. 76–77° alone or mixed with an authentic sample.

α-Methylchalcone. A mixture of 5.5 g. α-methylchalcone, 4 g. of aluminum chloride, and 20 ml. of benzene gave an orange-red solution when it was boiled 15 min. Decomposition with iced hydrochloric acid, etc., furnished 5.1 g. of *2-methyl-3-phenylhydrindone*, a colorless oil b.p. 195–198° at 16 mm.

Anal. Calcd. for $C_{16}H_{14}O$: C, 86.4; H, 6.35. Found: C, 86.5; H, 6.30.

Treatment with the calculated amount of bromine in acetic acid, followed by potassium hydroxide in methanol gave a nearly quantitative yield of 2-methyl-3-phenylindone, yellow prisms m.p. 83–84° alone or mixed with an authentic sample.[8]

α-Phenylchalcone. A mixture of 1.5 g. of aluminum chloride and 2.8 g. of α-phenylchalcone in 15 ml. of benzene gave a clear yellow-brown solution after it had been boiled 2 min. There was obtained 2.8 g. of solid product, separated by fractional crystallization from alcohol into 0.9 g. of 2,3-diphenylhydrindone, m.p. 98–100° alone or mixed with an authentic sample,[9] and 1.3 g. of colorless needles m.p. 135–153°. The latter substance was probably largely a stereoisomeric form of 2,3-diphenylhydrindone, since both products gave 2,3-diphenylindone on treatment with oromine and then potassium hydroxide.

α-Bromochalcone. Crystalline α-bromochalcone (1.5 g.) in 10 ml. of benzene containing 1.5 g. of aluminum chloride gave a green-brown solution after 10-min. boiling. There was obtained 1.5 g. of 2-bromo-3-phenylhydrindone which had m.p. 84–87° after crystallization from alcohol.

Anal. Calcd. for $C_{15}H_{11}BrO$: C, 62.7; H, 3.84. Found: C, 62.6; H, 3.92.

This product was a stereoisomer of the compound m.p. 88–90°, obtained by brominating 3-phenylhydrindone.[10] A mixture of the two had m.p. 78–83°; infrared spectra were identical except that the 87° isomer absorbed at 765, 745, and 703 cm.$^{-1}$, whereas in the 90° isomer these bands occurred at 760, 742, and 700 cm.$^{-1}$ Each of the compounds gave 3-phenylindone-semicarbazone, m.p. 205° dec. (reported[11] 212° dec.), characterized by infrared spectra.

α-Carbethoxychalcone. This substance (1.5 g.) reacted rapidly with 2 g. of aluminum chloride in 10 ml. of benzene to form a yellow oily complex which dissolved after the mixture had been boiled for 15 min. There was obtained 1.45 g. of pale yellow product that crystallized completely when it was rubbed with ether. Recrystallization from alcohol gave *2-carbethoxy-3-phenylhydrindone*, faintly pink needles, m.p. 86–88° that gave a blue-violet color with ferric chloride.

Anal. Calcd. for $C_{18}H_{17}O_3$: C, 76.9; H, 6.05. Found: C, 77.1; H, 5.90.

The product was identical (mixed melting point and infrared spectrum) with the one obtained from 2-carbethoxy-3-phenylindone by (a) catalytic reduction[12] or (b) reduction with zinc and acetic acid. Condensation of 3-phenylhydrindone with ethyl carbonate[13] in this laboratory also gave the same substance and not the form m.p. 103–104° reported by the British investigators. The latter form is more likely an allotropic modification than a stereoisomer, for it is difficult to believe configuration would be preserved in a substance so easily enolized. The instability reported by Yost and Burger is not simply steric inversion, as suggested by Baker, and is really not very pronounced. A sample kept in this laboratory for two years had become brown and sticky in spots, but still contained over 50% unchanged material.

Acknowledgment. The author thanks Mrs. O. Hamerston for analytical results.

SCHOOL OF CHEMISTRY
UNIVERSITY OF MINNESOTA
MINNEAPOLIS, MINN.

(8) E. Bergmann and H. Weiss, *Ann.*, **480**, 73 (1930).
(9) C. F. Koelsch, *J. Am. Chem. Soc.*, **56**, 1338 (1934).
(10) R. Weiss and S. Luft, *Monatsh.*, **48**, 337 (1927).
(11) E. P. Kohler, G. L. Heritage, and M. C. Burnley, *Am. Chem. J.*, **44**, 73 (1910).
(12) W. L. Yost and A. Burger, *J. Org. Chem.*, **15**, 1113 (1950).
(13) W. Baker *et al.*, *J. Chem. Soc.*, 4026 (1957).

The Stevens Rearrangement in the Benzomorphan Synthesis

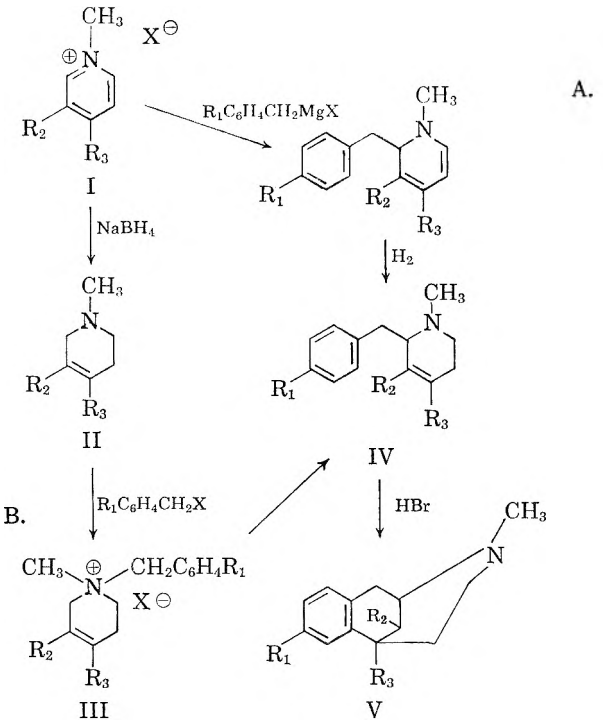
EDWARD M. FRY AND EVERETTE L. MAY

Received November 14, 1960

Synthesis of analgesics of the benzomorphan type has been accomplished either by means of the Grewe synthesis[1] as in diagram A, or through a β-tetralone.[2] This note concerns a synthesis based on the Stevens rearrangement of the *N*-benzyl quaternary salt (III) and is diagrammed in B.

The action of basic reagents on quaternary ammonium salts may yield a variety of products depending on the nature of the reactants.[3] A recent example related to this work is that of benzylmethylpiperidinium iodide which with sodium amide in liquid ammonia gave three rearrangement products as a result of aryl- and alkyl-migrations.[4] One of these was 2-benzyl-1-methylpiperidine, obtained in 23% yield. It was felt that in the tetrahydro system (III) the most readily formed ylid would be that conjugated with the double bond and that substitution at the desired site (2- position) might thereby be favored. At present it is not possible to say what percentage of the total re-

(1) R. Grewe, *Agnew. Chem.*, **59**, 194 (1947).
(2) E. L. May and E. M. Fry, *J. Org. Chem.*, **22**, 1366 (1957).
(3) S. W. Kantor and C. R. Hauser, *J. Am. Chem. Soc.*, **73**, 4122 (1951); G. Wittig and T. F. Burger, *Ann.*, **631**, 85 (1960).
(4) L. P. A. Fery and L. van Hove, *Bull. Soc. Chim. Belg.* **69**, 63 (1960).



I and II

b. $R_2 = H, R_3 = CH_3$
c. $R_2 = R_3 = CH_3$
d. $R_2 = R_3 = C_2H_5$

III and IV

a. $R_1 = H, R_2 = R_3 = CH_3$
b. $R_1 = OCH_3, R_2 = H, R_3 = CH_3$
c. $R_1 = OCH_3, R_2 = R_3 = CH_3$
d. $R_1 = OCH_3, R_2 = R_3 = C_2H_5$

V

a. $R_1 = H, R_2 = R_3 = CH_3$
b. $R_1 = OH, R_2 = H, R_3 = CH_3$
c. $R_1 = OH, R_2 = R_3 = CH_3$
d. $R_1 = OH, R_2 = R_3 = C_2H_5$

arrangement is directed to the 2- position for only the Stevens product IV has as yet been identified.

The tetrahydropyridine bases were easily obtained by sodium borohydride reduction of the *N*-methyl quaternary pyridine salts[5] and then converted to the quaternary salts III. The NMR spectrum of IIIb showed a line at 5.33 p.p.m. due to vinylic hydrogen. No corresponding line was present in the spectra of IIIa and IIIc. Furthermore the line at 1.78 p.p.m. (CH_3—C=C—) was half that of IIIa and IIIc (CH_3—C=C—CH_3) in this region. Thus the correct position of the double bond is assured and its position is also consistent with the results of other work on the hydride reduction of 3-substituted pyridine quaternary salts.[5] Rearrangements with phenyllithium gave in part the desired compounds (IV). Whether a base IV was isolated or was part of a mixture, its structural identification rests on that of the known benzomorphan resulting from ring closure. In one case (IVa) NMR showed no vinylic hydrogen and hence no bond migration.

Although the rearrangement step has not been carefully investigated, yields thus far indicate that the method has no advantage over the older one except that possibly use of the rearranging base is preferable to that of the Grignard reagent utilized in the Grewe synthesis. Yield comparisons are given in the experimental section.

(5) M. Ferles, *Collection of Czechoslov. Chem. Communs.*, **23**, 479 (1958); **24**, 2221 (1959).

EXPERIMENTAL

Melting points are uncorrected. Microanalyses are by Paula Parisius of the Analytical Services Unit of this Laboratory, Harold McCann, director. NMR spectra, 60 Mc, are with tetramethylsilane as internal reference standard and deuterchloroform as solvent.

The *N-methyltetrahydropyridines* (II) were prepared in *N* sodium hydroxide solution using a molar equivalent of sodium borohydride. The ratio of solution to the weight of hydride was approximately 50 to 1. If the reduction did not start spontaneously the solution was warmed to *ca.* 50°. The exothermic reaction was gentle and the end was marked by disappearance of yellow color and cessation of effervescence. The bases were recovered with ether and converted to the quaternary salts (III) by addition of the benzyl halide to either an acetone or ether solution of the base.

1-p-Methoxybenzyl-1,4-dimethyl-1,2,5,6-tetrahydropyridinium (IIIb) *chloride*. A mixture of 12 g. (0.05 mole) of γ-picoline methiodide, 100 ml. of *N* sodium hydroxide, and 2 g. of sodium borohydride was stirred (temperature rose to 54° during 15 min.) for 3 hr. Sodium chloride was added and the mixture was extracted thrice with ether. Drying (sodium sulfate) and distillation of the ether at atmospheric pressure gave a quantitative yield of apparently stable IIb which, in 25–30 ml. of acetone, was treated with 9 g. (slight excess) of *p*-methoxybenzyl chloride. After 1 hr. at room temperature and 2–3 hr. at −5° the crystalline chloride IIIb was obtained in a yield of 11 g. (82% from Ib) and was purified from absolute ethanol-ether. Hygroscopic, it was dried at 60°/50 mm. prior to analysis; m.p. 181–182°.

Anal. Calcd. for $C_{15}H_{22}ClNO$: C, 67.27; H, 8.28. Found: C, 67.36; H, 8.37.

1-Benzyl-1,3,4-trimethyl-1,2,5,6-tetrahydropyridinium bromide (IIIa), obtained in 73% yield from Ic was purified from acetone-alcohol, m.p. 206–208°.

Anal. Calcd. for $C_{15}H_{22}BrN$: C, 60.81; H, 7.49. Found: 60.61; H, 7.43.

1-p-Methoxybenzyl-1,3,4-trimethyl-1,2,5,6-tetrahydropyridinium chloride (IIIc) was obtained from Ic in 61% yield. It crystallized from acetone containing a little absolute alcohol in rods of m.p. 169–171°. The somewhat hygroscopic material was dried at 60°/40 mm. for analysis.

Anal. Calcd. for $C_{16}H_{24}ClNO$: C, 68.20; H, 8.58. Found: C, 68.09; H, 8.86.

The iodide was obtained by adding KI to an aqueous solution of the chloride. Purified from alcohol it melted at 175–178°.

Anal. Calcd. for $C_{16}H_{24}INO$: C, 51.48; H, 6.48. Found: C, 51.28; H, 6.47.

1-p-Methoxybenzyl-1-methyl-3,4-diethyl-1,2,5,6-tetrahydropyridinium chloride (IIId), obtained in 39% yield from Id, was purified from acetone and melted at 157–160°. The hygroscopic crystals were dried at 78°, high vacuum, prior to analysis.

Anal. Calcd. for $C_{18}H_{28}ClNO \cdot 1/2\ H_2O$: C, 67.77; H, 9.16. Found: C, 68.06; H, 9.40.

After drying at 135° in high vacuum the weight loss was 2.94% (calcd. for 1/2 H_2O, 2.82%).

Anal. Calcd. for $C_{18}H_{28}ClNO$: C, 69.76; H, 9.11. Found: C, 70.04; H, 9.38.

The 2-benzyl-1,2,5,6-tetrahydropyridines (IV) were prepared by the addition of excess 0.9*N* phenyllithium in ether to the quaternary salts (III). The reaction was exothermic and at its completion (2–4 hr., stirring) the mixture was decomposed with ice and the product recovered by drying and evaporation of the ethereal layer.

2-Benzyl-1,3,4-trimethyl-1,2,5,6-tetrahydropyridine (IVa) is an oil. Its picrate was isolated in 13% yield (9.5% from Ic) and was purified from alcohol. It proved identical with the compound (45% from Ic) isolated in the Grewe synthesis (not characterized in previous publication[2]), m.p. 127–129°.

Anal. Calcd. for $C_{21}H_{24}N_4O_7$: C, 56.75; H, 5.44. Found: C, 56.88; H, 5.45.

2-p-Methoxybenzyl-1,3,4-trimethyl-1,2,5,6-tetrahydropyridine (IVc) is an oil. Its picrate was obtained in 38% yield (23% from Ic). Purified from alcohol it melted at 168–174°.

Anal. Calcd. for $C_{22}H_{26}N_4O_8$: C, 55.69; H, 5.52. Found: C, 55.92; H, 5.40.

2-p-Methoxybenzyl-1,4-dimethyl-1,2,5,6-tetrahydropyridine (IVb) was a constituent of an oil obtained from 9 g. of the chloride IIIb. The base was distilled at 95–105°/0.1 mm., weighed 7.4 g., and was subjected to ring closure.

2-p-Methoxybenzyl-1-methyl-3,4-diethyl-1,2,5,6-tetrahydropyridine (IVd) was part of a mixture. Six grams of chloride IIId yielded after rearrangement 5.4 g. of evaporatively distilled oil (0.07 mm., bath at 150–175°) which was used in the ring closure.

The benzomorphans were prepared by ring closure of IV with 48% hydrobromic acid using the published procedure[2,6] and were identified by melting points, mixed melting points, and infrared spectrograms.

2,5,9-Trimethyl-6,7-benzomorphan (Va) *hydrochloride.* Yield from Ic, this work, 6.5%; yield from Grewe synthesis.[2] 20%.

2'-Hydroxy-2,5,9-trimethyl-6,7-benzomorphan (Vc). Yield from Ic, this work, 18%; yield from Grewe synthesis, 25%.[6]

2'-Hydroxy-2,5-dimethyl-6,7-benzomorphan (Vb). Yield from Ib, this work, 25%; yield from Grewe synthesis, 5%.[7]

2'-Hydroxy-2-methyl-5,9-diethyl-6,7-benzomorphan (Vd). Yield from Id, this work, 11%; yield from Grewe synthesis, 12%.[8]

Acknowledgment. The authors are indebted to Mr. R. B. Bradley and to Dr. E. D. Becker of this Institute for the NMR data.

LABORATORY OF CHEMISTRY
NATIONAL INSTITUTES OF HEALTH
BETHESDA 14, MD.

(6) E. L. May and J. H. Ager, *J. Org. Chem.*, **24**, 1432 (1959).

(7) N. B. Eddy, J. G. Murphy, and E. L. May, *J. Org. Chem.*, **22**, 1370 (1957).

(8) J. H. Ager and E. L. May, unpublished work.

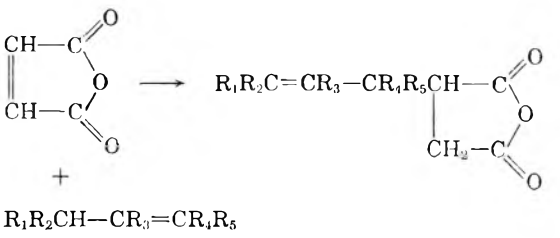
Reaction of Propene-1-C^{14} with Maleic Anhydride

BOBBY J. SUBLETT[1] AND N. S. BOWMAN

Received November 14, 1960

In conjunction with a study involving labeled propene, propene-1-C^{14} was condensed with maleic anhydride. Reactions of this nature between mono-olefins and dienophiles have been known for some time.[2–4] The similarity between these reactions and the familiar Diels-Alder condensation involving a diene is obvious. However, it is likewise apparent that it is impossible to draw a rigid analogy between the reaction mechanism of mono-olefins and those postulated for dienes.[5] The localization of the double bond, the lack of secondary bonding electrons, and the transfer of hydrogen during the course of the reactions are significant differences which must be considered in the case of mono-olefins.

Although the first investigators assumed these reactions were examples of addition of an acidic hydrogen across a double bond,[2,3] it has later been shown that for many unsymmetrical mono-olefins of the type $R_1R_2CH—CR_3=CR_4R_5$, the reaction proceeds with migration of the double bond as illustrated below.



$R_1R_2CH—CR_3=CR_4R_5$

This bond migration has been variously attributed to an initial formation of a rearranging ionic or free radical intermediate of the olefin which then reacts in its more stable form,[2] and to a cyclic six-membered transition state involving a concerted mechanism.[6–8]

For those symmetrical olefins which have been studied (*e.g.*, propene, isobutylene, 2-pentene, cyclopentene, and cyclohexene), the product which would be obtained by the "direct" mechanism[6] without migration of the bond, and that obtained by the "indirect" mechanism with migration are identical. Consequently studies of the structure of the product do not aid in elucidating the mechanistic route of the reaction.

When propene-1-C^{14} was condensed with maleic anhydride and the adduct (I) saponified, allylsuccinic acid (II) was obtained with an activity of 5.48 ± 0.01 mc./mole. Ozonolysis of this product followed by oxidation yielded 3-carboxyglutaric acid (III) of activity 5.45 ± 0.01 mc./mole.

These results confirm the migration of the double bond. The lack of scrambling in the adduct is in

(1) Present address: Tennessee Eastman Corporation, Kingsport, Tenn.

(2) K. Alder, F. Pascher, and A. Schmitz, *Ber.*, **76**, 27 (1943).

(3) E. H. Farmer, *Trans. Faraday Soc.*, **38**, 340 (1942).

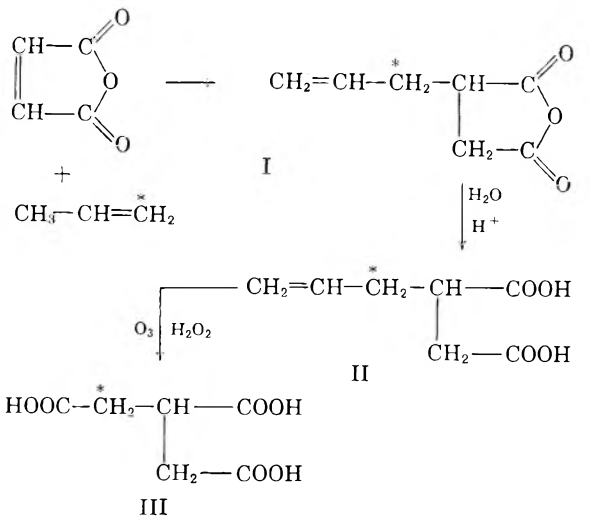
(4) I. G. Farbenind. A.-G., Fr. 801,919, August 21, 1936.

(5) For a discussion of recent proposals of the Diels-Alder mechanism, see R. B. Woodward and T. J. Katz, *Tetrahedron*, **5**, 70 (1959).

(6) K. Alder and H. Soll, *Ann.*, **565**, 73 (1949).

(7) Charles C. Price, Mechanisms of Reactions at Carbon-Carbon Double Bonds, Interscience Publishers, Inc., New York, N. Y., 1949, p. 49.

(8) R. T. Arnold and W. W. Lee, *J. Am. Chem. Soc.*, **75**, 5396 (1953).



agreement with a concerted mechanism since any long-lived independent ionic or free radical species of propene would be expected to distribute the isotopic carbon between the one and three positions of the propene. For the same reason, it is evident that no isomerization of propene occurred under the reaction conditions (250°, 4300 p.s.i.).

EXPERIMENTAL

Propene-1-C^{14}. Propionic acid-1-C^{14} was obtained by carbonation of ethylmagnesium iodide as described by Ostwald[9] for the preparation of acetic acid-1-C^{14}. Reduction of the acid with lithium aluminum hydride gave propanol-1-C^{14} in 65% yield which was converted to propene-1-C^{14} *via* the quaternary ammonium hydroxide using the method of Fries and Calvin.[10]

Allylsuccinic anhydride. In an autoclave of 50-ml. capacity was placed 33 ml. of benzene and 1.8 g. of maleic anhydride. After cooling the autoclave in Dry Ice-acetone and evacuating, 16 g. of propene-1-C^{14} was added. The reaction vessel was heated to 250° with shaking for 12 hr.; a maximum pressure of 4300 p.s.i. was recorded. After removal of the benzene, 0.81 g. of allylsuccinic anhydride was obtained on distillation as a colorless oil, b.p. 133–140°/16 mm.

Allylsuccinic acid. The product obtained in the previous experiment was hydrolyzed by warming with 50 ml. of 10% sodium hydroxide, acidifying with hydrochloric acid, and extracting with ether. The residue remaining after removal of the ether was recrystallized twice from ethyl acetate–ligroin. A yield of 0.76 g. of allylsuccinic acid-C^{14} melting at 96–97° was obtained.

Anal. Calcd. for $C_7H_{10}O_4$: C, 53.19; H, 6.73. Found: C, 53.50, 53.28; H, 6.52,6.29. Radioactive assay: 5.48 ± 0.01 mc./mole.

Oxidation of allylsuccinic acid to 3-carboxyglutaric acid. The ozonolysis of 0.4 g. of allylsuccinic acid was carried out in the usual manner using ethyl acetate as a solvent. The ethyl acetate was then removed under diminished pressure while simultaneously adding acetic acid until all ethyl acetate had been distilled and the ozonide was contained in 30 ml. of acetic acid. This solution was added dropwise with stirring to a mixture of 0.7 g. sulfuric acid, 7 g. water, and 7 g. of 30% hydrogen peroxide. The reaction temperature was slowly raised to reflux during the course of the addition, and reflux maintained for 2 hr. After dilution to twice the reaction volume with water, the mixture was extracted twice with ether, and the ether extract discarded. To remove the sulfuric acid, the solution was made basic to sodium hydroxide and reacidified with hydrochloric acid. After evaporation to dryness under diminished pressure, the residual solid was extracted in a Soxhlet extractor with ethyl acetate. The product which remained after removal of the solvent and four recrystallizations from acetonitrile melted 157–158°. A mixed melting point with authentic 3-carboxyglutaric acid gave no depression.

Anal. Calcd. for $C_6H_8O_6$: C, 40.91; H, 4.54. Found: C, 40.73; H, 4.52. Radioactive assay: 5.45 ± 0.01 mc./mole.

DEPARTMENT OF CHEMISTRY
THE UNIVERSITY OF TENNESSEE
KNOXVILLE, TENN.

(9) R. Ostwald, *J. Biol. Chem.*, **173**, 207 (1948).

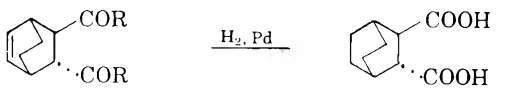
(10) B. A. Fries and M. Calvin, *J. Am. Chem. Soc.*, **70**, 2235 (1948).

Convenient Synthesis of Bicyclo[2.2.2]-octane-*trans*-2,3-dicarboxylic Acid

JOHN B. CLEMENTS[1]

Received November 17, 1960

In another connection, a considerable quantity of bicyclo[2.2.2]octane-*trans*-2,3-dicarboxylic acid (II) was required. Previous syntheses[2–4] have been tedious, multi-step processes and did not appear to lend themselves to the preparation of this acid in the quantities needed. Acid II is easily prepared in the required amounts by taking advantage of the facile condensation of 1,3-cyclohexadiene with fumaryl chloride to give acid chloride Ia which is hydrolyzed to bicyclic acid Ib. This acid was previously reported by Alder and Stein[5] but no yield or analytical data were given. Catalytic hydrogenation of Ib affords the desired acid in good yields. This method has the advantage of convenience in manipulation and very good over-all yields (85%).



Ia. R = Cl
Ib. R = OH

II

EXPERIMENTAL[6]

Bicyclo[2.2.2]octene-5-trans-dicarbonyl chloride (Ia). To 168.3 g. (1.10 mole) of fumaryl chloride was added 80.1 g. (1.00 mole) of 1,3-cyclohexadiene[7] dropwise with stirring while controlling the mildly exothermic reaction at 40–45°. The reaction mixture was allowed to stand at room tempera-

(1) Present address: Chemstrand Research Center, Inc., P. O. Box 731, Durham, N. C.

(2) O. Diels and K. Alder, *Ann.*, **478**, 137 (1930).

(3) K. H. McNeely, A. Rodgman, and G. F. Wright, *J. Org. Chem.*, **20**, 714 (1955).

(4) R. C. Cookson and N. S. Wariyar, *Chem. & Ind. (London)*, **1955**, 915.

(5) K. Alder and G. Stein, *Ann.*, **514**, 1 (1934).

(6) All melting points are corrected. Analyses are by Mr. Grant Gustin of our analytical department.

(7) C. S. Marvel and G. E. Hartzell, *J. Am. Chem. Soc.*, **81**, 448 (1959).

ture overnight, then vacuum distilled to give 211.5 g. (92.0%) of adduct boiling at 87–89°/0.25 mm.

The *diamide*, prepared from the above diacid chloride and excess concentrated ammonium hydroxide, was recrystallized from ethanol for analysis. It melted at 261–262°.

Anal. Calcd. for $C_{10}H_{14}N_2O_2$: C, 61.84; H, 7.27; N, 14.43. Found: C, 61.6, 61.4; H, 7.07, 7.17; N, 14.3, 14.3.

Bicyclo[2.2.2]octene-5-trans-2,3-dicarboxylic acid (Ib). A mixture of 176.3 g. (0.75 mole) of bicyclo[2.2.2]octene-5-*trans*-2,3-dicarbonyl chloride and 1 l. of water was allowed to stand at room temperature overnight. The resulting white solid, after filtering, washing well with water, and drying, weighed 141.4 g. (96.2%) and melted at 213–215°. For analysis it was recrystallized from water and it then melted at 214–215°. Alder and Stein[5] reported a melting point of 211°.

Anal. Calcd. for $C_{10}H_{12}O_4$: C, 61.21; H, 6.17. Found: C, 61.4, 61.4; H, 6.17, 6.07.

Bicyclo[2.2.2]octane-trans-2,3-dicarboxylic acid (II). A solution of 78.4 g. (0.40 mole) of bicyclo[2.2.2]octene-5-*trans*-2,3-dicarboxylic acid and 650 ml. of 10% sodium carbonate was hydrogenated using 0.78 g. of 10% palladium-on-charcoal. After the theoretical amount of hydrogen was consumed, the catalyst was filtered and the product precipitated with concentrated hydrochloric acid. The white solid, after filtering and drying, weighed 76.3 g. (92.2%) and melted at 234–235.5°. After recrystallizing from 1:1 methanol-water the melting point was 234–235°. A mixture with authentic bicyclo[2.2.2]octane-*trans*-2,3-dicarboxylic acid[2] melted at 233–234.5°. The authentic diacid and the present acid have identical infrared spectra (Nujol mull).

Anal. Calcd. for $C_{10}H_{14}O_4$: C, 60.60; H, 7.12. Found: C, 60.3, 60.5; H, 7.28, 7.31.

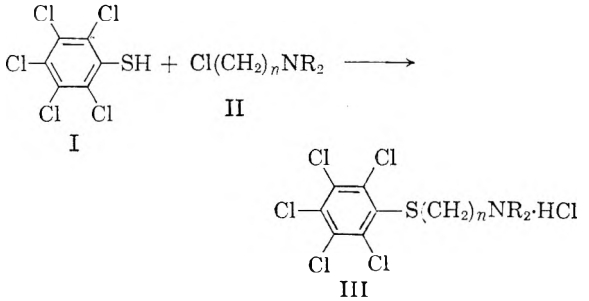
SUMMIT RESEARCH LABORATORIES
CELANESE CORPORATION OF AMERICA
SUMMIT, N. J.

Dialkylaminoalkyl Pentachlorophenyl Sulfides

JAMES H. SHORT

Received November 28, 1960

The availability of pentachlorothiophenol (I) prompted the synthesis of a few dialkylaminoalkyl pentachlorophenyl sulfides (III). The desired compounds were prepared by the condensation of I with dialkylaminoalkyl chlorides (II).



One compound, 3-dimethylaminopropyl pentachlorophenyl sulfide (III. $n = 3$, R = CH_3), was quaternized with methyl iodide and *o*-bromobenzyl bromide.

The six compounds were tested for various pharmacological and chemotherapeutic activities including effect on blood pressure, anti-serotonin activity, monamine oxidase inhibition, psychopharmacological activity, and anticancer activity. They were tested for ability to inhibit growth of various gram-negative bacteria such as *E. coli*, and for their effect on parasites such as *S. obvelata*, *E. tenella*, *S. mansoni*, *T. cruzi* and *H. nana*. No particularly outstanding activity was observed.

EXPERIMENTAL[1]

3-Dimethylaminopropyl pentachlorophenyl sulfide hydrochloride. To a mixture of 14 g. (0.05 mole) of pentachlorobenzenethiol and 8 g. (0.05 mole) of dimethylaminopropyl chloride hydrochloride in 350 ml. of 2-propanol was added a solution of 6.6 g. (0.1 mole) of 85% potassium hydroxide in 10 ml. of water. The resulting solution was refluxed overnight. The reaction mixture was poured into 1.0 l. of water, extracted with ether, and dried. Alcoholic hydrogen chloride was added to give 12.6 g. (63%) of fine, white leaflets, m.p. 229–230.5°. Recrystallization twice from dry ethanol raised the melting point to 230.5–231°.

Anal. Calcd. for $C_{11}H_{12}Cl_5NS{\cdot}HCl$: C, 32.70; H, 3.24; Cl, 52.66; N, 3.47; S, 7.93. Found: C, 32.95; H, 3.35; Cl, 52.73; N, 3.54; S, 8.08.

2-Dimethylaminoisopropyl pentachlorophenyl sulfide hydrochloride. Pentachlorobenzenethiol, 14 g. (0.05 mole), and 8.0 g. (0.05 mole) of dimethylaminoisopropyl chloride hydrochloride were allowed to react and the reaction worked up as described above, to yield 9.1 g. (45%) of material melting at 184–190°. Three recrystallizations from ethanol-acetone raised the melting point to 198–200°.

Anal. Calcd. for $C_{11}H_{12}Cl_5NS{\cdot}HCl$: C, 32.70; H, 3.24; Cl, 52.66; N, 3.47; S, 7.93. Found: C, 32.87; H, 3.24; Cl, 52.89; N, 3.58; S, 8.03.

2-Dimethylaminoethyl pentachlorophenyl sulfide hydrochloride. A mixture of 14 g. (0.05 mole) of pentachlorobenzenethiol, 5.4 g. (0.05 mole) of 2-dimethylaminoethyl chloride in an equal weight of xylene, and 2.7 g. (0.05 mole) of sodium methoxide in 400 ml. of dry ethanol was heated under reflux overnight. After working up as described above, 13.6 g. (70%) of product was obtained, m.p. 228–231°. One recrystallization from dry ethanol, with the aid of charcoal, raised the melting point to 232–234°.

Anal. Calcd. for $C_{10}H_{10}Cl_5NS{\cdot}HCl$: C, 30.80; H, 2.84; Cl, 54.55; N, 3.59; S, 8.22. Found: C, 30.86; H, 3.00; Cl, 54.26; N, 3.50; S, 8.26.

2-Di-n-butylaminoethyl pentachlorophenyl sulfide hydrochloride. Pentachlorobenzenethiol, 14 g. (0.05 mole), and 9.6 g. (0.05 mole) of di-*n*-butylaminoethyl chloride in an equal weight of xylene were allowed to react, and then worked up as described above. It was necessary to add ether to the alcoholic solution in order to induce the product to precipitate. The yield was 20.5 g. (86.5%), m.p. 121–124°. Recrystallization from ethanol-ether with the aid of charcoal gave white needles, and did not raise the melting point.

Anal. Calcd. for $C_{16}H_{22}Cl_5NS{\cdot}HCl$: C, 40.53; H, 4.89; Cl, 44.87; N, 2.95; S, 6.76. Found: C, 40.52; Y, 5.08; Cl, 44.79; N, 3.29; S, 6.87.

[3-(Pentachlorophenylthio)propyl]trimethylammonium iodide. 3-Dimethylaminopropyl pentachlorophenyl sulfide was prepared as described above on a 0.05 mole scale. The ether solution was taken to dryness, and the residual oil dissolved in 100 ml. of acetone. Methyl iodide, 42 g. (0.3 mole), was added and the solution was allowed to stand at room temperature for 6 hr., during which time a cream-colored solid precipitated. The solid weighed 25 g. (98%)

(1) Microanalyses are due to Mr. Elmer Shelberg and staff of the Abbott Microanalytical Laboratory.

and melted at 199–201°. One recrystallization from methanol raised the melting point to 207–208°.

Anal. Calcd. for $C_{12}H_{15}Cl_5INS$: C, 28.28; H, 2.96; N, 2.75. Found: C, 28.58; H, 2.97; N, 2.55.

(o-Bromobenzyl)dimethyl[3-(pentachlorophenylthio)propyl]-ammonium bromide. To 0.05 mole of 3-dimethylaminopropyl pentachlorophenyl sulfide in 100 ml. of acetone was added 12.5 g. (0.05 mole) of *o*-bromobenzyl bromide.[2] On standing 4 hr. at room temperature, an oil precipitated and solidified. The product was cream-colored and weighed 20 g. (65%), m.p. 181–182°. Two recrystallizations from a mixture of ethanol and 2-propanol did not raise the melting point.

Anal. Calcd. for $C_{18}H_{18}Br_2Cl_5NS$: C, 35.01; H, 2.94; N, 2.27. Found: C, 35.31; H, 3.19; N, 2.23.

ORGANIC CHEMISTRY DEPARTMENT
ABBOTT LABORATORIES
NORTH CHICAGO, ILL.

(2) D. F. DeTar and L. A. Carpino, *J. Am. Chem. Soc.*, **78**, 477 (1956).

Synthesis of Benzyl Vinylcarbamate and 3-*O*-Vinylcarbamoyl-D-mannitol Pentanitrate[1]

M. L. WOLFROM, G. H. MC.FADDEN, AND ALAN CHANEY

Received November 28, 1960

After completion of the investigation concerned with the preparation of poly(vinylamine),[2] further amounts of this polymer were desired for study. In the interim, Hart had described a new synthetic route for this material.[3,4] This report is concerned with the preparation of a monomer having potential use in this synthesis and certain anomalous reactions encountered.

In essence, the synthesis involves the application of the Curtius reaction to acryloyl chloride followed by conversion of the vinyl isocyanate (II) obtained to benzyl vinylcarbamate (III). Hart[3,4] has described a three-step process which involves the

$$CH_2{=}CHCOCl \xrightarrow{NaN_3} \underset{\text{I}}{CH_2{=}CHCON_3} \quad (1)$$

$$CH_2{=}CHCON_3 \xrightarrow{\text{Heat}} \underset{\text{II}}{CH_2{=}CHNCO} \quad (2)$$

$$CH_2{=}CHNCO \xrightarrow{C_6H_5CH_2OH} \underset{\text{III}}{CH_2{=}CHNHCO_2CH_2C_6H_5} \quad (3)$$

isolation of the intermediate materials. It has been found that this process can be considerably simplified and the isolation of the intermediates eliminated. Thus, acryloyl chloride[5] was converted to the azide by treatment in toluene solution with aqueous sodium azide solution.[3] The acryloyl azide (I) was then heated in the presence of benzyl alcohol to produce the benzyl vinylcarbamate (m.p. 43–44°) in 60% over-all yield from the acryloyl chloride. Lower yields were experienced if attempts were made to isolate the intermediate vinyl isocyanate. Furthermore, if the acryloyl azide solution in toluene was not carefully purified to remove all traces of acid contamination, the expected product was not obtained. In the best method, pyridine was added to the azide decomposition mixture to ensure the absence of acid conditions.

The product obtained in the above process, if the system was contaminated with acid, was dibenzyl ethylidenedicarbamate (IV).

$$RCH(NHCO_2CH_2C_6H_5)_2$$
IV. R = CH_3
V. R = CH_3CH_2

The structure of this new compound was established by direct synthesis from acetaldehyde and benzyl carbamate and by hydrolysis and isolation of derivatives in addition to elemental analysis and molecular weight determination. Dibenzyl ethylidenedicarbamate (IV) also resulted from the acid-catalyzed reaction of benzyl alcohol and vinyl isocyanate (II), from the treatment of benzyl vinylcarbamate (III) with various acids, and from the acid-catalyzed reaction of benzyl carbamate and benzyl vinylcarbamate (III). In this last instance, the yield was higher than could have been due to the benzyl vinylcarbamate alone.

The acid-catalyzed conversion of benzyl vinylcarbamate (III) to dibenzyl ethylidenedicarbamate (IV) probably proceeds by initial cleavage of the reactant to benzyl carbamate and an unidentified fragment. The benzyl carbamate subsequently condenses with the unchanged benzyl vinylcarbamate to afford the product. Martell and Herbst[6] have made similar suggestions about the course of the reaction between benzyl carbamate and aldehydes.

Martell and co-workers,[6,7] in their studies of the condensation of benzyl carbamate with aldehydes, investigated only a single aliphatic aldehyde, isovaleraldehyde. Thus, an attempt was made to explore the generality of the reaction; following the method developed for acetaldehyde, propanal afforded dibenzyl propylidenedicarbamate (V). However, the corresponding derivatives could not be obtained with methanal, butanal, 2-propanone,

(1) This work was carried out under contract between the Ordnance Corps (DA-33-019-ORD-2025) and The Ohio State University Research Foundation (Project 675). The support of the supervising agency, the Ballistic Research Laboratories of Aberdeen Proving Ground, Md., is gratefully acknowledged.

(2) M. L. Wolfrom and A. Chaney, *J. Org. Chem.*, **26**, 1319 (1961).

(3) R. Hart, *Ind. chim. belge*, **20**, Numéro Special, Vol. 3, 403 (1955).

(4) R. Hart, *Ind. chim. belge*, **23**, 251 (1958).

(5) G. H. Stemple, Jr., R. P. Cross, and P. P. Mariella, *J. Am. Chem. Soc.*, **72**, 2299 (1950).

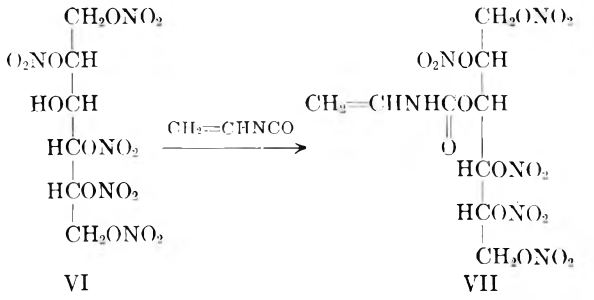
(6) A. E. Martell and R. M. Herbst, *J. Org. Chem.*, **6**, 879 (1941).

(7) T. R. Lewis, Jr., F. R. Butler, and A. E. Martell, *J. Org. Chem.*, **10**, 145 (1945).

or 3-pentanone. No reason for the apparent selectivity of the reaction can be offered.

In part of this study, vinyl isocyanate was isolated by distillation from the decomposing acryloyl azide. The walls of the apparatus became coated with a white solid which was subjected to elemental analysis. Excellent concordance with the expected values for poly(vinyl isocyanate) was obtained. However, the polymer was undoubtedly highly cross-linked and its insolubility prevented further study.

D-Mannitol 1,2,3,5,6-pentanitrate[8] (VI) was found to react with vinyl isocyanate to give crystalline 3-*O*-vinylcarbamoyl-D-mannitol pentanitrate (VII).



EXPERIMENTAL

Acryloyl chloride. Following the method of Stemple, Cross, and Mariella,[5] acrylic acid (216 g.) benzoyl chloride (844 g.) and 2 g. of hydroquinone were mixed and distilled (hood) at atmospheric pressure. All the distillate collected below 85° was redistilled through a Snyder column; yield 206 g. (75%), b.p. 71.5–72.0°.

Anal. Calcd. for C_3H_3ClO: C, 39.81; H, 3.34; Cl, 39.17. Found: C, 39.89; H, 3.53; Cl, 39.01.

Acryloyl azide (I). This material was prepared according to the directions of Hart[9] and was not isolated from the resulting toluene solution. Although Hart indicated that the toluene solution should be washed until neutral, the importance of the neutrality cannot be overemphasized. In the current study, the solution was washed with water until the washings failed to give a precipitate on the addition of silver nitrate.

Benzyl vinylcarbamate (III). Acryloyl chloride (55. g.) was converted[9] to the azide (see above) and the toluene solution (150 ml.) was added dropwise to a stirred (under nitrogen) and heated (110°) mixture of benzyl alcohol (76 g.), 3 g. of hydroquinone and 3 g. of pyridine. The solution was stirred at 100° for 30 min. and distilled under reduced pressure; yield 64 g. (60%), b.p. 116–120° (0.1 mm.), m.p. 43–44°.

Anal. Calcd. for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 68.04; H, 6.31; N, 8.03.

The melting point of this substance was unchanged after crystallization from either ethanol-water or petroleum ether-benzene at low temperatures; purification by distillation appeared preferable.

Dibenzyl ethylidenedicarbamate (IV). Benzyl carbamate (5.0 g.) was dissolved in 50 ml. of paraldehyde; no reaction was noted until 2 drops of 95% sulfuric acid (hydrogen chloride gas or *p*-toluenesulfonic acid will also serve) were added. A white precipitate formed immediately and was recovered after 1 hr. by filtration and washed with ether; yield 4.3 g. (78%), m.p. 207–208° after crystallization from hot ethyl acetate.

Anal. Calcd. for $C_{18}H_{20}N_2O_4$: C, 65.83; H, 6.14; N, 8.53; mol. wt., 328. Found: C, 65.78; H, 6.19; N, 8.52; mol wt., 311 (Rast) and 344 (ebullioscopic, chloroform).

If the acryloyl azide toluene solution employed for the synthesis of benzyl vinylcarbamate was not completely free of acid or if the neutral solution was treated with trace amounts of either hydrochloric acid or acryloyl chloride, dibenzyl ethylidenedicarbamate was the only isolable product.

Benzyl vinylcarbamate (III, 10 g.), dissolved in ethanol, diethyl ether, or benzyl alcohol, afforded dibenzyl ethylidenedicarbamate (IV) on treatment of the solution with either gaseous hydrogen chloride, *p*-toluenesulfonic or sulfuric acids; yield 5–6 g. in some ten trials under the varying conditions. If half the benzyl vinylcarbamate was replaced by benzyl carbamate, yields of 6.5–7.0 g. were obtained. Efforts to recover two-carbon fragments from these reactions were not fruitful.

Dibenzyl ethylidenedicarbamate (1.94 g.) was stirred with 250 ml. of 0.1999*N* sulfuric acid at 100°. The ammonia formed by the hydrolysis was determined by subsequent titration of the mixture with standard alkali; yield 0.17 g. (85%). The acetaldehyde generated was swept into a solution of 2,4-dinitrophenylhydrazine in 95% ethanol with a stream of nitrogen. The solid formed was collected by filtration; yield 0.85 g. (65%), m.p. 163–165° after crystallization from ethanol; melting point undepressed on admixture with authentic acetaldehyde 2,4-dinitrophenylhydrazone. The carbon dioxide formed in the hydrolysis was swept into a trap containing standard alkali which was titrated with acid; yield 0.42 g. (81%). The only alternate possible structure is the known[10] dibenzyl ethylenedicarbamate and this is eliminated by its melting point of 165°.

Dibenzyl propylidenedicarbamate (V). A solution of 5.8 g. of propanal and 5.0 g. of benzyl carbamate in 100 ml. of ether was treated with 0.5 ml. of concd. hydrochloric acid and stirred at room temperature. After 20 hr., the crystals were filtered, washed with ether and crystallized from absolute ethanol; yield 5.1 g. (90%), m.p. 174–175° after two additional crystallizations.

Anal. Calcd. for $C_{19}H_{22}N_2O_4$: C, 66.65; H, 6.48; N, 8.18. Found: C, 66.79; H, 6.42; N, 8.21.

In the above procedure, the propanol was replaced by formaldehyde, butanal, acetone, and 3-pentanone; none of these reactants afforded solid products.

Reactions of vinyl isocyanate (II). Vinyl isocyanate was prepared in 72% yield (basis acryloyl chloride) from acryloyl azide (above) following the procedure of Hart.[9]

During the distillation (b.p. 41.5–42.0°) of this material (n_D^{20} 1.4223), the walls of the apparatus in contact with the distilling vapor became coated with a white, solid, polymeric material; the only solvent found was concd. sulfuric acid.

Anal. Calcd. for $(C_3H_3NO)_n$: C, 52.16; H, 4.35; N, 20.28. Found: C, 51.99; H, 4.15; N, 20.03.

Benzyl alcohol (65 g.) containing 2 g. of pyridine was stirred at room temperature while adding 42 g. of vinyl isocyanate dropwise. On cooling overnight at 5°, crystals of benzyl vinylcarbamate (III) formed; yield 105 g. (99%) after washing with petroleum ether. Repetition of this experiment, except that the pyridine was replaced by an equal weight of concd. sulfuric acid, resulted in the formation of dibenzyl ethylidenedicarbamate (IV) as the sole product.

3-O-Vinylcarbamoyl-D-mannitol pentanitrate (VII). A solution of D-mannitol 1,2,3,5,6-pentanitrate[8] (VI, 9.0 g., 22 mmoles) in 100 ml. of acetonitrile containing 2 ml. of

(8) M. L. Wolfrom, E. P. Swan, K. S. Ennor, and A. Chaney, *J. Am. Chem. Soc.*, **81**, 5701 (1959); L. Hayward, *J. Am. Chem. Soc.*, **73**, 1974 (1951); J. H. Wigner, *Ber.*, **36**, 794 (1903).

(9) R. Hart, *Bull. soc. chim. Belg.*, **65**, 291 (1956).

(10) R. P. Linstead, B. R. Shephard, and B. C. L. Weedon, *J. Chem. Soc.*, 2854 (1951).

pyridine was treated at 0° with 9 g. (130 mmoles) of vinyl isocyanate dissolved in 100 ml. of acetonitrile. The mixture was stirred and allowed to warm to room temperature slowly. After 18 hr., the mixture was concentrated under reduced pressure and the residue was dissolved in warm ethanol. Activated carbon was added and the mixture was filtered. Addition of water to the filtrate afforded an oil which slowly crystallized. After two further crystallizations from ethanol-water, using carbon for decolorization, pure material was obtained; yield 6.4 g. (61%), m.p. 136–137°, $[\alpha]_D^{28}$ +61.6° (*c*, 4.44, acetonitrile).

Anal. Calcd. for $C_9H_{12}N_6O_{17}$: C, 22.70; H, 2.54; N, 17.65. Found: C, 22.71; H, 2.61; N, 17.73.

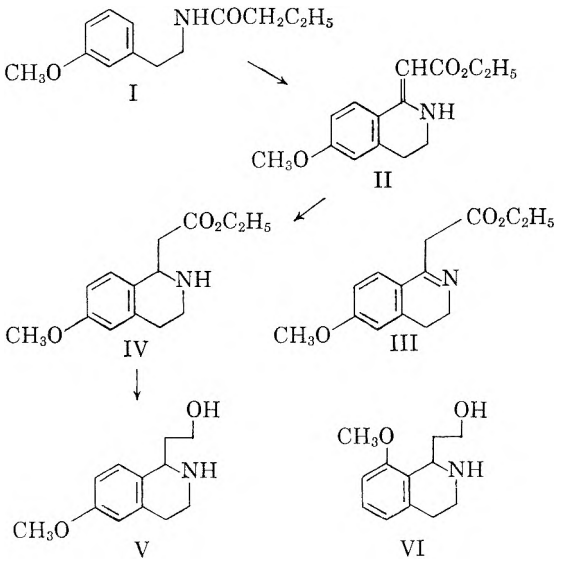
DEPARTMENT OF CHEMISTRY
THE OHIO STATE UNIVERSITY
COLUMBUS 10, OHIO

1-(β-Hydroxyethyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline[1]

N. A. NELSON,[2] K. O. GELOTTE, Y. TAMURA, H. B. SINCLAIR, J. M. SCHUCK, V. J. BAUER, AND R. W. WHITE

Received November 29, 1960

In work directed at the total synthesis of azasteroids, we had occasion to prepare 1-(β-hydroxyethyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline (V), a substance possessing the A and B rings of an azasteroid nucleus. This note gives the details for the preparation of V and describes spectroscopic data which were used to distinguish alternative structures for the compounds produced.



Treatment of ethyl *N*-*m*-methoxyphenethylmalonamate (I) with phosphorus pentoxide in refluxing toluene[3] gave a noncrystalline red-colored product which resisted purification.[4] The infrared spectrum of the product is not consistent with structure III, which is the usual structure written for the product of a Bischler-Napieralski reaction.[3–6] For example, the spectrum exhibits an absorption band at 3320 cm.$^{-1}$ (presumably N—H stretching)[7] and no appreciable absorption in the range 1660–1800 cm.$^{-1}$ (indicating the absence of a normal ester carbonyl group). Structure II fits the spectral data and is also consistent with the known tendency of a β-imino-carbonyl compound (such as III) to exist in the tautomeric β-amino-α,β-unsaturated carbonyl system.[8]

Hydrogenation of the crude 1-carbethoxymethylene-6-methoxy-1,2,3,4-tetrahydroisoquinoline (II)[3] in acetic acid using Adams catalyst resulted in the absorption of one molecular equivalent of hydrogen and gave ethyl 6-methoxy-1,2,3,4-tetrahydro-1-isoquinolylacetate (IV). This material could be purified by distillation under highly reduced pressure, but ordinarily it was sufficiently pure to be used directly in the next step. Reduction of IV with lithium aluminum hydride yielded the crystalline 1-(β-hydroxyethyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline (V). The ultraviolet spectrum of V is very similar to that of 6-methoxy-1,2,3,4-tetrahydroisoquinoline,[9] thus demonstrating the point of ring closure in the cyclization of the malonamate I. This result is in accord with the generally accepted fact that the Bischler-Napieralski reaction of *N*-*m*-methoxyphenethylamides results in cyclization at the position *para* to the methoxyl group.[6]

(1) This investigation was supported in part by research grants, CY-2999 (C1-C3), from the National Cancer Institute, Public Health Service.

(2) Research Laboratories of the Upjohn Company, Kalamazoo, Mich.

(3) Using the procedure of A. R. Battersby, H. T. Openshaw, and H. C. S. Wood, *J. Chem. Soc.*, 2463 (1953).

(4) *Cf.* A. Brossi, H. Lindlar, M. Walter, and O. Schnider, *Helv. Chim. Acta*, **41**, 119 (1958).

(5) J. M. Osbond, *J. Chem. Soc.*, 3464 (1951).

(6) W. M. Whaley and T. R. Govindachari, *Org. Reactions*, **VI**, 74 (1951). These authors also list some examples of products in which the newly created double bond is exocyclic.

(7) N. H. Cromwell, F. A. Miller, A. R. Johnson, R. L. Frank, and D. J. Wallace [*J. Am. Chem. Soc.*, **71**, 3337 (1949)], have described several *N*-alkyl-β-amino-α,β-unsaturated ketones in which no N—H stretching band was observed in the region of 3300 cm.$^{-1}$ They concluded that this absorption band was probably broadened and shifted to lower frequencies due to strong chelation and was thereby obscured by the C—H absorption bands. In our case this absorption band may be due to a weaker chelated N—H stretching, or the N—H stretching of the *trans* isomer of II. Since the position of absorption does not shift appreciably in going to very dilute solutions (0.01*M*), the former assignment is preferred. Finally, since the product is not crystalline, the possibility that this absorption band is caused by an impurity cannot be excluded.

(8) S. A. Glickman and A. C. Cope, *J. Am. Chem. Soc.*, **67**, 1017 (1945).

(9) Prepared as described by W. M. Whaley and T. R. Govindachari, *Org. Reactions*, **VI**, 172 (1951). The sample had the following physical constants: b.p. 144° (9 mm.); $\lambda_{max}^{C_2H_5OH}$ 221.5 (ε 7200), 278.5 (ε 2010), and 287 mμ (ε 1800) with minima at 246 and 285 mμ.

In one experiment an effort was made to isolate the other possible amino alcohol VI which would be derived from a cyclization product in which ring closure occurred *ortho* to the methoxyl group. The residue remaining after isolation of the major product V was purified by distillation and chromatography. A forerun obtained in the distillation step appears to be 6-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline on the basis of spectral evidence and analytical data of its picrate derivative. Such a product could arise through loss of the ester function of I or II by hydrolysis and decarboxylation. Chromatographic purification of the high boiling fraction from the distillation yielded the isomeric 1-(β-hydroxyethyl)-8-methoxy - 1,2,3,4 - tetrahydroisoquinoline (VI). The ultraviolet spectrum of VI, being quite similar to that of 5-methoxy-1,2,3,4-tetrahydronaphthalene[10] and related systems,[11] confirms the structural assignment.

EXPERIMENTAL[12]

1-(β-Hydroxyethyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline (V). To a boiling solution of 30 g. of crude ethyl *N-m*-methoxyphenethylmalonamate[13] in 450 ml. of toluene was added three 30-g. portions of phosphorus pentoxide at 10- to 15-min. intervals. The solid cake which formed was periodically broken up by means of a stirring rod. After heating the mixture at reflux for a total of 1 hr., it was cooled in an ice bath and 750 g. of ice and water was added in one portion with stirring. As soon as the red mass had dissolved, the mixture was filtered through a pad of 545 Celite. The layers of the filtrate were separated and the organic layer was extracted with dilute hydrochloric acid (work-up of the organic layer yielded 2.6 g. of unchanged starting material). All aqueous portions were combined without delay and washed with ether, cooled to 0°, and made basic with either solid potassium carbonate or 50% potassium hydroxide solution. The basic solution was extracted with ether and the ether extract dried and concentrated *in vacuo* giving 22.2 g. (79%) of crude II; $\nu_{max}^{CCl_4}$ 3320 (m, N—H), 1640 (s), 1630(s), 1605(s) and 1570 (s) cm.$^{-1}$ associated with the vibrational modes of the vinylogous urethan and aromatic systems (there is no absorption band in the range of 1660–1800 cm.$^{-1}$); $\nu_{max}^{CCl_4}$ (0.01 *M*, 1-cm. cell) 3320 (m, intramolecular hydrogen bonded N—H) cm.$^{-1}$ In another run this material decomposed when an attempt was made to purify it by distillation at 0.001 mm.

A mixture of 22.2 g. of crude II in 175 ml. of glacial acetic acid was hydrogenated at 1–2 atm. pressure in the presence of 300 mg. of Adams catalyst. The hydrogen uptake ceased in about 40 min. when 1 molecular equivalent of hydrogen had been absorbed. Work-up of the reaction mixture[3] gave 21.2 g. of crude ethyl 6-methoxy-1,2,3,4-tetrahydro-1-isoquinolylacetate which was sufficiently pure to be used directly in the next step (see below).

In an earlier run, the crude product (17.9 g.) was purified by distillation giving 14.2 g. of IV as a colorless viscous oil, b.p. 98–103° (0.004 mm.), n_D^{25} 1.5362, $\nu_{max}^{CCl_4}$ 3350 (w, N—H) and 1735 (s, ester C=O) cm.$^{-1}$ [lit.[4] b.p. 132° (0.02 mm.)].

Ethyl 6-methoxy-1,2,3,4-tetrahydro-1-isoquinolylacetate picrate was prepared by heating equivalent amounts of the amino ester and picric acid for 5 min. at 115°. Addition of 95% ethanol gave 91% of the picrate, m.p. 164–166°, raised to 167.5–168° after several recrystallizations from ethanol.

Anal. Calcd. for $C_{20}H_{22}N_4O_{10}$: C, 50.21; H, 4.64; N, 11.71. Found: C, 50.39; H, 4.65; N, 11.50.

To a stirred solution of 4.0 g. of lithium aluminum hydride in 250 ml. of ether was added dropwise a solution of 10.0 g. of crude ethyl 6-methoxy-1,2,3,4-tetrahydro-1-isoquinolylacetate in 25 ml. of anhydrous tetrahydrofuran. The mixture was refluxed for 1 hr., then cooled in an ice bath. With vigorous stirring of the mixture there was added dropwise successively 4.0 ml. of water, 4.0 ml. of 15% sodium hydroxide solution, 12 ml. of water, and after 1 hr. a small amount of 545 Celite. The solid material was separated by filtration and washed with ether. The filtrate and washings were combined and concentrated *in vacuo* giving a red oil which was purified by chromatography on Florisil using benzene as the eluent. Fractions containing product were combined and recrystallized from cyclohexane giving 5.3 g. of 1-(β-hydroxyethyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline, m.p. 85–86°, $\lambda_{max}^{C_2H_5OH}$ 221 (ε 7850), 278 (ε 1970) and 286 mμ (ε 1860) with minima at 217, 247, and 283.5 mμ, $\nu_{max}^{CHCl_3}$ 3300 (s, N—H and O—H) and 1605 (s), 1580 (m) and 1500 (s, aromatic C=C). The analytical sample melted at 87–88°.

Anal. Calcd. for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.42; H, 8.42; N, 7.07.

1-(β-Hydroxyethyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline picrate was obtained in the usual way and recrystallized from ethanol, m.p. 143–144°.

Anal. Calcd. for $C_{18}H_{20}N_4O_8$: C, 49.54; H, 4.62; N, 12.84. Found: C, 49.55; H, 4.38; N, 12.67.

1-(β-Hydroxyethyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline hydrobromide, obtained by passing hydrogen bromide into an ethereal solution of the amine, was recrystallized from ethanol-ether, m.p. 170–171°.

Anal. Calcd. for $C_{12}H_{18}BrNO_2$: C, 50.01; H, 6.29; N, 4.86. Found: C, 50.25; H, 6.11; N, 4.52.

In a different run involving the reduction of 28.5 g. of crude ethyl 6-methoxy-1,2,3,4-tetrahydro-1-isoquinolylacetate(IV) the product was isolated without resort to chromatography by direct crystallization of it from ether giving 11.0 g. of 1-(β-hydroxyethyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline, m.p. 86–87.5°, and 1.25 g. with m.p. 84–85.5°. The filtrates from the crystallizations were combined and distilled giving two main fractions. The material from the first fraction amounted to 3.7 g. (12%) and had b.p. 92–105° (0.45 mm.), $\lambda_{max}^{C_2H_5OH}$ 220(ε 7950), 277 (ε 2540), and 286 mu (ε 2180) with minima at 217, 246, and 283.5 mμ. The infrared spectrum of this material is very similar to that of 1-(β-hydroxyethyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline (V) except for weaker absorption in the former case at 3300, 1060, and 930 cm.$^{-1}$ (implying lack of an alcoholic hydroxyl group) and stronger absorption at 1375 cm.$^{-1}$ (implying the presence of a C-methyl group). The infrared and ultraviolet spectral data are consistent for a 6-methoxy-1,2,3,4-tetrahydroisoquinoline system. It is possible that this side-reaction product is 6-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline. This side reaction product was characterized further by conversion to its picrate (crystallized from ethanol), m.p. 187.5–188.5°.

Anal. Calcd. for $C_{17}H_{18}N_4O_8$: C, 50.24; H, 4.47; N, 13.79. Found: C, 50.02; H, 4.30; N, 13.55.

The material from the second fraction amounted to 1.8 g. (6%) and had b.p. 167–170° (0.7 mm.), $\lambda_{max}^{C_2H_5OH}$ 278.5 mμ (ε

(10) The sample had the following physical constants: b.p. 118–118.5° (12 mm.); n_D^{25} 1.5455; $\lambda_{max}^{C_2H_5OH}$ 270.5 (ε 1120) and 278 mμ (ε 1175) with minima at 244 and 275.5 mμ.

(11) See, for example, W. S. Johnson *et al.*, *J. Am. Chem. Soc.*, 78, 6289 (1956).

(12) The infrared spectra were determined with a Baird (model B) or Perkin-Elmer (models 21 or 137) spectrophotometer fitted with a sodium chloride prism. In reporting infrared spectra, (s) denotes strong, (m) medium, and (w) weak absorption. Ultraviolet spectra were determined with a Cary recording spectrophotometer (model 11 MS).

(13) Prepared by ammonolysis of diethyl malonate with *m*-methoxyphenethylamine,[3,4] $\lambda_{max}^{C_2H_5OH}$ 273 (ε 1960), 279.5 (ε 1830) and an inflection at 214 mμ (ε 9900).

1930) with an inflection at 272 mμ (ε 1670) and a shoulder at 285.5 mμ (ε 1160). The infrared spectrum of the material was similar to that of 1-(β-hydroxyethyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline, but had a number of additional absorption bands in the finger-print region. One gram of this material was chromatographed on 170 g. of Florisil which had been washed with methanol and air dried briefly to give a free-flowing powder (the Florisil contained about 35% methanol). Elution with benzene gave several fractions amounting to 0.49 g. which had ultraviolet spectra (λ_{max} 271.5 and 278.5 mμ) characteristic of the 8-methoxy isomer VI. Distillation of this material and crystallization of the distillate from hexane gave 0.27 g. of *1-(β-hydroxyethyl)-8-methoxy-1,2,3,4-tetrahydroisoquinoline* (VI), m.p. 96–97°, $\lambda_{max}^{C_2H_5OH}$ 223 (ε 7200), 271 (ε 1600), and 278.5 mμ (ε 1700) with minima at 246 and 276 mμ.

Anal. Calcd. for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.50; H, 8.19; N, 6.98.

Department of Chemistry
Massachusetts Institute of Technology
Cambridge 39, Mass.

The Decomposition of 11-Cyano-12-tricosanone

C. C. Cochrane and H. J. Harwood[1]

Received December 1, 1960

Early investigations of the properties of low-molecular-weight dinitriles (I; diacetonitrile[2], R = H; dipropionitrile[3], R = CH_3) have shown that upon boiling with water these substances slowly decompose with the formation of ammonia, hydrogen cyanide, and a substance which is easily oxidized by ammoniacal copper and silver solutions. It was postulated that the easily oxidizable material was an α-hydroxy ketone (ketol or acyloin) which was formed in the following manner:

$$\underset{\text{I}}{RCH_2C(=NH)CHRCN} \xrightarrow{H_2O} \underset{\text{II}}{RCH_2COCHRCN} \xrightarrow{H_2O} RCHCOCHOHR + HCN$$
$$\text{III}$$

In this Laboratory it has been observed that crystallized 11-cyano-12-tricosanone (II. R = $C_{10}H_{21}$) upon standing in air slowly evolves hydrogen cyanide leaving a liquid residue. Analysis of this residue by gas chromatography indicates that it is a mixture of equimolar amounts of undecanoic and dodecanoic acids. In an atmosphere of dry nitrogen the keto nitrile undergoes no change. Presumably moisture and oxygen are required to bring about the decomposition with formation of the mixture of acids although this has not been proved.

If 11-cyano-12-tricosanone were to decompose according to the reaction proposed above it would lead to the formation of 11-hydroxy-12-tricosanone (III. R = $C_{10}H_{21}$) which differs from the acyloin 13-hydroxy-12-tetracosanone (lauroin) by only one carbon atom. So far as we are aware the acyloins derived from higher fatty acids are not susceptible to decomposition upon exposure to the atmosphere. Mild oxidizing agents such as iodine in acetic acid[4] or ferric chloride in acetic acid[5] oxidize these compounds to the diketone. Strong oxidizing agents such as chromic oxide are required to effect cleavage to the fatty acid.[5] We do not believe that the decomposition of the keto nitrile proceeds through the acyloin but do not have a reasonable alternative to offer.

EXPERIMENTAL

Dimeric lauronitrile. To 9.2 g. (0.2 g.-atom) of 50% sodium dispersion in xylene, in 200 ml. of dry ether was added over 0.5 hr., with stirring 45 g. (0.25 mole) of lauronitrile. The ether refluxed gently after a short induction period during the addition. When the exothermic reaction had subsided, the mixture was stirred and refluxed for 24 hr. The supernatant liquid was decanted from residual sodium into a separatory funnel. The sodium was destroyed with methanol and the alcoholic solution was added to the separatory funnel. The organic extracts were washed three times with water, dried over anhydrous sodium sulfate, the solvent removed, and the residue distilled to give 2.1 g. lauronitrile, b.p. 88–89°/0.25 mm.; 22.9 of dinitrile b.p. 220–240°/0.15 mm. and a significant residue. Redistillation of the dinitrile afforded 20.9 g. b.p. 208–212°/0.10 mm.

11-Cyano-12-tricosanone. A mixture of 5 g. of dinitrile, 100 ml. of 95% alcohol and 2 ml. of concd. hydrochloric acid was warmed until solution was effected, then chilled overnight in the icebox. The solid was filtered and dried under vacuum in a desiccator, m.p. 46–47°[6] The keto nitrile was stable in an atmosphere of dry nitrogen. Left standing open to the air, an odor of hydrogen cyanide was evolved and the material passed from solid through semisolid to liquid during 1 week. Gas chromatography of the liquid[7] yielded two peaks of equal area, which were identical in position with those of a mixture of undecanoic and dodecanoic acids run under the same conditions. A sample sealed in an atmosphere of dry nitrogen underwent no change during a period of several years.

Armour Industrial Chemical Co.
Chicago, Ill.

(1) Address communications to this author.
(2) R. Holtzwart, *J. prakt. Chem.*, 39, 230 (1889).
(3) E. von Meyer, *J. prakt. Chem.*, 39, 188 (1889).
(4) V. L. Hansley, *J. Am. Chem. Soc.*, 57, 2303 (1935).
(5) F. Bonquet and C. Paquot, *Bull. soc. chim. France*, 1165 (1948).
(6) M. R. McCorkle, *Iowa State Coll. J. Sci.*, 14, 64 (1939); *Chem. Abstr.*, 34, 6220 (1940), reports the m.p. 44-45°.
(7) Through the courtesy of L. D. Metcalfe of this Laboratory. A phosphoric-acid-treated diethylene glycol–adipic acid polyester column was employed. *Cf.* L. D. Metcalfe, *Nature*, 188, 142 (1960).

Preparation and Reduction of 3-Nitro-*p*-terphenyl

Robert G. Splies

Received December 9, 1960

Three of the four possible mononitro derivatives of *p*-terphenyl have been reported.[1,2] The prepara-

tion of the remaining isomer, 3-nitro-*p*-terphenyl is reported in this study.

p-Terphenyl was nitrated using a modification of the method of Allen and Burness.[3] Slow addition of a dilute nitrating mixture apparently decreased dinitration and oxidation and gave an improved yield of the desired 4-nitro-*p*-terphenyl (I). Reduction of I was carried out in a high pressure bomb with a Raney nickel catalyst. The resulting 4 amino-*p*-terphenyl (II) was acetylated by treatment with acetic anhydride. The amide thus produced was nitrated directly without isolation, affording 3-nitro-4-acetylamino-*p*-terphenyl (III) in good yield. Hydrolysis of III in a warm dioxane solution was effected by aqueous potassium hydroxide. The brightly colored hydrolysis product proved to be the desired 3-nitro-4-amino-*p*-terphenyl (IV).[4]

A diazotized solution of IV was deaminated by refluxing with ethyl alcohol. The resulting 3-nitro-*p*-terphenyl (V), on oxidation, yielded the known 3-nitrodiphenyl-4′-carboxylic acid.[5] This is in accordance with the observation of France, Heilbron, and Hey[2] who reported that oxidation of I and 2-nitro-*p*-terphenyl yielded 4-nitrodiphenyl-4′-carboxylic acid and 2-nitrodiphenyl-4′-carboxylic acid respectively.

Catalytic hydrogenation of V gave 3-amino-*p*-terphenyl (VI). Acetylation of VI with acetic anhydride gave 3-acetylamino-*p*-terphenyl (VII).

EXPERIMENTAL[6]

4-Nitro-p-terphenyl (I). A suspension of 23.0 g. of *p*-terphenyl in 110 ml. refluxing glacial acetic acid was stirred vigorously while a mixture of 15 ml. of red fuming nitric acid and 25 ml. of acetic acid was added during 3.5 hr. After cooling in an ice bath the yellow solid was removed by filtration on a sintered glass funnel. The crude yield of I was 23.3 g. (85%). Recrystallization from nitromethane yielded I as a pale yellow solid, m.p. 210–211°.

4-Amino-p-terphenyl (II). A suspension of 11.0 g. of I in 130 ml. of dioxane was reduced by hydrogen under a cold pressure of 2200 p.s.i. The reduction was carried out with 1 teaspoon of Raney nickel catalyst in a 270-ml. void bomb. The reduction required 2 hr. at 90° after which the bomb was cooled and rinsed with a small amount of dioxane. The catalyst was removed by filtration and evaporation of the solvent under reduced pressure yielded 9.15 g. (94%) of II, m.p. 186–193°. Recrystallization from ethyl alcohol produced light tan crystals melting at 199.5–200.5°.

3-Nitro-4-acetylamino-p-terphenyl (III). A solution of 12.25 g. of II in 300 ml. of acetic acid was warmed and stirred while 10 ml. of acetic anhydride was added dropwise. Heating and stirring were continued for an hour. The reaction mixture was cooled to 70° and a mixture of 10 ml. of fuming nitric acid (*d.* 1.5) and 20 ml. of acetic acid was added during 20 min. Nitration was completed by warming to 90° for 0.5 hr. After chilling, the suspension was filtered and 13.24 g. (88%) of an orange solid was obtained, m.p. 202.5–205°. An analytical sample, m.p. 204.7–206°, was prepared by recrystallization from acetic acid.

Anal. Calcd. for $C_{20}H_{16}N_2O_3$: C, 72.27; H, 4.85; N, 8.42. Found: C, 72.38; H, 4.89; N, 8.42.

3-Nitro-p-terphenyl (V). A suspension of 3.24 g. of IV in 110 ml. of acetic acid was added to 30 ml. of cold, concentrated sulfuric acid containing 0.84 g. of sodium nitrite. The resulting deep red diazonium solution was added dropwise to a refluxing solution of 0.25 g. of copper sulfate and 20 ml. of water in 400 ml. of ethyl alcohol. The mixture, contained in a 1000-ml. flask, was stirred vigorously during the addition which required 2.5 hr. Refluxing and stirring were continued for 1 hr. after which the mixture was diluted with water. The solid was removed by filtration and dried by suction. After crystallization from petroleum ether (b.p. 110–120°) 2.69 g. (88%) of a light orange solid was obtained, m.p. 178–180°. Three recrystallizations from petroleum ether gave an analytical sample, m.p. 180–181.2°.

Anal. Calcd. for $C_{18}H_{13}NO_2$: C, 78.53; H, 4.76. Found: C, 78.21; H, 4.83.

Oxidation of 3-nitro-p-terphenyl. The method of France, Heilbron, and Hey[2] was employed in the oxidation of 0.25 g. of V. The yield of 2-nitrodiphenyl-4′-carboxylic acid was 0.12 g., m.p. 308–312°. Two recrystallizations from absolute ethanol raised the m.p. to 312–312.3° (lit.,[5] m.p. 313–315.1°).

3-Amino-p-terphenyl (VI). A solution of 5.5 g. of V in 130 ml. of dioxane was reduced catalytically using the method reported above for the preparation of II. A cream-colored solid, 4.43 g. (91%), was obtained, m.p. 163–173°. Recrystallization from petroleum ether gave a solid, m.p. 181–181.9°.

Anal. Calcd. for $C_{18}H_{15}N$: C, 88.13; H, 6.16. Found: C, 87.68; H, 6.12.

3-Acetylamino-p-terphenyl (VII). A solution of 2.27 g. of VI in 150 ml. of refluxing benzene was stirred while 4 ml. of acetic anhydride and 5 drops of pyridine were added. After stirring at room temperature for 1 hr. the solvent was removed by warming on a steam bath in a current of air. The amide was crystallized from an alcohol-petroleum ether mixture. The fine, white needles weighed 2.08 g. (76%), m.p. 218–219°.

Anal. Calcd. for $C_{20}H_{17}ON$: C, 83.59; H, 5.97. Found: C, 83.36; H, 5.96.

Department of Chemistry
University of Wisconsin
Milwaukee 3, Wis.

(1) F. R. Bashford, *J. Chem. Soc.*, 1442 (1937).

(2) H. France, I. M. Heilbron, and D. H. Hey, *J. Chem. Soc.*, 1364 (1938).

(3) C. F. H. Allen and D. M. Burness, *J. Org. Chem.*, **14**, 177 (1949).

(4) E. Sawicki and F. E. Ray, *J. Org. Chem.*, **19**, 1903 (1954).

(5) E. Berliner and E. A. Bloomers, *J. Am. Chem. Soc.*, **73**, 2479 (1951).

(6) Melting points are uncorrected.

α-Oximino Ketones. IX. The Synthesis of α,ω-Diamino Acids from Cyclic Ketones

Arthur F. Ferris, Francis E. Gould, Grannis S. Johnson,[1] and Hugo Stange

Received December 12, 1960

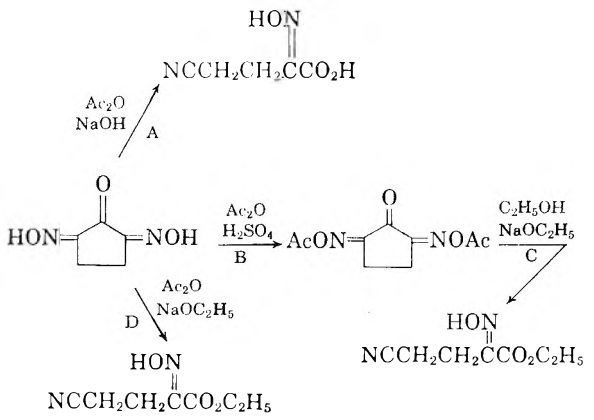
In a series of publications from this laboratory several related routes for the conversion of cyclohexanone to DL-lysine have been described.[2–5]

(1) Present address: General Aniline and Film Corp., Linden, N. J.

(2) A. F. Ferris, F. E. Gould, G. S. Johnson, H. K. Latourette, and H. Stange, *Chem. & Ind. (London)*, 1959, 996.

In all of these syntheses the first step was the nitrosation of cyclohexanone to 2,6-dioximinocyclohexanone, the second and key step was the partial cleavage of this molecule or an acylated derivative under the conditions of the second order Beckmann rearrangement[6] to 5-cyano-2-oximinovaleric acid or one of its esters, and the final step was the reduction of the acid or ester to DL-lysine. In the most successful variant of this reaction scheme an ethanolic solution of the sodium salt of 2,6-dioximinocyclohexanone was treated with acetic anhydride to give ethyl 5-cyano-2-oximinovalerate, and the ester was hydrogenated in acetic anhydride over Raney nickel and a basic co-catalyst. The overall yield of DL-lysine monohydrochloride from cyclohexanone was 63%.

In more recent work a study has been made to determine whether the techniques developed in the lysine work can be extended to the synthesis of other α,ω-diamino acids from cyclic ketones. Cyclopentanone and 4-methylcyclohexanone were chosen as model compounds. The nitrosation of these ketones to the α,α'-dioximino derivatives was described first by Borsche.[7] Nitrosation of the latter has been studied more recently by Batesky and Moon.[8] In our work 2,5-dioximinocyclopentanone was prepared in 47% yield and 2,6-dioximino-4-methylcyclohexanone was prepared in 72% yield by the technique described previously,[3] namely the treatment of the cyclic ketone in ether with methyl nitrite in the presence of hydrochloric acid. All three methods developed in the lysine studies for bringing about the partial cleavage of 2,6-dioximinocyclohexanone were tried with the new α,α'-dioximino compounds. The reactions involved were treatment of a solution of the dioxime in aqueous base with a deficiency of acetic anhydride (A), conversion of the α,α'-dioximino compound to the diacetyl derivative and treating the latter with sodium ethoxide in ethanol (B + C), and treatment of a suspension of the monosodium salt of the dioxime in ethanol with the stoichiometric amount of acetic anhydride (D). The three reaction schemes are shown in equation form below, using 2,5-dioximinocyclopentanone as the example.



As expected, relatively poor yields were obtained with reaction sequence A, almost certainly because of the fact, noted previously,[3] that the α-oximino acids themselves are cleaved under second order Beckmann conditions. Better yields were obtained in sequences BC and D, wherein advantage was taken of the discovery made in the course of the lysine work[4] that esters of α-oximino acids are not cleaved by Beckmann reagents. Since the ester partial cleavage products were obtained in much better yields than the free acids, reduction studies were carried out only with the esters. As in the lysine work[5] much better yields of α,ω-diamino acids were obtained when Raney nickel catalyst was used with acetic anhydride solvent in the hydrogenation step than when platinum was used. A summary of all yields obtained is presented in Table I.

TABLE I

YIELDS IN CONVERSION OF CYCLIC KETONES TO α,ω-DIAMINO ACIDS

Step	% Yields	
	Cyclopentanone	4-Methyl-cyclohexanone
Nitrosation	47	72
A[a]	18	24
B	30	53
C	82	86
D	59	62
Hydrogenation, Ni	77	63
Hydrogenation, Pt	16	18
Overall[b]	21	28

[a] Capital letters refer to letter steps in equations above. [b] Cyclic ketone to α,ω-diamino acid by best route.

The overall yields of ornithine and 4-methyllysine are considerably poorer than the 63% yield of lysine obtained from cyclohexanone, but this probably reflects only the more extensive study given to the lysine synthesis. It thus appears reasonable to predict that many α,ω-diamino acids can be obtained from the corresponding cyclic ketones in overall yields of 20–30%, with considerably better yields being possible if the significance of the synthesis justifies a study of refinements.

EXPERIMENTAL

All the techniques used in this study have been described in previous papers.[3-5] The physical properties and analyses of the compounds prepared are reported in Table II. The final column of the table gives the footnote number of the paper wherein the procedure used to prepare each compound was described in detail.

(3) A. F. Ferris, G. S. Johnson, F. E. Gould, and H. K. Latourette, *J. Org. Chem.*, **25**, 492 (1960).

(4) A. F. Ferris, G. S. Johnson, and F. E. Gould, *J. Org. Chem.*, **25**, 496 (1960).

(5) A. F. Ferris, G. S. Johnson, F. E. Gould, and H. Stange, *J. Org. Chem.*, **25**, 1302 (1960).

(6) A. F. Ferris, *J. Org. Chem.*, **25**, 12 (1960).

(7) W. Borsche, *Wallach Fest.*, 301 (1909); *Chem. Abstr.*, 5, 883 (1911).

(8) D. C. Batesky and N. S. Moon, *J. Org. Chem.*, **24**, 1694 (1959).

TABLE II

INTERMEDIATES IN THE CONVERSION OF CYCLIC KETONES TO α,ω-DIAMINO ACIDS

Compound	M.P.[a]	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Ref.
2,5-Dioximinocyclopentanone	214 d.[b]	42.25	4.26	19.72	42.41	4.23	19.97	(3)
2,6-Dioximino-4-methylcyclohexanone	[c]	49.40	5.92	16.47	49.72	5.64	16.22	(3)
4-Cyano-2-oximinobutyric acid	123–125	42.25	4.26	19.72	42.24	4.11	19.84	(3)
5-Cyano-4-methyl-2-oximinovaleric acid	109–111	49.40	5.92	16.47	49.30	5.72	16.56	(3)
2,5-Diacetoximinocyclopentanone	177 dec.	47.79	4.46	12.39	48.02	4.42	12.38	(4)
2,6-Diacetoximino-4-methylcyclohexanone	171–172	51.96	5.55	11.02	51.80	5.64	11.32	(4)
Ethyl 4-cyano-2-oximinobutyrate	Liq.[d]	49.40	5.92	16.47	49.31	6.14	16.29	(5)
Ethyl 5-cyano-4-methyl-2-oximinovalerate	61	54.53	7.12	14.14	54.71	6.87	14.25	(5)
DL-Ornithine monohydrochloride	205–211 dec.	[e]						(5)
DL-4-Methyllysine monohydrochloride	229–230	42.74	8.71	14.25[f]	42.71	8.71	14.46[f]	(5)

[a] All melting points are uncorrected. [b] Lit.[7] m.p. 215° dec. [c] Decomposed at about 200°. [d] Not distilled, n_D^{25} 1.4750. [e] Infrared spectrum identical to that of authentic DL-ornithine monohydrochloride. [f] Calcd.: Cl, 18.03. Found: Cl, 18.10.

Acknowledgment. The assistance of John E. Zarembo and his staff in carrying out the analyses reported herein and of Herman Adelman and his staff in obtaining and assisting in the interpretation of infrared spectra is gratefully acknowledged.

CHEMICAL RESEARCH AND DEVELOPMENT CENTER
FOOD MACHINERY AND CHEMICAL CORP.
PRINCETON, N. J.

Neopentyl Group Analogs. IV. Trimethylsilylmethyldichlorophosphine[1]

DIETMAR SEYFERTH AND WALTER FREYER

Received December 19, 1960

Our recent work on the tris(trimethylsilylmethyl) derivatives of the Group VB elements[2] has prompted further work in the area of silicon-substituted phosphorus compounds. Of particular interest as a possible intermediate in the synthesis of silicon-substituted phosphonitrilic compounds was trimethylsilylmethyldichlorophosphine.

Conventional methods used to synthesize alkyldichlorophosphines utilize the reaction of phosphorus trichloride with mild alkylating agents, such as dialkylmercury[3] or tetraalkyllead[4] compounds. Accordingly, bis(trimethylsilylmethyl)-mercury and tetrakis(trimethylsilylmethyl)lead, both new compounds, were prepared by the usual Grignard procedure, and their action on phosphorus trichloride was investigated. The mercurial did not react with phosphorus trichloride either when a mixture of the reactants was refluxed in hexane solution, or in the absence of solvent at *ca.* 76°. In contrast, the lead compound was cleaved by phosphorus trichloride, giving crystalline, sublimable tris(trimethylsilylmethyl)lead chloride and trimethylsilylmethyldichlorophosphine. However, the isolated yield of the phosphine was not very high, and a better synthesis was desired.

$$[(CH_3)_3SiCH_2]_4Pb + PCl_3 \longrightarrow [(CH_3)_3SiCH_2]_3PbCl + (CH_3)_3SiCH_2PCl_2$$

Although the Grignard procedure is not generally applicable to the synthesis of pure $RPCl_2$ compounds because mixtures of mono-, di-, and trisubstituted products result, it seemed possible that with the relatively bulky trimethylsilylmethyl group, monosubstitution could be realized in acceptable yield. Indeed, our previous work[2] showed that complete substitution of all three chlorine atoms of phosphorus trichloride with trimethylsilylmethyl groups by the Grignard procedure requires drastic conditions. It was found in the present work that addition of one equivalent of trimethylsilylmethylmagnesium chloride to one mole of phosphorus trichloride in ether at low temperature resulted in the desired trimethylsilylmethyldichlorophosphine in *ca.* 40% yield.

Attempted conversion of trimethylsilylmethyldichlorophosphine to trimethylsilylmethyltetrachlorophosphorane was not successful. Even at −20° in the dark addition of a solution of chlorine in *sym*-tetrachloroethane to trimethylsilylmethyldichlorophosphine caused cleavage of the carbon-silicon bond to form trimethylchlorosilane. This facile cleavage of the carbon-silicon bond may be due to the inductive effect of the PCl_4 group; electron withdrawal by this group would make the Si-C bond more polar, hence more susceptible toward ionic fission.

Investigation of the solid formed in the chlorination reaction showed it to be impure phosphorus pentachloride rather than the expected chloromethyltetrachlorophosphorane. The hydrolysis product of this solid formed a barium salt of very low carbon content, and an anilinium salt could be prepared which was shown to be $[C_6H_5NH_3][H_2PO_4]$. It is not known at what point fission of the

(1) Part III: D. Seyferth, *J. Am. Chem. Soc.*, 81, 1844 (1959).
(2) D. Seyferth, *J. Am. Chem. Soc.*, 80, 1336 (1958).
(3) G. M. Kosolapoff, *Organophosphorus Compounds*, John Wiley and Sons, Inc., New York, 1950, p. 42.
(4) M. S. Kharasch, E. V. Jensen, and S. Weinhouse, *J. Org. Chem.*, 14, 429 (1949).

the P-C bond took place, nor is the fate of the methylene group of the trimethylsilylmethyldichlorophosphine known. It is, however, very likely that such cleavage took place after cleavage of the Si—C bond, since initial cleavage of trimethylsilylmethyldichlorophosphine at the P—C linkage would have given chloromethyltrimethylsilane, a compound which is stable to Si—C cleavage under these conditions, although side chain chlorination does take place.

EXPERIMENTAL[5]

(1) *Bis(trimethylsilylmethyl)mercury.* The Grignard reagent, prepared from 0.6 g.-atom of magnesium turnings and 0.6 mole of chloromethyltrimethylsilane in 450 ml. of tetrahydrofuran (THF), was cooled to −10°, and a solution of 0.28 mole of mercuric chloride in 125 ml. of tetrahydrofuran was added slowly with stirring. The mixture subsequently was heated at reflux for 1 hr., cooled, and hydrolyzed with 50 ml. of saturated ammonium chloride solution. The organic layer was separated; the aqueous phase was extracted with ether. The combined organic layer and ether washings were dried over anhydrous sodium sulfate. Fractional distillation gave 51 g. (48.5%) of bis(trimethylsilylmethyl)mercury, b.p. 49–50° at 0.35 mm., n_D^{25} 1.4869.

Anal. Calcd. for $C_8H_{22}Si_2Hg$: C, 25.62; H, 5.91; Hg, 53.49. Found: C, 25.89; H, 6.04; Hg, 53.43.

(2) *Tetrakis(trimethylsilylmethyl)lead.* To the vigorously stirred solution of *ca.* 0.6 mole of trimethylsilylmethylmagnesium chloride in 450 ml. of tetrahydrofuran at −10° was added a suspension of 83.5 g. (0.3 mole) of lead dichloride in tetrahydrofuran. The mixture became deep red-brown immediately. In order to effect the complete disproportionation of the divalent lead species formed initially, the solution was heated at reflux for 5 hr. until the reaction mixture was gray-green in color. The mixture was cooled to −10° and hydrolyzed with 100 ml. of saturated ammonium chloride solution. The metallic lead formed in the reaction was filtered off, and the organic layer was separated. The dried organic phase was fractionally distilled to give colorless liquid which became turbid on standing. Filtration and a second distillation gave 31 g. (37%) of tetrakis(trimethylsilylmethyl)lead, b.p. 104–105° at 0.01 mm.

Anal. Calcd. for $C_{16}H_{44}Si_4Pb$: C, 34.57; H, 7.97. Found: C, 34.14; H, 7.86.

(3) *Trimethylsilymethyldichlorophosphine.* (a) *Attempted preparation via the mercurial.* A solution of 90 g. (0.65 mole) of freshly distilled phosphorous trichloride in 100 ml. of hexane was heated at reflux while 50 g. (0.13 mole) of bis(trimethylsilylmethyl)mercury was added slowly. The resulting solution was heated for 12 hr. at reflux. Since no reaction appeared to have occurred, the hexane and the phosphorus trichloride were distilled off, and 90 g. of fresh phosphorus trichloride was added to the residue. This mixture was heated at reflux for 12 hr. Distillation led to a 96% recovery of the mercurial.

(b) *Preparation via the lead derivative.* A mixture of 39 g. (0.7 mole) of tetrakis(trimethylsilylmethyl)lead and 480 g. (3.5 moles) of phosphorus trichloride was heated at reflux for 16 hr. During this time white needles precipitated. After filtration of the reaction mixture, the excess of phosphorus trichloride was distilled from the filtrate; fractional distillation of the residue gave only 2.2 g. of trimethylsilylmethyldichlorophosphine. The filtered solid was washed with hexane and sublimed at 1 mm. (bath temperature 225°) to give 19.5 g. (55%) of tris(trimethylsilylmethyl)lead chloride; m.p. 214–216° after two sublimations.

Anal. Calcd. for $C_{12}H_{33}Si_3PbCl$: C, 28.6; H, 6.60; Cl, 7.04. Found: C, 28.38; H, 6.79; Cl, 6.75.

(c) *Preparation by the Grignard method.* The Grignard reagent prepared from 0.6 g.-atom of magnesium turnings and 0.6 mole of chloromethyltrimethylsilane in 450 ml. of diethyl ether was filtered through glass wool and added, with stirring, to a solution of 68.5 g. (0.6 mole) of phosphorus trichloride in 300 ml. of ether at −10°. The initially white solid formed turned deep yellow as the reaction progressed. The reaction mixture was stirred at room temperature for 1 hr. The solution was cooled, and anhydrous hydrogen chloride was bubbled into it for 0.5 hr. (Omission of this step resulted in very low yields of product; possibly destruction of a solid $(CH_3)_3SiCH_2PCl_2$-$MgCl_2$ complex is involved in the hydrogen chloride treatment). The mixture was filtered, and the salts were washed thoroughly with ether. Distillation of the ether solution gave 49 g. (43%) of trimethylsilylmethyldichlorophosphine, b.p. 50° at 1.5 mm., a liquid that fumed when exposed to moist air.

Anal. Calcd. for $C_4H_{11}Cl_2PSi$: C, 25.41; H, 5.85. Found: C, 25.75; H, 6.15.

(4) *Chlorination of trimethylsilylmethyldichlorophosphine.* A solution of 47 g. (0.25 mole) of trimethylsilylmethyldichlorophosphine in 100 ml. of 1,1,2,2-tetrachloroethane was cooled to −20° and protected from the light. The slow addition of a solution of 0.5 mole of chlorine in the same solvent was carried out in an atmosphere of nitrogen. A pale yellow solid precipitated (24 g.). The mixture was filtered under nitrogen. Fractional distillation gave 22 g. (81%) of trimethylchlorosilane, b.p. 55–56°, n_D^{25} 1.3855 (Dow Corning Corp. purest grade trimethylchlorosilane: n_D^{25} 1.3860), further identified by its infrared spectrum and the infrared spectrum of its hydrolysis product, hexamethyldisiloxane.

Two grams of the solid formed during the chlorination reaction was added in portions to 15 ml. of ice-cold water; a vigorous reaction was apparent. The resulting solution was treated with decolorizing charcoal and filtered. Evaporation of the filtrate at reduced pressure gave a noncrystallizable oil. This was diluted with 5 ml. of water. The acidic solution was neutralized to *p*H 6 with aqueous ammonia and treated with barium chloride solution. The resulting crystalline barium salt was washed well with hot water and dried.

Anal. Calcd. for $ClCH_2PO_3Ba$: C, 4.5; H, 0.75. Found: C, 0.49; H, 0.55.

Treatment of an aqueous solution of the hydrolysis product of the solid chlorination product with aniline caused precipitation of an anilinium salt, m.p. 183–184° after recrystallization from absolute alcohol. This was not the anilinium salt of chloromethylphosphonic acid, m.p. 198–199°, rather the monoanilinium salt of phosphoric acid.

Anal. Calcd. for $C_6H_{10}O_4NP$: C, 37.8; H, 5.25; N, 7.32. Found: C, 37.73; H, 5.12; N, 7.46.

A mixture of the anilinium salts prepared from the chlorination product and from phosphoric acid did not have a depressed melting point.

The reaction of trimethylsilylmethyldichlorophosphine with chlorine in 1:1 molar ratio also appeared to result in cleavage, since instead of trimethylsilylmethyltetrachlorophosphorane (18.5% C and 4.23% H), solids containing 8–9.5% C and 2.2–2.5% H were obtained.

Acknowledgment. This work was supported by the United States Air Force under Contract No. AF 33(616)-7124, monitored by the Materials Laboratory, Wright Air Development Division, Wright-Patterson Air Force Base, Ohio.

DEPARTMENT OF CHEMISTRY
MASSACHUSETTS INSTITUTE OF TECHNOLOGY
CAMBRIDGE 39, MASS.

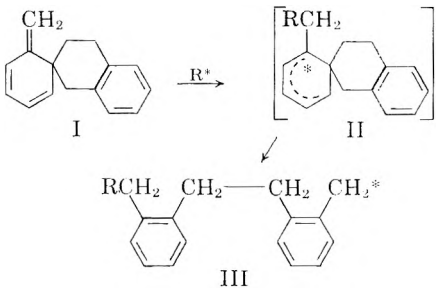
(5) Analyses were performed by the Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. All reactions were carried out under an atmosphere of prepurified nitrogen.

The Chemistry of Xylylenes. XII. Reactions of Spirodi-o-xylylene That Occur with Retention of the Spirostructure

L. A. Errede

Received December 31, 1960

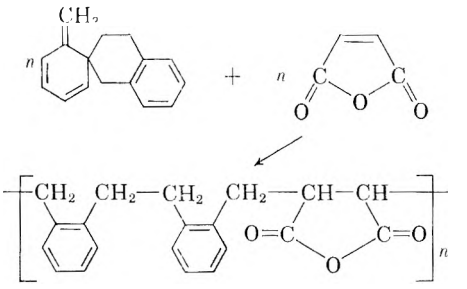
The synthesis of spirodi-*o*-xylylene (I) was reported in a previous publication.[1] The compound undergoes reaction by either free radical[1,2] or cationic mechanisms.[3] In both reaction sequences, however, addition of the attacking moiety occurs at the *exo*-methylene group to produce an unstable spiro intermediate (II) which undergoes aromatization affording a linear di-*o*-xylyl intermediate (III), the fate of which is determined by the choice of experimental conditions.



Thus, homopolymer or copolymers, and monofunctional or difunctional derivatives, of di-*o*-xylylene were prepared selectively by reaction with the appropriate reagents.[1-3] When reaction was carried out cationically, the di-*o*-xylyl cation intermediate (III) underwent intramolecular or intermolecular aromatic substitution by proper control of the reaction conditions.[3]

The structure of spirodi-*o*-xylylene suggests that it might be possible to effect Diels-Alder addition across the conjugated endo-diene system[4] despite the ease with which ring opening to di-*o*-xylylene occurs. In this respect, maleic anhydride appeared to be an interesting dienophile, as it is known that it is capable of undergoing Diels-Alder addition[4] as well as copolymerization[5] to give high molecular weight products.

When spirodi-*o*-xylylene was added at room temperature to maleic anhydride in benzene an exothermic reaction occurred and the product was isolated subsequently as the free acid in the form of a gummy mass that slowly solidified to a friable solid. Copolymer was not isolated and all of the reaction product appeared to be Diels-Alder adduct,



IV, as shown in Fig. 1. The compound was identified by its elemental analysis, molecular weight, neutral equivalent, infrared spectrum, and NMR spectrum (Table I). Samples of the dicarboxylic acid (V) were reconverted to the anhydride (IV) by vacuum sublimation or by prolonged heating at 80°. The dicarboxylic acid and the corresponding anhydride were converted to the dimethyl ester by reaction at reflux temperature in methanol containing a trace amount of sulfuric acid. The assigned structures for these derivatives were verified by their respective infrared and NMR spectra (Table I). These results demonstrated that reaction occurred in every case with retention of the spiro configuration as shown in Fig. 1.

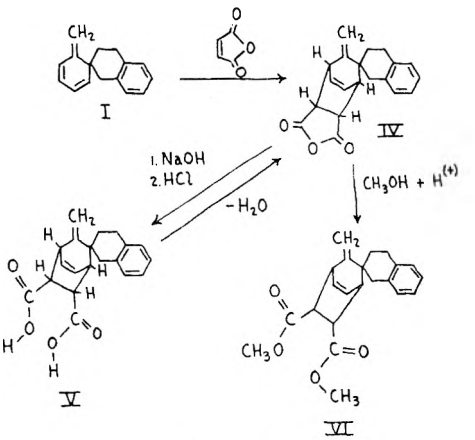


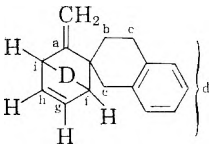
Figure 1

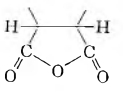
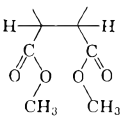
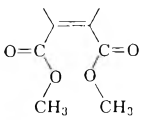
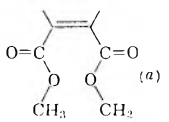
Spirodi-*o*-xylylene was allowed to react at room temperature with dimethyl acetylenedicarboxylate, and again the corresponding Diels-Alder adduct (VII) was obtained in good yield. The spiro configuration was retained when compound VII was reduced with hydrogen in the presence of Raney nickel. Only two of the three possible hydrogen equivalents were taken up as a result of the reduction. The infrared spectra and NMR data (Table I) indicate that the *exo*-CH_2= was converted to CH_3 and that the residual double bond was conjugated with the ester carbonyl groups. Similarly, the spiro configuration was also retained intact when spirodi-*o*-xylylene (I) was hydrogenated in the presence of Raney Nickel to afford spiro[5.5]-2,3-benz-6-methylcyclane (IX).[1]

(1) L. A. Errede, *J. Am. Chem. Soc.*, **83**, 949 (1961).
(2) L. A. Errede, *J. Polymer Sci.*, in press.
(3) L. A. Errede, *J. Am. Chem. Soc.*, **83**, 959 (1961).
(4) M. C. Kloetzel, *Org. Reactions*, **4**, [illegible] (1948); H. L. Holmes, *Org. Reactions*, **4**, 60 (1948); L. W. Butz, *Org. Reactions*, **5**, 253 (1950).
(5) M. C. deWilde and G. Smets, *J. Polymer Sci.*, **5**, 253 (1950).

TABLE I

NUCLEAR MAGNETIC RESONANCE DATA[13] FOR SPIRODI-*o*-XYLYLENE AND SOME OF ITS DIELS-ALDER ADDUCTS



Compound	D	a	b	c	d	e	f	g	h	i	H Atoms on D
I	None	5.07	8.1	7.2	3.0	7.2	4.2	4.2	4.2	4.2	
IV		4.97 5.27	8.3	7.2	2.97	6.47	7.2	3.68	3.68	6.77 7.02	7.20 for H–C–C=O
VI		5.07 5.38	8.3	7.2	3.00	7.2	7.2	3.8	3.8	7.2	6.34 + 6.60 for CH_3O; 7.2 for H–C–C=O
VII		4.93 5.32	8.3	7.3	2.98	7.3	5.6	3.5	3.5	5.6	6.28 + 6.44 for CH_3O
VIII		9.17[a]	8.3	7.2	3.06	7.2	7.2	8.3[a]	8.3[a]	7.2	6.25 + 6.41 for CH_3O
X or XI		4.90 5.16	8.2	7.3	2.96	7.3	6.1	3.5	3.49	6.1	

[a] *Exo*-double bond at "a" and double bond at h-g converted to the corresponding saturated bonds by hydrogenation.

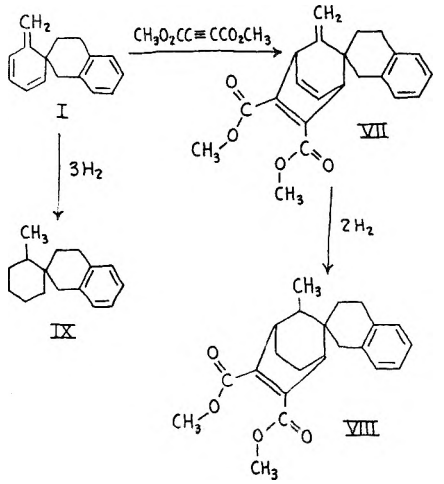
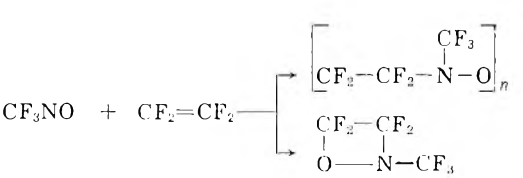


Figure 2

It is known that nitrosobenzene can undergo Diels-Alder addition[6–9] or copolymerization[10] depending upon the experimental conditions and the choice of comonomer. Thus, nitrosobenzene reacts with butadienes[6–9] to afford the corresponding Diels-Alder adduct, but it copolymerizes with *p*-xylylene to afford high molecular weight polymer.[10] Similarly, it was reported that nitrosotrifluoromethane reacts readily with tetrafluoroethylene to give selectively either high molecular weight copolymer[11] or perfluoromethyloxazetidine[12]:



Neither a copolymer nor an oxazetidine was obtained, however, when spirodi-*o*-xylylene was caused to react at room temperature with nitroso-

(6) O. Wichterle and M. Kolinsky, *Chem. Listy*, **47**, 1787 (1953); *Chem. Abstr.*, **47**, 4342 (1953).

(7) S. Kojima, *J. Chem. Soc. Japan (Ind. Chem. Section)*, **57**, 371 and 819 (1954); *Chem. Abstr.*, **49**, 10966f (1955); *Chem. Abstr.* **50**, 4903a (1956).

(8) Y. A. Arbuzov and T. A. Pisha, *Doklady Akad. Nauk.*, 116, 71 (1957); *Chem. Abstr.*, **52**, 6357d (1958).

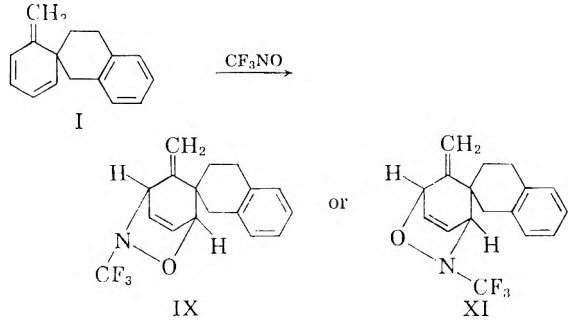
(9) Y. A. Arbuzov and T. A. Pisha, *Proc. Acad. Sci. U.S.S.R.*, **116**, 817 (1958).

(10) L. A. Errede and J. M. Hoyt, *J. Am. Chem. Soc.*, **82**, 436 (1960).

(11) G. H. Crawford, D. E. Rice, and J. C. Montermoso, Abstract of Papers presented at 137th Meeting, American Chemical Society, p. 7L (1960).

(12) D. A. Barr and R. N. Haszeldine, *J. Chem. Soc.* 1881 (1955).

trifluoromethane. Instead, the corresponding Diels-Alder adduct was obtained in good yield. This adduct is a white crystalline compound that melts at 142.5–143.0°. Its infrared and NMR spectra verified that Diels-Alder addition had occurred across the endo-diene system but it was not possible to differentiate between X or XI as the correct structure for the reaction product.



Furthermore, addition of a dienophile to the conjugate endo-diene system of spirodi-*o*-xylylene can occur either *endo* or *exo* to the methylene bridge. The NMR data and the sharpness of the melting point of the reaction products suggest that predominantly one form may have been produced. These problems of stereoisomerism have not as yet been resolved.

EXPERIMENTAL

Maleic anhydride adduct (IV) *and its dimethyl ester* (VI). Spirodi-*o*-xylylene (8 g. crude) was added to room temperature to maleic anhydride (8 g.) dissolved in benzene (about 20 cc.). The reaction was slightly exothermic and the temperature increased from room temperature to about 40°. The solution was cooled to room temperature and then extracted with dilute aqueous sodium hydroxide. The aqueous alkaline extract was acidified with dilute hydrochloric acid and a white tacky product precipitated from solution. This was redissolved in dilute base and again a tacky product was obtained on acidification. The material slowly solidified to a friable solid (5.6 g., m.p. 70–85°). Its infrared spectrum indicated the presence of *o*-xylene (bands at 6.31, 5.58, and 13.43 μ), *exo*-methylene (band at 11.22 μ) and carboxylic acid groups (broad band at 3–4 μ, band at 5.83, broad at 10.5–11 μ). Its neutral equivalent was 166 (Calcd. for $C_{20}H_{20}O_4$: 162). A small sample was dehydrated by vacuum sublimation thereby converting the free acid groups to the anhydride (bands at 5.39, 5.65 μ) as indicated by its infrared spectrum. The product now melted at 95–97°.

Anal. Calcd. for $C_{20}H_{18}O_3$: C, 78.41; H, 5.89; mol. wt. 306.36. Found: C, 77.7; H, 6.1; mol. wt. 307.

The NMR data[13] for the anhydride (Table I) support structure IV.

A sample (1 g.) of the product melting at 70–85° was dissolved in 50 cc. methanol to which 4 drops of sulfuric acid was added. The mixture was kept at reflux temperature for 2 days. The excess solvent was removed by evaporation at room temperature. The residue was dissolved in carbon tetrachloride, washed with water, dried, and again evaporated to dryness leaving an amber oil as residue.

Anal. Calcd. for $C_{22}H_{24}O_4$: C, 74.97; H, 6.87; mol. wt. 352.4. Found: C, 74.5; H, 7.1; mol. wt. 387.

Its infrared spectrum (no broad absorption at 3–4 μ for acid OH, sharp bands around 3.42 μ for CH; 5.75 μ for ester C=O; 6.33, 6.66, 13.88 μ for *o*-xylene structure, 6.08 μ for C=C; 11.28 μ for *exo*-methylene) is consistent with compound VI. The NMR data (Table I) are consistent with the anticipated dimethyl ester derivative of the Diels-Alder adduct of maleic anhydride and spirodi-*o*-xylylene (VI).

Dimethyl acetylene dicarboxylate adduct (VII). Crude spirodi-*o*-xylylene (6 g.) dissolved in dimethyl acetylenedicarboxylate (10 g.) was allowed to react at room temperature for 2 days and then separated by distillation at 0.17 mm. into four fractions: (1) 5.0 g., b.p. 40–43°, (2) 1.5 g., b.p. 110–115°, (3) 4.5 g., b.p. 182–195°, (4) 1.5 g. residue, b.p. 185°. Fraction (1) was identified as starting material by its infrared spectrum. Fraction (2) was a mixture of cyclodi-*o*-xylylene (m.p. 112.0–112.5°) and bis(*o*-methylbenzyl)-ether (m.p. 45–50) also identified by infrared analyses. Fraction (3) was crystallized from methanol and then from heptane to afford the Diels-Alder adduct (VII) in the form of fine white needles (m.p. 123–124°).

Anal. Calcd. for $C_{22}H_{22}O_4$: C, 75.40; H, 6.33; mol. wt. 350.4. Found: C, 75.1; H, 6.2; mol. wt. 365.

Its infrared spectrum (bands at 5.78, 5.87 μ for ester C=O; 6.12 μ for C=C; 11.23 μ for *exo*-methylene and 6.62, 6.70, 13.37 μ for *o*-xylene group) is consistent with compound VII. Its NMR spectrum data (Table I) also verified that the compound was the anticipated Diels-Alder adduct (VII).

Hydrogenation of compound VII. The Diels-Alder adduct (VII, m.p. 123–124°) obtained *via* reaction of dimethyl acetylenecarboxylate with spirodi-*o*-xylylene was dissolved in benzene and then hydrogenated in an Aminco Bomb at room temperature using molecular hydrogen at 67 atm. and Raney Nickel catalyst. About 2 molar equivalents of hydrogen were consumed as indicated by the drop in pressure. The product was purified by distillation at 0.14 mm. pressure (b.p. 150–160°).

Anal. Calcd. for $C_{22}H_{26}O_4$: C, 74.55; H, 7.39; mol. wt. 354. Found: C, 74.7; H, 7.4; mol. wt. 360.

Its infrared spectrum verified the formation of a CH_3 group, as indicated by the appearance of a band at 7.36 μ and the corresponding large decrease of the *exo*-methylene band at 11.23 μ. Absorption bands associated with the disubstituted dimethyl maleate group (5.82, 6.10 μ) were still present. The NMR data (τ values: 3.06, 6.25, 6.41, 7.2, 8.32, 9.17) and the infrared spectrum are consistent with structure VIII.

CF_3NO Diels-Alder adduct X *or* XI. Spirodi-*o*-xylylene (5 g.) and nitrosotrifluoromethane (1.7 g.) were sealed at −78° in a 25-cc. evacuated ampoule. The mixture was allowed to react heterogeneously at room temperature with continuous rocking for 3 days. During this time the characteristic blue color associated with nitrosotrifluoromethane disappeared completely from the gas phase. The reaction mixture was dissolved in heptane and then chilled to −78°. A white solid precipitated from solution. The precipitate (1.3 g., m.p. 130–140°) was purified by recrystallization from a methanol water solution to afford the adduct in the form of white needles (m.p. 142.5–143.0°).

Anal. Calcd. for $C_{17}H_{16}ONF_3$: C, 66.46; N, 4.56; F, 18.55; mol. wt. 307. Found: C, 66.7; N, 4.38; F, 18.4; mol. wt. 311.

Its infrared spectrum (bands at 11.13 μ for *exo*-methylene; bands 6.25, 6.33, 6.69 μ and in the region 13.1–13.35 μ for *o*-xylene group; strong absorption 8.0–8.8 μ for nitrosotrifluoromethane) and its NMR data (Table I) are consistent with structures X or XI.

Acknowledgment. The author is indebted to Dr. G. V. D. Tiers for interpretation of the nuclear magnetic resonance data, to Dr. J. J. McBrady for interpretation of the infrared spectra and to the Analytical Section of Minnesota Mining and Manufacturing Company for the elemental analyses.

ST. PAUL 19, MINN.

(13) The NMR data refer to τ values as described by G. V. D. Tiers, *J. Phys. Chem.*, **62**, 1151 (1953).

Ring-Expansion of Pyrrole and Indole

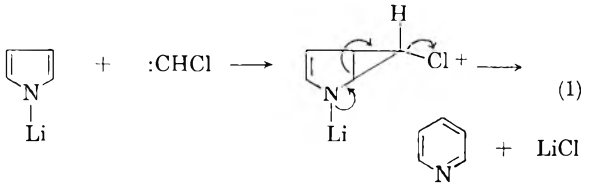
GERHARD L. CLOSS AND GERALD M. SCHWARTZ

Received January 20, 1961

The formation of halogen-substituted ring-expansion products in the Reimer-Tiemann reaction of pyrrole and indole with haloforms is well known.[1] There can be little doubt that these reactions involve the intermediate formation of dihalocarbenes[2] which are known to be generated from haloforms in basic reaction media.[3]

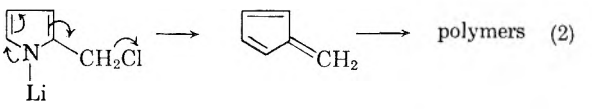
Electrophilic addition of the carbene to the double bond of the heterocycle may lead to a hypothetical bicyclic intermediate which can rearrange with loss of halide ion to form the halogenated six-membered aromatic system. Methylene halides are known to be unreactive under Reimer-Tiemann conditions, the only exception being methylene iodide which produces traces of pyridine on reaction with pyrrole and sodium ethoxide.[4] This observation is readily understood in terms of a carbene mechanism, since much a stronger base than aqueous alkali hydroxide is required to effect α-elimination from methylene halides Recent work in this laboratory has shown that chlorocarbene can be generated *via* α-elimination from methylene chloride when such strong bases as alkyllithium compounds are employed.[5] It was of interest to investigate the reaction of this carbene with pyrrole and indole, ring expansion of which would lead to pyridine (sequence 1) and quinoline, respectively.

$$CH_3Li + CH_2Cl_2 \longrightarrow :CHCl + CH_4 + LiCl$$



(1)

When a solution of methyllithium in diethyl ether was slowly added to a solution of pyrrole in methylene chloride, 32% of pyridine was isolated from the reaction mixture. Similarly, when indole was used as the substrate, quinoline was found in 13% yield. Both reactions were accompanied by the formation of large amounts of polymers, and no other products could be identified. The absence of substitution products, which predominate in the Reimer-Tiemann reaction, is readily understood considering that chloromethylpyrrole and 3-chloromethylindole will not survive the reaction conditions. Instead, elimination of lithium chloride can be expected to convert these compounds into polymeric materials (sequence 2).



(2)

EXPERIMENTAL

Reaction of pyrrole with methylene chloride and methyllithium. A solution of methyllithium (0.4 mole) in diethyl ether (235 ml.) was added with vigorous stirring to a solution of pyrrole (7.0 g.; 0.104 mole) in methylene chloride. The addition was carried out under a protective atmosphere of nitrogen, and the temperature was maintained at 25°. After the addition was complete (2 hr.) the reaction mixture was hydrolyzed with ice water and the polymeric material removed by filtration over cellulose powder. The solution was acidified and nonbasic material was extracted with ether. The aqueous layer was then made basic, saturated with potassium carbonate and exhaustively extracted with ether. The combined ether extracts were dried with potassium carbonate and the solvent was distilled off over a Vigreux column. The residue was distilled over a micro Vigreux column. Pyridine (2.60 g.; 0.033 mole; 32%) was collected between 114 and 114.5° and was identified through its infrared spectrum and mixed melting point of its picrate with an authentic sample (m.p. 162–163°).

A similar run in which the ratio of pyrrole to methyllithium was 1:3 gave 24% of pyridine.

Reaction of indole with methylene chloride and methyllithium. A solution of methyllithium (0.4 mole) in diethyl ether (230 ml.) was added with vigorous stirring to a solution of indole (12 g.; 0.1 mole) in methylene chloride. The addition was carried under nitrogen and the temperature was held at 25 to 30°. After the addition was complete (2 hr.) the reaction mixture was worked up in the same manner as described for the reaction of pyrrole with methyllithium and methylene chloride. Quinoline (1.7 g.; 0.013 mole; 13%) was identified by its infrared spectrum and mixed melting point of its picrate with an authentic sample (207–209°).

Acknowledgment. We are indebted to the Research Corp. for granting a research fellowship to G. M. Schwartz.

DEPARTMENT OF CHEMISTRY
THE UNIVERSITY OF CHICAGO
CHICAGO 37, ILL.

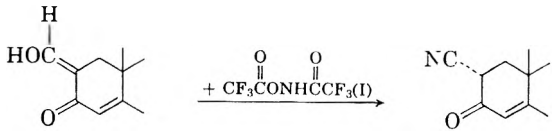
(1) H. Wynberg, *Chem. Revs.* **60**, 169 (1960).
(2) J. Hine and J. M. Van Der Veen, *J. Am. Chem. Soc.*, **81**, 6446 (1959).
(3) J. Hine, *J. Am. Chem. Soc.*, **72**, 2438 (1950).
(4) M. Dennstedt and J. Zimmerman, *Ber.*, **18**, 3316 (1885); G. L. Ciamician, *Ber.*, **37**, 4201 (1904); E. R. Alexander, A. B. Herrick, and J. M. Roder, *J. Am. Chem. Soc.*, **72**, 2760 (1950).
(5) G. L. Closs and L. E. Closs, *J. Am. Chem. Soc.*, **82**, 5723 (1960).

Communications TO THE EDITOR

Synthesis of Certain Steroidal α-Cyano Ketones

Sir:

We wish to report the synthesis of certain steroid hormones substituted at C-2 or C-16 with the cyano group. These compounds were prepared from the corresponding 2- or 16-hydroxymethylene steroid derivatives by application of the method of Pomeroy and Craig,[1] whereby an aldehyde is converted to a nitrile through reaction with *O,N*-bis-(trifluoroacetyl)hydroxylamine (I). Thus, treatment of 2-hydroxymethylenetestosterone[2] with two equivalents[3] of I for two hours in refluxing benzene containing pyridine afforded 70% 2α-cyanotestosterone trifluoroacetate [m.p. 212–217°; $(\alpha)_D$ + 83.3°; λ_{max} 242 mμ (ε 16,400)].[4] Hydrolysis gave *2α-cyanotestosterone (64%)* [*m.p. 155–156°; $(\alpha)_D$* +119°; λ_{max} 242 mμ (ε 15,600)].



In a similar manner, *2 α-cyanoprogesterone* [m.p. 193–195°; $(\alpha)_D$ + 212°; λ_{max} 242 mμ (ε 16,300)], *2α-cyanodeoxycorticosterone* [m.p. 183–184°; $(\alpha)_D$ + 208°; λ_{max} 242 mμ (ε 15,280)], *2α-cyanohydrocortisone* [m.p. 235–237°, $(\alpha)_D$ + 172° (*c* 0.26 in methanol); λ_{max} 243 mμ (ε 14,330)], *2α-cyanocortisone*[5] [m.p. 246–247°; $(\alpha)_D$ +194° (dioxane); λ_{max} 235 mμ (ε 18,500)], and *2α-cyano-9α-fluoro-11β,21-dihydroxy-16α, 17α-isopropylidenedioxy-4-pregnene-3,20-dione* [m.p. 293–296°; $(\alpha)_D$ +132° (acetone); λ_{max} 238 mμ (ε 17,300)] were prepared by the reaction of I with 2-hydroxymethylene-progesterone 20-ethylene ketal [m.p. 160–164°; $(\alpha)_D$ +42 4°], 2-hydroxymethylenedeoxycorticosterone 20-ethylene ketal [m.p. 191–192°; $[\alpha]_D$ +41.2°], 2-hydroxymethylenehydrocortisone 20-ethylene ketal [m.p. 233–236°; $(\alpha)_D$ +47.1°],[6] 2-hydroxymethylene-17α,20;20,21-bismethylenedioxy-4-pregnene-3,11-dione[5] [m.p. 206–209° $(\alpha)_D$ +9.2°] and 9α-fluoro-11β-hydroxy-2-hydroxymethylene-16α,17α-isopropylidenedioxy-21-(tetrahydropyran-2-yloxy)-4-pregnene-3,20-dione [m.p. 125–128°; $(\alpha)_D$ +68.5°], respectively, followed by acid-catalyzed hydrolysis of the side-chain blocking groups. The requisite 2-hydroxymethylene derivatives were prepared in the usual manner[2] by formylation with sodium hydride and ethyl formate of progesterone 20-ethylene ketal,[7] deoxycorticosterone 20-ethylene ketal [m.p. 163–165°, prepared from the corresponding 21-acetate[8]], hydrocortisone 20-ethylene ketal,[9] 17α,20;20,21-bismethylenedioxy-4-pregnene-3,11-dione[10] and 9α-fluoro-11β-hydroxy-16α,17α-isopropylidenedioxy-21-(tetrahydropyran-2-yloxy)-4-pregnene-3,20-dione[11] respectively.

The introduction of the 2-cyano group (λ_{max} 4.43–4.45 μ) results in a hypsochromic shift of the 3-carbonyl band (to 5.90–5.95 μ) in the infrared and does not affect the location of the maximum of the Δ^4-3-keto chromophore in the ultraviolet. The differences in molecular rotation between the 2-cyano compounds and the respective parent compounds are in the range of +15 to +81. These values are in general agreement with the effect on molecular rotation caused by substitution of halogen,[12] hydroxy,[13] acetoxy,[13] and methyl[14] groups at the 2 α-position.[15] In view of the foregoing, it is concluded that the various 2-cyano steroids are most probably in the α (equatorial) configuration.

(1) J. H. Pomeroy and C. A. Craig, *J. Am. Chem. Soc.*, **81**, 6340 (1959).

(2) F. L. Weisenborn, D. C. Remy, and T. L. Jacobs, *J. Am. Chem. Soc.*, **76**, 552 (1954).

(3) In general it was found that, under these conditions, I will effect trifluoroacetylation of accessible hydroxy groups such as the 17β-hydroxy group in testosterone or the 21-hydroxy group in hydrocortisone 20-ethylene ketal, but will not attack the 11β- or the 17α-hydroxy groups of the latter compound.

(4) M.p., corrected; $[\alpha]_D$ in chloroform unless stated otherwise, *c* approx. 0.5 to 1.5; infrared spectra in potassium bromide disks and ultraviolet spectra in methanol. Combustion analysis values for all new compounds were satisfactory.

(5) Prepared from 2α-cyanocortisone BMD. Recently J. A. Zderic et al. [Chem. & Ind., 1625 (1960)] reported the preparation of 2α-cyanocortisone BMD from 2-hydroxymethylenecortisone BMD *via* alkaline treatment of the BMD derivative of 4-pregnene-[2,3-d]isoxazole-17α,21-diol-11,20-dione [(BMD = 17α, 20; 20, 21 (bismethylenedioxy)].

(6) Australian Patent Specifications No. 23,672, May 12, 1956, assigned to Merck and Co., Inc.

(7) M. Gut, *J. Org. Chem.*, **21**, 1327 (1956).

(8) F. Sondheimer and Y. Klibansky, *Tetrahedron*, **5**, 15 (1959).

(9) H. M. Kissman, A. M. Small, and M. J. Weiss, *J. Am. Chem. Soc.*, **82**, 2312 (1960).

(10) R. E. Beyler, F. Hoffman, and L. H. Sarett, *J. Am. Chem. Soc.*, **82**, 178 (1960).

(11) L. J. Lecson and J. Weidenheimer, *J. Pharm. Sci.*, **50**, 86 (1961).

(12) B. Ellis and V. Petrow, *J. Chem. Soc.*, 1179 (1956).

(13) G. Rosenkranz, O. Mancera, and F. Sondheimer, *J. Am. Chem. Soc.*, **77**, 145 (1955).

(14) H. J. Ringold and G. Rosenkranz, *J. Org. Chem.*, **21**, 1333 (1956).

(15) The cyano group at C-6 has an effect on molecular rotation similar to that caused by the above groups [see A. Bowers, E. Denot, M. B. Sánchez, L. M. Sánchez-Hidalgo, and H. J. Ringold, *J. Am. Chem. Soc.*, **81**, 5233 (1959)].

By the same general method, 16-hydroxymethylene-3-ethylenedioxy-5-androsten-17-one [m.p. 203–206°; $(\alpha)_D$ +26.8°], prepared from 3-ethylenedioxy-5-androsten-17-one,[16] gave the corresponding 16 ξ-cyano derivative [m.p. 240–242°; $(\alpha)_D$ +4.3° (±21°, *c* 0.23)] which was converted to 16ξ-cyanotestosterone [m.p. 218–219°; $(\alpha)_D$ +88.5°; λ_{max} 240 mμ (ε 16,170)] by lithium borohydride reduction and acid-catalyzed removal of the ring-A blocking group. 16-Hydroxymethyleneestrone 3-methyl ether[17] and I yielded 16ξ-cyanosterone 3-methyl ether [m.p. 138–148°; $(\alpha)_D$ +189°] which on subsequent reduction with lithium borohydride afforded 16ξ-cyanoestradiol 3-methyl ether [m.p. 197–200°; $(\alpha)_D$ +54°].

The results of the as yet incomplete biological evaluation of these compounds will be reported in a forthcoming paper. No outstanding endocrinological activities have been discovered thus far.

ORGANIC CHEMICAL RESEARCH SECTION
LEDERLE LABORATORIES DIVISION
AMERICAN CYANAMID CO.
PEARL RIVER, N. Y.

HENRY M. KISSMAN
ARLENE SMALL HOFFMAN
MARTIN J. WEISS

Received March 13, 1961

(16) H. J. Dauben, Jr., B. Löken, and H. J. Ringold, *J. Am. Chem. Soc.*, **76**, 1359 (1954).

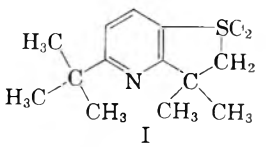
(17) J. C. Bardhan, *J. Chem. Soc.*, 1848 (1936).

Reactivity of 2,6-Di-*t*-butylpyridine Toward Sulfur Trioxide at Elevated Temperature

Sir:

It has been known for several years that 2,6-di-*t*-butylpyridine can be sulfonated with sulfur trioxide at low temperature.[1] In an extensive investigation of the reactivity of 2,6-dialkylpyridines one of us (v. d. Pl.), together with den Hertog, has shown that during this reaction the sulfonic acid group entered the 3-position,[2-4] as in the sulfonation of pyridine below 300°. Since sulfonation of pyridine above 300° leads to the formation of pyridine-4-sulfonic acid and 4-hydroxypyridine, together with the 3-sulfonic acid,[5] we also studied the behaviour of 2,6-di-*t*-butylpyridine toward sulfur trioxide at elevated temperatures.

When 2,6-di-*t*-butylpyridine was heated with sulfur trioxide at 240–250° for fifteen hours in a sealed tube, neither 2,6-di-*t*-butylpyridine-4-sulfonic acid nor 2,6-di-*t*-butylpyridone-4 was formed. Instead, together with unchanged 2,6-di-*t*-butylpyridine (30–35%) and the 3-sulfonic acid (30–35%), a compound was isolated (15–20%) melting at 140–141°. It was insoluble in water but easily soluble in ether and ethanol. From elemental analysis and molecular weight determination its composition was established as $C_{13}H_{19}NO_2S$. *Anal.* Calcd. for $C_{13}H_{19}NO_2S$: C, 61.62; H, 7.56; N, 5.53; S, 12.66; mol. wt. 253. Found: C, 61.9; H, 7.4; N, 5.5; S, 12.1; mol. wt. (according to Rast) 245. Taking into account its composition, mode of formation and the fact that the compound could not be hydrolyzed in an alkaline medium, it was considered to be best represented by structure I,[4] 2,3-dihydro-3,3-dimethyl-5-*t*-butylthieno[3,2-*b*]pyridine 1-dioxide.



I

We now wish to report that this conclusion was correct. The infrared spectrum of I in chloroform shows two strong bands at 1134 cm.$^{-1}$ and 1316 cm.$^{-1}$, both indicating the presence of a sulfone group in the molecule.[6] That no rearrangement of the *t*-butyl group occurred during heating of the 2,6-di-*t*-butylpyridine with sulfur trioxide was established by considering the NMR spectrum of I (internal reference tetramethylsilane, solvent tetrachloromethane, 60 mc., magnetic field approximately 14,100 gauss). In this spectrum two peaks were observed with τ-values,[7] 2.38 and 2.88, both peaks being characterized by doublet structures with coupling constants J = 8 c.p.s. The τ-values agree with those given for the β- and γ-protons of the pyridine nucleus.[8] The coupling constants, J = 8 c.p.s. also affirm the presence of both β- and γ-protons in the pyridine nucleus, being in good agreement with $J_{\beta\gamma}$ = 7.35 c.p.s. given for 2,3-substituted pyridines.[9] These data exclude the possibility of an α-proton being present in the pyridine nucleus. Further, the NMR spectrum shows peaks at τ-values 6.74, 8.45, and 8.63, attributed, respectively, to the proton resonance peaks of the methylene-, the two methyl groups, and the *t*-butyl group. The intensity ratio of these three peaks, 2:6.1:9, supports these assignments. The paramagnetic shift of the protons of the methylene group is due to the deshielding by the adjacent electron-withdrawing sulfone group.

(1) H. C. Brown and B. Kanner, *J. Am. Chem. Soc.*, **75**, 3865 (1953).

(2) H. C. van der Plas and H. J. den Hertog, *Chem. Weekblad.* **53**, 560 (1957).

(3) H. C. van der Plas and H. J. den Hertog, *Tetrahedron Letters*, No. 1, 13 (1960).

(4) H. C. van der Plas, Thesis, Amsterdam, 1960.

(5) H. J. den Hertog, H. C. van der Plas, and D. J. Buurman, *Rec. Trav. Chim.*, **77**, 963 (1958).

(6) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley and Sons, Inc., New York, N. Y., 1958, page 360.

(7) G. V. D. Tiers, *J. Phys. Chem.*, **62**, 1151 (1958).

(8) L. H. Jackman. *Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, Pergamon Press, New York 1959, page 64.

(9) H. J. Bernstein, J. A. Pople, and W. G. Schneider, *Can. J. Chem.*, **35**, 65 (1957).

The infrared and the NMR data thus provide strong evidence for structure I. The peculiar formation of a substituted dihydro-thiophene ring from a reaction of sulfur trioxide on an alkylated aromatic compound has not previously been reported and an investigation of the mechanism of this reaction and its applicability to other compounds is being continued.

Acknowledgment. The authors are indebted to Professor Dr. H. J. den Hertog (Wageningen) for many helpful discussions and to Professor Dr. Richard H. Wiley (Louisville) for use of the NMR spectrometer.

LABORATORY OF ORGANIC CHEMISTRY
AGRICULTURAL UNIVERSITY
WAGENINGEN
THE NETHERLANDS
H. C. VAN DER PLAS[10]

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF LOUISVILLE
LOUISVILLE 8, KY.
T. H. CRAWFORD[11]

Received March 22, 1961

(10) Temporary address: University of Louisville, Louisville 8, Ky.

(11) National Science Foundation Cooperative Graduate Fellow.

Aqueous Mesitoate Electrolysis, Kolbe-Inhibited[1]

Sir:

We wish to report that the aqueous potassium 2,4,6-trimethylbenzoate fails to give typical Kolbe products on electrolysis.[2] This failure will be termed Kolbe inhibition.

Kolbe inhibition is more common in water than in organic solvents and the feature of inhibition in water is the production of oxygen with, sometimes, oxidative degradation. Certain features of structure encourage inhibition such as the presence of a double bond, a cycloalkyl group or an aromatic ring[3] near the carboxyl group.

If the published[4] mechanism is correct then benzenoid inhibition can be explained by an electron deficiency at the carboxyl group. However, Hammett and Treffers[5] showed that when benzoic acid is compared with mesitoic acid as the solute in pure sulfuric acid for freezing point lowering at high dilution, benzoic acid acquires a proton from the solvent to form two particles for every molecule of benzoic acid, while mesitoic acid gives hydroxide ion to the solvent to form four particles for every molecule of mesitoic acid. Presumably, the electron concentration at the carboxylate end of mesitoic acid could be due to the electron donation by *ortho-para* methyls, transmitted by resonance through the benzene ring. Thus, it seems possible that electrons could be withdrawn from the mesitoate ion at the anode to give the Kolbe reaction. Attempted Kolbe electrolysis of potassium mesitoate in water showed that during the course of reaction measurable amounts of carbon dioxide appeared in the anode gas. The electrolyte turned dark with no oil or solid separating, except a minute amount of yellow ether-insoluble material judged polymeric. Absence of other insoluble material negates the formation of any hydrocarbons RR, (R minus H), or mesityl mesitoate, RCOOR. As ROH is a frequent Kolbe product, mesitol was sought in the dark electrolyte. Conventional organic qualitative chemical analysis yielded negative results.

According to Porter and Thurber,[6] mesitol is oxidized by silver oxide to give a quinone free radical of the mesitol, which by proton bonding with a molecule of mesitol gives an analogue of quinhydrone. It is conceivable that the electrolysis of mesitoic acid should yield such a quinhydrone-type organic compound by anodic oxidation if ArOH is present.

Isolation of this compound was attempted without success. Polarographic analysis shows no similarity between the chemically oxidized and the electrolyzed compounds.

We therefore conclude that ring-rupture by anodic oxidation accounts for the carbon dioxide and polymer, and that mesitoic acid is aromatic-inhibited in water. We hypothesize that either carboxylate electron congestion does not occur upon this acid in aqueous solution, or that electron unavailability at the carboxyl is not the cause of benzenoid inhibition. The former idea is supported by the fact that the ionization constant of mesitoic acid is not much lower than that of benzoic acid, both in water at 25°; methyl electron-donation should reduce extent of proton loss. Steric hindrance to carboxyl-and-ring planarity can reasonably account for the lack of electronic transmission, but requires a different explanation for the Hammett[5] results. Perhaps the steric hindrance would tend to push off the hydroxyl group but at the same time prevent the carboxylate ion from getting close to the anode.

DEPARTMENT OF CHEMISTRY
MONMOUTH COLLEGE
MONMOUTH, ILL.
TIMOTHY G. LEE
FLOYD RAWLINGS
BENJAMIN T. SHAWVER
GARRETT W. THIESSEN

Received March 27, 1961

(1) Acknowledgment is made to the National Science Foundation, Contract No. G5244.

(2) M. J. Allen, *Organic Electrode Processes*, Reinhold Publishing Corporation, New York, 1958, pp. 97–102.

(3) F. Fichter and T. Holbro, *Helv. Chim. Acta*, **20**, 333 (1937).

(4) C. L. Wilson and W. T. Lippincott, *J. Amer. Chem. Soc.*, **78**, 4290 (1956).

(5) H. P. Treffers and L. P. Hammett, *J. Amer. Chem. Soc.*, **59**, 1708 (1937).

(6) C. W. Porter and F. H. Thurber, *J. Amer. Chem. Soc.*, **43**, 1194 (1921).

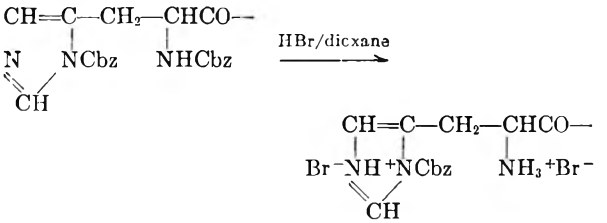
New Method for Synthesis of Peptides Containing Histidine

Sir:

In recent years it has been suggested that a histidine residue occupies a site of the biological activity in some naturally occurring peptides and proteins. Synthesis of histidine peptides is, therefore, very important for the study of protein biochemistry. However, the synthetic procedure has not been substantially improved for lack of the simple and satisfactory method to protect selectively the imidazole function of histidine.[1]

The purpose of this communication is to describe a new method for the synthesis of peptides containing histidine by selective blocking of the imidazole ring with a carbobenzoxy group.

Akabori *et al.*[2,3] have reported that $N(\alpha)$,N(Im)-dicarbobenzoxyhistidine is an excellent starting material in the synthesis of histidyl peptides. We have now found that the carbobenzoxy group linked at the imidazole-nitrogen (N(Im)-cbz) of histidine is surprisingly resistant to the treatment with hydrogen bromide in dioxane or in glacial acetic acid.



$N(\alpha)$,N(Im)-Di-cbz-histidine methyl ester hydrochloride (II) (m.p. 121–122.5° dec.[6]),[4] which was derived from di-cbz-histidine (I)[5] with thionyl chloride in methanol, and $N(\alpha)$,N(Im)-di-cbz-histidylphenylalanine methyl ester (III) (m.p. 136–137°) were treated with 35–40% (w/w)–hydrogen bromide in dioxane at room temperature for 30 min. to give N(Im)-cbz-histidine methyl ester dihydrobromide (IV) [94% yield, m.p. 167–167.5° dec., $\lambda_{max}^{CH_3OH}$ 234 mμ (ε 3140). *Anal.* Calcd. for $C_{15}H_{19}N_3O_4Br_2$: C, 38.75; H, 4.12; N, 9.04; Br, 34.4. Found: C, 37.23; H, 4.44; N, 9.43; Br, 35.03] and N(Im)-cbz-histidylphenylalanine methyl ester dihydrobromide (V) [99% yield, m.p. 126.5–127.5° dec., $\lambda_{max}^{CH_3OH}$ 234 mμ (ε 3300). *Anal.* Calcd. for $C_{24}H_{28}N_4O_5Br_2$: C, 47.15; H, 4.61; N, 9.15; Br, 26.15. Found: C, 46.87; H, 4.75; N, 9.05; Br, 26.26], respectively. These $N(\alpha)$-free derivatives are reactive to ninhydrin and their absorptions at 234 mμ were extremely depressed by adding sodium methoxide within a few minutes. This phenomenon shows the presence of an N-(Im)-cbz group.[6] On the other hand, these derivatives can react somewhat slowly with the Pauly reagent different from the disubstituted histidine analogs. This fact may show that the N(Im)-cbz group is very unstable in an alkaline medium in the absence of an $N(\alpha)$-substituting function.

IV or V could, however, be safely neutralized with dilute aqueous ammonia in methylene chloride at 0°. The resulting free esters were coupled with cbz-glycine by means of the carbodiimide method[7] to yield cbz-glycyl-N(Im)-cbz-histidine methyl ester (VI) [85% yield, m.p. 74–75.5°, $[\alpha]_D^{29}$ +24.5° (ethyl acetate), $\lambda_{max}^{CH_3OH}$ 236 mμ (ε 3755). *Anal.* Calcd. for $C_{25}H_{26}N_4O_7$: C, 60.7; H, 5.31; N, 11.3. Found: C, 60.61; H, 5.45; N, 11.43] and cbz-glycyl-N(Im)-cbz-histidylphenylalanine methyl ester(VII) [90% yield, m.p. 154–154.5°, $[\alpha]_D^{18}$ −8.6° (methanol), $\lambda_{max}^{CH_3OH}$ 236 mμ (ε 3655). *Anal.* Calcd. for $C_{34}H_{35}N_5O_8$: C, 63.7; H, 5.51; N, 10.9. Found: C, 63.69; H, 5.63; N, 10.34]. In a similar fashion we have obtained cbz-glycyl-N-(Im)-cbz-histidylleucine methyl ester (VIII) [82% yield, m.p. 152–152.5°, $[\alpha]_D^{18}$ −11.6° (methanol), $\lambda_{max}^{CH_3OH}$ 236 mμ (ε 3610). *Anal.* Calcd. for $C_{31}H_{37}N_5O_8$: C, 61.3; H, 6.14; N, 11.5. Found: C, 61.39; H, 6.31; N, 11.44], $N(\alpha)$, N(Im)-dicbz-histidyl-N-(Im)cbz-histidylphenylalanine benzyl ester(IX) [81% yield, m.p. 138–140°, $[\alpha]_D^{22}$ −17.9° (methanol), $\lambda_{max}^{CH_3OH}$ 236 mμ (ε 7830). *Anal.* Calcd. for $C_{52}H_{49}N_7O_{10}$: C, 67.1; H, 5.79; N, 10.5. Found: C, 67.05; H, 5.41; N, 10.69] and formyl-γ-methylglutamyl-N(Im)-cbz-histidylphenylalanine benzyl ester (X) [87% yield, m.p. 165–165.5° dec., $[\alpha]_D^{24}$ −12.1° (dimethylformamide), $\lambda_{max}^{CH_3OH}$ 236 mμ (ε 3415). *Anal.* Calcd. for $C_{37}H_{39}N_5O_9$: C, 63.7; H, 5.63; N, 10.02. Found: C, 63.79; H, 5.90; N, 10.36] which has a sequence contained in corticotropin and MSH. These histidine peptide derivatives (VI to X) are negative to both ninhydrin and the Pauly reagent and have moderate solubilities in common organic solvents.

The treatment of VII with hydrogen bromide/dioxane or with 2 equivalent amounts of sodium hydroxide gave glycyl-N(Im)-cbz-histidylphenyl-

(1) Benzyl [D. Theodoropoulos, *J. Org. Chem.*, **21**, 1550 (1956)] or trityl group [G. C. Stelakatos, D. M. Theodoropoulos, and L. Zervas, *J. Am. Chem. Soc.*, **81**, 2884 (1959)] has been used for the protection of the imidazole function but there are some defects for practical purposes.

(2) S. Akabori, K. Okawa, and F. Sakiyama, *Nature*, **181**, 772 (1958).

(3) F. Sakiyama, K. Okawa, T. Yamakawa, and S. Akabori, *Bull. Chem. Soc. Japan*, **31**, 926 (1958).

(4) Amino acids used are of L-configuration and all melting points are uncorrected.

(5) This could be crystallized in granules from a concentrated ethyl acetate solution [m.p. 90.5–92° dec., $[\alpha]_D^{19}$ +29.1° (ethyl acetate). *Anal.* Calcd. for $C_{22}H_{21}N_3O_6$: N, 9.93. Found: N, 9.86]. This crystal is readily soluble in methanol and from the solution is soon separated a second form of crystal containing one molecule of methanol, m.p. 105–107° dec.[3,6]

(6) A. Patchornik, A. Berger, and E. Katchalski, *J. Am. Chem. Soc.*, **79**, 6416 (1957).

(7) J. C. Sheehan and G. P. Hess, *J. Am. Chem. Soc.*, **77**, 1067 (1955).

alanine methyl ester dihydrobromide (XI) [$\lambda_{max}^{CH_3OH}$ 234 mμ (ε 3640). *Anal.* Calcd. for $C_{26}H_{31}N_5O_6Br_2$: C, 46.7; H, 4.68; N, 10.01; Br, 23.9. Found: C, 45.73; H, 4.99; N, 10.40; Br, 22.59] or cbz-glycylhistidylphenylalanine (XII) [77.5% yield, m.p. 200° dec., $[\alpha]_D^{30}$ + 15.4° (methanol). *Anal.* Calcd. for $C_{25}H_{27}N_5O_6$: C, 60.8; H, 5.52; N, 14.2. Found: C, 60.51; H, 5.65; N, 14.11], respectively. The *N*(Im)-cbz group may be removed also with catalytic hydrogenation.

From these results it has been demonstrated that *N*(Im)-cbz-histidine derivatives, which can be prepared by the simple and convenient procedure, are of potential utility as intermediates in the synthesis of histidine peptides.

Acknowledgment. The authors wish to express their sincere thanks to Professors S. Akabori and K. Narita, Institute for Protein Research, Osaka University, for kind guidance and discussions and to Dr. K. Tanaka of this laboratory for very helpful suggestions.

Biochemistry Division
Shionogi Research Laboratory
Shionogi & Co., Ltd.
192, Imafuku, Amagasaki
Hyohgo Pref., Japan

Ken Inouye
Hideo Otsuka

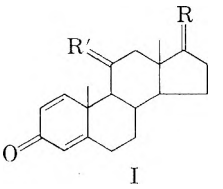
Received April 3, 1961

An Aromatization Reaction of A Cross-Conjugated Dienone System with Zinc

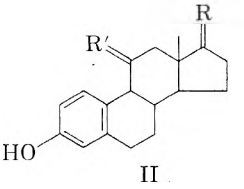
Sir:

We wish to report a new A-ring aromatization reaction of the dienone system with zinc under mild conditions. When refluxed with zinc in pyridine[1] or ethylene glycol, androstan-1,4,9(11)-triene-3,17-dione (Ia) undergoes A-ring aromatization with elimination of the angular methyl group to form Δ^9-estrone (IIa)[2] in excellent yield (75%). In a similar manner the treatment of 17α,21-dihydroxypregnan-1,4,9(11)-triene-3,20-dione acetate (Ib; 21-acetate) or its BMD derivative (Ic) in pyridine yielded, respectively, A-ring aromatic corticoids,[3] IIb 21-acetate, (yield: 35%), m.p. 210–212°, $[\alpha]_D^{20}$ +174° (dioxane), $\lambda_{max}^{CH_3OH}$ 263, 298 mμ (ε 18,000, 3,100), λ_{max}^{Nujol} 814 cm.$^{-1}$, (*Anal.* Calcd. for $C_{22}H_{26}O_5$: C, 71.33; H, 7.08. Found: C, 71.48; H, 6.98); IIb, m.p. 248–250°; $[\alpha]_D^{20}$ +176° (dioxane); IIb, 3,21-diacetate, m.p. 188–190°, $[\alpha]_D^{20}$ +136° (chloroform), or IIc (yield: 72%), m.p. 247–248°, $[\alpha]_D^{20}$ +31° (dioxane), which was converted to IIb by acetic acid hydrolysis. 3-Keto-1,4,6-triene (Id) gave Δ^6-estrone (IId)[4] (yield, 10–15%) in the same reaction.

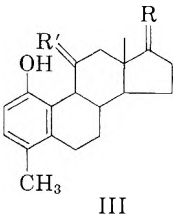
In the case of 3-keto-1,4-dienes or their C-11 substituted derivatives different rearrangement products were obtained. Treatment of Ie with zinc in pyridine provided a mixture of *p*-cresol type rearrangement product (IIIe)[5] (yield, 80%) and estrone (IIe) (yield, 4%). The 11β-hydroxy compound (If) yielded IIIf, m.p. 223–224°, $[\alpha]_D^{15}$ +249° (chloroform), $\lambda_{max}^{CH_3OH}$ 282–286 mμ (ε 2,340), methyl ether, m.p. 213–214°, $[\alpha]_D^{15}$ +303° (chloroform), which was confirmed by conversion to the IIIe methyl ether by dehydration and hydrogenation. However, the 11-keto compound (Ig) suffered rupture of C_9-C_{10} bond with concomitant A-ring aromatization to give the 9/10 seco compound (IV), m.p. 212–214°. It was identical in all respects with an authentic specimen of IV obtained from Ig by pyrolysis.[6]



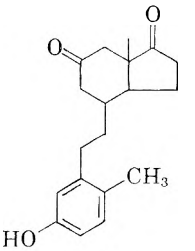
I



II



III



IV

a. R = O, R′ = H, $\Delta^{9(11)}$
b. R = α-OH, —CO—CH_2OH, R′ = H, $\Delta^{9(11)}$
c. R =  R′ = H, $\Delta^{9(11)}$
d. R = O, R′ = —H, —H, Δ^6
e. R = O, R′ = —H, —H
f. R = O, R′ = β-OH, —H
g. R = R′ = O

Santonin was converted to desmethyldesmotroposantonin (V) (yield, 40%), m.p. 223–227°, $[\alpha]_D^{20}$ +115° (chloroform), $\lambda_{max}^{CH_3OH}$ 286.5 mμ (ε 2,820), λ_{max}^{Nujol} 811 cm.$^{-1}$, NMR[7] τ, 7.60 ppm. (one benzenoid methyl) (*Anal.* Calcd. for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.10; H, 6.93), acetate, m.p. 144–146° (*Anal.* Calcd. for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61. Found: C, 70.08; H, 6.50.), by the same reaction in pyridine. The structure of V was confirmed by the palladium-charcoal dehydrogenation which led to 1-methyl-7-ethyl-

(1) Pyridine containing *ca.* 10 mole equivalents of water was used.

(2) B. J. Magerlein and J. A. Hogg, *J. Am. Chem. Soc.*, **80**, 2220 (1958).

(3) B. J. Magerlein and J. A. Hogg, *J. Am. Chem. Soc.*, **80**, 2226 (1958).

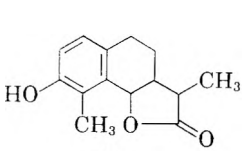
(4) St. Kaufman, J. Pataki, G. Rosenkranz, J. Romo, and C. D. Djerassi, *J. Am. Chem. Soc.*, **72**, 4531, 4534 (1950).

(5) A. S. Dreiding and A. Voltman, *J. Am. Chem. Soc.*, **76**, 537 (1954).

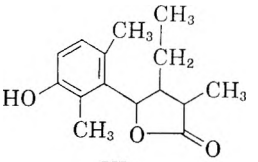
(6) B. J. Magerlein and J. A. Hogg, *Tetrahedron*, 2, 80 (1958).

(7) τ values were calculated assuming τ chloroform (solvent) = 2.75 ppm.

2-naphthol,[8] m.p. 93–94°. The reation in ethylene glycol gave the 9//10 seco compound (VI) as a solvated crystal, m.p. 100–108°, λ_{max}^{Nujol} 815 cm.$^{-1}$ NMR[7] τ, 7.69, 7.75 ppm. (two benzenoid methyl), 9.13 ppm. triplet (methyl of ethyl group). The substance after the crystal solvent is removed is an oil, $[\alpha]_D^{20}$ −25° (chloroform), $\lambda_{max}^{CH_3OH}$ 288 mμ (ε 3,000), (*Anal.* Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.26; H, 8.12), acetate, m.p. 145–150° (*Anal.* Calcd. for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.58; H, 7.61).



V



VI

Methane generated from all the reactions involving the loss of the angular methyl group, was detected by gas chromatography. As only starting material was recovered from the reaction in anhydrous pyridine, ethylene glycol or water in pyridine may be a hydrogen donor in the reaction. The treatment of the above dienone (Ie) or trienone (Ia or Id) in acetic acid with zinc[9] does not give an aromatic A-ring steroid, but a substance assumed to be a bis compound showing polyene absorption. The detailed presentation of these reactions will be published in a forthcoming report.

INSTITUTE OF APPLIED MICROBIOLOGY
THE UNIVERSITY OF TOKYO
HONGO, BUNKYO-KU,
TOKYO, JAPAN

K. TSUDA
E. OHKI
S. NOZOE
N. IKEKAWA

Received April 3, 1961

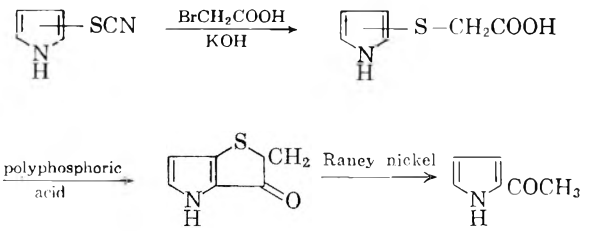
(8) T. Kariyone, T. Fukui, and T. Omoto, *Yakugakuzassi* (Tokyo), **78**, 710 (1958).

(9) The reaction of a B-ring dienone to an aromatic compound and that of santonin to the bis compound with zinc in acetic acid has been reported. D. H. R. Barton and B. R. Thomas, *J. Chem. Soc.*, 1842 (1953). K. Tsuda, E. Ohki, and J. Suzuki, *Chem. and Pharm. Bull.* **9**, 131 (1961). J. Simonsen, *The Terpenes*, Vol. III, p. 273, Cambridge Univ. Press (1952).

On the Thiocyanation of Pyrrole

Sir:

Matteson and Snyder[1] have recently claimed that thiocyanation of pyrrole with methanolic thiocyanogen at −70° or with cupric thiocyanate at 0° yields 3-thiocyanopyrrole (I) (m.p. 41.5–43°). This is rather unexpected since most reagents attack pyrroles at an unsubstituted α-position in preference to an unsubstituted β-position. They proved the structure of the thiocyanopyrrole by converting it to the (pyrrolylthio)acetic acid (II) which was ring closed to 2*H*,3*H*-thieno[3,2-*b*]pyrrole-3-one (III) and desulfurized to authentic 2-acetylpyrrole (IV)



In connection with our work on the NMR spectra of heteroaromatic compounds,[2–5] we have studied the NMR spectrum of thiocyanopyrrole and some of its derivatives. The three bands in the aromatic region of thiocyanopyrrole display the shifts[6] τ_A = 3.10, τ_B = 3.47, τ_C = 3.85 p.p.m. and the coupling constants J_{AB} = 1.5, J_{AC} = 2.9, and J_{BC} = 3.6 c/s, which prove that the compound formed is the 2- isomer. This conclusion is based on comparison of the above NMR parameters with those observed in other pyrroles[5] and in 2- and 3-thiocyanothiophenes.[2] Furthermore, the NMR spectrum of the methylthiopyrrole obtained through the reaction of the thiocyanopyrrole with alkali and methyl iodide[1] is in agreement only with that expected for the 2- isomer (τ_A = 3.28, τ_B = 3.77, τ_C = 3.90 p.p.m., J_{AB} = 1.5, J_{AC} = 2.8, and J_{BC} = 3.4 c/s). The same methylthiopyrrole (b.p. 87–90°/17 mm., n_D^{20} 1.5730. *Anal.* Calcd. for C_5H_7NS: C, 53.06; H, 6.23; N, 12.38; S, 28.33: Found: C, 53.17; H, 6.42; N, 12.35; S, 28.25) is obtained by treating pyrrolemagnesium iodide with dimethyl disulfide and also by treating pyrrole with methylsulfenyl chloride. These results provide independent evidence that the methylthiopyrrole is the 2-isomer, as it is known that these types of reactions lead to α-substitution.[7,8]

The NMR spectrum of the aldehyde obtained through Vilsmeier formylation of the methylthiopyrrole shows that the compound formed is 2-

(1) D. S. Matteson and H. R. Snyder, *J. Org. Chem.*, **22**, 1500 (1957).

(2) S. Gronowitz, and R. A. Hoffman, *Arkiv Kemi*, **16**, 539 (1960).

(3) R. A. Hoffman and S. Gronowitz, *Arkiv Kemi*, **16**, 563 (1960).

(4) S. Gronowitz and R. A. Hoffman, *Arkiv Kemi*, **16**, 459 (1960).

(5) S. Gronowitz, A-B. Hörnfeldt, B. Gestblom, and R. A. Hoffman, *Arkiv Kemi, in press.*

(6) The NMR spectra were obtained with a Varian Associates Model V-4300b spectrometer operating at 40 Mc/s. The chemical shifts [τ-values, *cf.* G. V. D. Tiers, *J. Phys. Chem.*, **62**, 1151 (1958)] were obtained from dioxane solutions to which were added traces of piperidine in order to eliminate the complicating effects of the couplings with the *N*-hydrogens.

(7) M. S. Kharasch and O. Reinmuth, *Grignard Reaction of Nonmetallic Substances*, Prentice-Hall, Inc., New York, N. Y., 1954 pp. 75 ff.

(8) A. H. Corwin in R. C. Elderfield, ed., *Heterocyclic Compounds*, Vol. I, John Wiley & Sons, Inc., New York, N. Y., 1950, Chapter VI.

methylthio-5-pyrrolealdehyde (m.p. 105–106°, τ_{CHO} = 0.69, τ_3 = 3.78, τ_4 = 3.12, τ_{SCH} = 7.59 p.p.m., J_{34} = 3.8 c/s. *Anal.* Calcd. for C_6H_7NOS C, 51.04; H, 4.99; N, 9.92; S, 22.71: Found: C, 51.41; H, 5.15; N, 10.08; S, 22.56), thus giving further evidence that the original methylthiopyrrole is the 2- isomer. Additional evidence against preferential β-thiocyanation in pyrroles is obtained from the fact that 2-methylpyrrole yields 5-thiocyano-2-methylpyrrole (m.p. 65.5–66°, τ_3 = 4.13, τ_4 = 3.56 p.p.m., $J_{CH_3\text{-}3}$ = 0.80, $J_{CH_3\text{-}4}$ = 0.35, J_{34} = 3.55 c/s. *Anal.* Calcd. for $C_6H_6N_2S$: C, 52.15; H, 4.38; N, 20.28; S, 23.19: Found: C, 52.22; H, 4.39; N, 20.21; S, 22.86:) upon thiocyanation with cupric thiocyanate, the NMR evidence for its structure being based on the values of the chemical shifts and ring-coupling constants, in addition to the side-chain couplings.[3]

Since the structure of III is proved beyond any doubt by Snyder *et al.*[1,9] and since it is very improbable that any rearrangement occurred in the transformation of the thiocyanopyrrole to methylthiopyrrole or (pyrrolylthio)acetic acid, the discrepancy between our results and those of Matteson and Snyder regarding the structure of the thiocyanopyrrole must be ascribed to a rearrangement during the cyclization of (2-pyrrolylthio)acetic acid with polyphosphoric acid to III. Rearrangements during treatment with polyphosphoric acid, although not analogous to that found here, have been observed by others.[10,11]

A detailed account of the observations reported here will be published in *Arkiv Kemi*.

Acknowledgments. Financial support from the Swedish Natural Science Research Council and from the Swedish Technical Research Council is acknowledged.

INSTITUTE OF CHEMISTRY
INSTITUTE OF PHYSICS
UNIVERSITY OF UPPSALA
UPPSALA, SWEDEN

SALO GRONOWITZ
ANNA-BRITTA HÖRNFELDT
BO GESTBLOM
RAGNAR A. HOFFMAN

Received April 17, 1961

(9) H. R. Snyder, L. A. Carpino, J. F. Zack, Jr., and J. F. Mills, *J. Am. Chem. Soc.*, 79, 2556 (1957).

(10) J. E. Banfield, W. Davies, N. W., Gamble, and S. Middleton, *J. Chem. Soc.*, 4791 (1956).

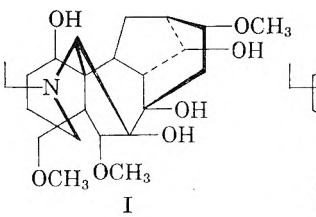
(11) W. Davies and S. Middleton, *Chem. & Ind.*, 599 (1957).

On Anhydrodiacetyllucaconine (Diacetyldelcosine,[1] M.P. 159–161°) and Its Derivatives

Sir:

Previously, it was shown that an aconite alkaloid, lucaconine (I) ($C_{24}H_{39}O_7N$), gave anhydrodiacetyllucaconine (II) ($C_{28}H_{41}O_8N$) on treatment with acetyl chloride.[4] Compound II has been found to have a ketone carbonyl group formed with elimination of one mole of water, and to absorb one mole of hydrogen without reduction of the carbonyl group.[5] Moreover, it has been shown that this dehydration takes place between two tertiary hydroxyl groups of compound I.[5]

On the other hand, on the basis of the biogenetical viewpoint as well as experimental results, Marion and his co-workers[6–8] have pointed out that delcosine[1] (lucaconine) (I) probably possesses the same carbon-nitrogen nucleus as lycoctonine, and also that this base is represented by the structure I shown below. In the belief that their conclusions



I

II. R = H_2, R′ = R″ = Ac
III. R = O, R′ = R″ = H

are quite reasonable, the present authors now would like to propose structures II and III for anhydrodiacetyllucaconine[4] and anhydrooxolucaconine (III),[4] respectively. Compound III has previously been obtained from both compound II and oxolucaconine through two steps.[4] The mechanism of the above dehydration is considered to be analogous to that of the dehydration of oxolycoctonine or demethyleneoxodelpheline.[9]

The ultraviolet absorption spectrum of compound III in methanol shows a maximum at 301 mμ (log ε 2.01) while compound II manifests a maximum at 237 mμ (log ε 3.20). The limiting structure IIa of compound II seems to give a good explanation of the marked difference between these two absorption bands. A similar phenomenon was observed and interpreted in the case of some delphinine and neoline derivatives.[10]

(1) It has been shown that lucaconine is identical with delcosine,[2] and therefore anhydrodiacetyllucaconine is identical with diacetyldelcosine (m.p. 159–161°) obtained by Marion *et al.*.[3] The name "lucaconine" should be revised to "delcosine."

(2) T. Amiya and T. Shima, in preparation.

(3) W. I. Taylor, W. E. Walles, and L. Marion, *Can. J. Chem.*, 32, 780 (1954).

(4) S. Furusawa, *Bull. Chem. Soc. Japan*, 32, 399 (1959).

(5) T. Amiya and T. Shima, *Bull. Chem. Soc. Japan*, 31, 1083 (1958).

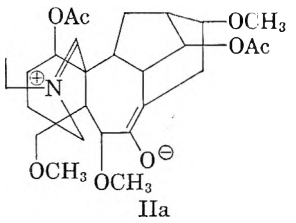
(6) V. Skaric and L. Marion, *J. Am. Chem. Soc.*, 80, 4434 (1958); V. Skaric and L. Marion, *Can. J. Chem.*, 38, 2433 (1960).

(7) R. Anet, D. W. Clayton, and L. Marion, *Can. J. Chem.*, 35, 397 (1957).

(8) R. Anet and L. Marion, *Can. J. Chem.*, 36, 766 (1958).

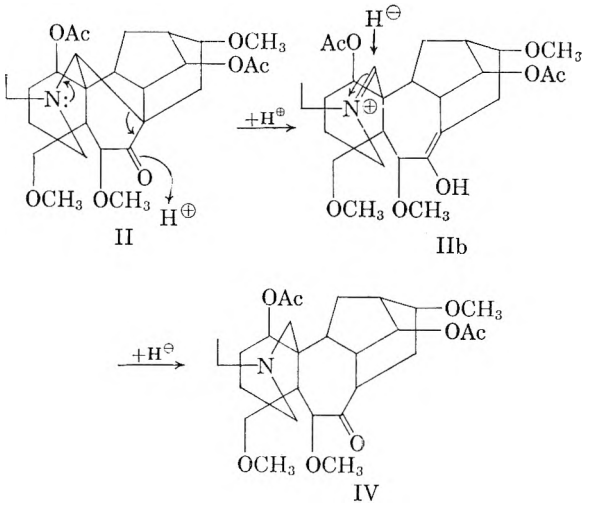
(9) E. S. Stern, *The Alkaloids, Chemistry and Physiology*, Vol. VII, R. H. F. Manske, ed., Academic Press Inc., New York, 1960, p. 473.

(10) K. Wiesner, H. W. Brewer, D. L. Simons, D. R. Babin, F. Bickelhaupt, J. Kallos, and T. Bogri, *Tetrahedron Letters*, No. 3, 17 (1960).



IIa

Furthermore, the formation of anhydrodihydrodiacetyllucaconine (IV) ($C_{28}H_{43}O_8N$)[5] from compound II by hydrogenation, may be expressed in the following way (II → IIb → IV) (Scheme A). The ultraviolet absorption spectrum of compound IV shows only end absorption. Compound III was recovered unchanged after being subjected to the conditions leading to the hydrogenation of compound II.



II IIb IV

Scheme A

Acknowledgment. The authors are grateful to Professor Harusada Suginome, President of Hokkaido University, for his unfailing kindness in encouraging this work.

DEPARTMENT OF CHEMISTRY
FACULTY OF SCIENCE
HOKKAIDO UNIVERSITY
SAPPORO, JAPAN

TAKASHI AMIYA
TAKEO SHIMA[11]

Received May 1, 1961

(11) Present address: Teikoku Rayon Research Laboratory, Iwakuni City, Japan.

Preparation of α-Diazo Ketones

Sir:

The preparation of α-diazo ketones by the oxidation of the monohydrazones of α-keto aldehydes or α-diketones has long been known.[1] The oxidizing agent most frequently used has been mercuric oxide,[1] often in the presence of bases[2]; silver oxide,[3] "mercuric acetamide,"[4] and mercuric trifluoroacetate[5] have also been used. An excellent variant of this method has been developed by Cava, Litle and Napier,[6] who prepared α-diazo ketones by the action of sodium hydroxide on the monotosylhydrazones of α-diketones. We now report on two new methods for the oxidation of the monohydrazones of α-diones which appear to have considerable general utility.

(i) "Activated" manganese dioxide[7] rapidly oxidizes the hydrazones in chloform solution to the corresponding α-diazo ketones in high yield. In a typical experiment 1.00 g. of 1-mesitylglyoxal 2-hydrazone[8] was dissolved in 15 ml. of chloroform (reagent grade) and to the solution was added 1.5 g. of "activated" manganese dioxide; the mixture was stirred for 1 hr. at room temperature, with initial cooling to abate the exothermic reaction. It was then filtered and the solvent was evaporated to give a quantitative yield of 2-diazo-2′,4′,6′-trimethylacetophenone, m.p. 59–61° dec. The infrared spectrum of this product was indistinguishable from that of a recrystallized sample, m.p. 59–61° dec., of the authentic diazo ketone prepared by oxidation of the hydrazone with mercuric oxide.[8] The latter method gives a less pure crude product in 75% yield. Manganese dioxide has also been used for the preparation of 2-diazopropiophenone, 2-diazo-2′,4′,6′-trimethylpropiophenone, 2-diazo-2-phenylacetophenone (azibenzil), 3-diazo-2-butanone, 3-diazo-D-camphor, and 2-diazo-1,5,5-trimethylbicyclo[2.2.1]heptan-3-one from the corresponding hydrazones; the scale varied from 0.060 g. to 10 g. of hydrazone and the weight of manganese dioxide used was *ca.* 1.5 times that of the hydrazone. In every case the diazo ketone was obtained directly from the reaction mixture in 90–100% yield and was free from significant amounts of impurities as vouchsafed by its infrared spectrum.[9]

(ii) α-Diazo ketones may also be prepared by oxidation of the corresponding hydrazones in methanolic solution containing sodium hydroxide with calcium hypochlorite. In a typical experiment, 0.100 g. of D-camphorquinone monohydrazone[4] was dissolved in 5 ml. of methanol and 1 ml. of 0.05*M* aqueous sodium hydroxide was added, the solution was stirred with 0.250 g. of calcium hypo-

(1) T. Curtius and K. Thun, *J. prakt. Chem.*, [2] **44**, 171 (1891).

(2) *Cf.* C. D. Nenitzescu and E. Solomonica, *Org. Syntheses*, Coll. Vol. II, 496 (1943).

(3) O. Diels and K. Pflaumer, *Ber.* **48**, 223 (1915).

(4) M. O. Forster and A. Zimmerli, *J. Chem. Soc.*, **97**, 2156 (1910).

(5) M. S. Newman and A. Arkell, *J. Org. Chem.*, **24**, 385 (1959).

(6) M. P. Cava, R. L. Litle, and D. R. Napier, *J. Amer. Chem. Soc.*, **80**, 2257 (1958).

(7) J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen, and T. Walker, *J. Chem. Soc.*, 1094 (1952).

(8) R. C. Fuson, L. J. Armstrong, and W. J. Shenk, Jr., *J. Amer. Chem. Soc.*, 66, 964 (1944).

chlorite (Baker, 30–35% available chlorine) for 2 hr. The mixture was added to 10 ml. of ice water and then extracted with chloroform. The extract was washed with saturated brine, dried, and evaporated to give 0.079 g. (80%) of 3-diazo-D-camphor with an infrared spectrum indistinguishable from that of an authentic sample, m.p. 74–75°.[10] A single recrystallization of the crude product from pentane gave an 80% recovery of material, m.p. 73–75°. This method has also been applied successfully to the preparation of 2-diazo-1,5,5-trimethylbicyclo[2.2.1]heptan-3-one, 2-diazo-2′,4′,6′-trimethylacetophenone, 2-diazo-2′,-4′,6′-trimethylpropiophenone, and azibenzil from the corresponding hydrazones. In every case the diazo ketone was obtained directly from the reaction mixture in 75–85% yield and was free from significant amounts of impurities.

In those cases where comparisons have been made, the use of manganese dioxide or calcium hypochlorite has been found to be preferable to that of mercuric oxide. In general, manganese dioxide appears to be the reagent of choice, although the use of calcium hypochlorite may be advantageous on occasion because of the concomitant solvent system.

DEPARTMENT OF CHEMISTRY
HARVARD UNIVERSITY
CAMBRIDGE 38, MASS.

HARRY MORRISON[11]
SAMUEL DANISHEFSKY
PETER YATES[12]

Received May 2, 1961

(9) Earlier mention has been made in the literature of the oxidation of simple hydrazones with manganese dioxide. M. Z. Barakat, M. F. Abdel-Wahab, and M. M. El-Sadr [*J. Chem. Soc.*, 4685 (1956)] observed the formation of a violet color during the oxidation of benzophenone hydrazone with manganese dioxide ("precipitated") which they attributed to the formation of diphenyldiazomethane. W. Schroeder, U.S. Patent **2,710,862** [*Chem. Abstr.*, **50**, 6510 (1956)], has reported that manganese dioxide is "much less effective" than silver oxide for the oxidation of substituted benzophenone hydrazones to the corresponding diazo compounds. Subsequently, "activated" manganese dioxide has been used successfully for the oxidation of this type of compound: E. J. Corey and L. H. Haefele, private communication.

(10) J. Bredt and W. Holz, *J. prakt. Chem.*, **95**, 148 (1917).

(11) Pre-doctoral Fellow of the National Institutes of Health, 1959–1961.

(12) Present address: Department of Chemistry, University of Toronto, Toronto, 5, Ontario, Canada.