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Reaction of *N*-Bromobenzamide with Allyl-1-d_2 Acetate[1]

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The reaction of *N*-bromobenzamide with allyl acetate in carbon tetrachloride has been shown to give 2,3-dibromopropyl acetate and benzamide as the major products. *N*-phenyl-*N'*-benzoylurea was also isolated but in low yield. The allylic hydrogen of the allyl acetate have been shown not to be the source of the hydrogen found to replace the bromide of the *N*-bromobenzamide by conducting the reaction with allyl-1-d_2 acetate and demonstrating that the benzamide obtained was free of deuterium. The synthesis and infrared spectra of allyl-1-d_2 alcohol, allyl-1-d_2 acetate, and benzamide-*N*,*N*-d_2 are presented.

During the course of a study concerning the reactivity of *N*-bromoamides toward unsaturated compounds, it was observed that the major products of the reaction of *N*-bromobenzamide with allyl acetate are 2,3-dibromopropyl acetate (57.4%) and benzamide (70%). The only other product identified was *N*-phenyl-*N* -benzoylurea, which was isolated in low yield.

In general, the most common course of the reaction of *N*-bromoamides and -imides with unsaturated compounds is the formation of allylic or benzylic bromides and regeneration of the parent amide or imide. The allylic bromination reaction, frequently referred to as the Wohl-Ziegler reaction,[3] has found wide synthetic applicability; particularly in conjunction with use of *N*-bromosuccinimide and *N*-bromoacetamide. Occasionally these reactions take another course resulting in the addition of bromine to the double bond of the unsaturated reactant and regeneration of the parent amide or imide.[4] A simple representation of the addition reaction fails to reveal the source of the hydrogen observed to replace the bromine of the *N*-bromoamide.

$$2\mathrm{RCONHBr} + \rangle\mathrm{C{=}C}\langle \longrightarrow 2\mathrm{RCONH_2} + \rangle\mathrm{CBrC}\langle\ \mathrm{Br}$$

This obvious discrepancy has been noted by several investigators[5] but, no satisfactory explanation of the hydrogen source has been forthcoming.

The addition reaction has variously been suggested to occur *via* free radical,[4,5a] polar,[5d] and combined heterolytic and homolytic paths.[5c] Indeed the reactions of *N*-bromoamides and -imides are so sensitive to structural and environmental influences that the diverse mechanisms postulated may well be compatible with the individual systems in reference. One common aspect of the postulated mechanisms is their failure to account for the hydrogen found to replace the bromine of of the brominating agent other than to suggest that it must be the result of a step in which an amidyl or imidyl radical abstracts hydrogen from a donor present in the reaction mixture.[4,5b,c,d] The identity of the hydrogen donor, HZ, has not

(1) (a) This research was aided through a fellowship supported by the Michigan Chemical Corporation, St. Louis, Mich. (b) Abstracted in part from the thesis submitted by F. William Millard to the School for Advanced Graduate Studies of Michigan State University in partial fulfillment of the requirements for the Ph.D. degree.

(2) Texas U. S. Chemical Co., Research Center, Parsippany, N. J.

(3) C. Djerassi, *Chem. Revs.*, **43**, 271 (1948).

(4) For a competent review of the literature of the addition reaction see R. E. Buckles, R. C. Johnson, and W. J. Probst, *J. Org. Chem.*, **22**, 55 (1957).

(5) (a) E. R. Buchman and D. R. Howton, *J. Am. Chem. Soc.*, **70**, 2517, 3510 (1948); (b) R. E. Buckles, *J. Am. Chem. Soc.*, **71**, 1157 (1949); (c) E. A. Braude and E. S. Waight, *J. Chem. Soc.*, 1116 (1952); (d) W. J. Bailey and J. Bello, *J. Org. Chem.*, **20**, 525 (1955).

$$2RCONHBr + \rangle C{=}C\langle \longrightarrow \rangle CBrCBr\langle + 2RCO\dot{N}H$$

$$RCO\dot{N}H + HZ \longrightarrow RCONH_2 + Z\cdot$$

HZ = hydrogen donor

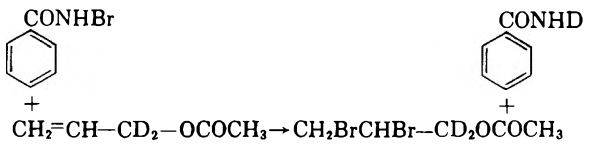
been elucidated nor have products resulting from the subsequent reaction of Z· been isolated.

For the reaction of excess allyl acetate with *N*-bromobenzamide in carbon tetrachloride as the reaction medium, the most readily available hydrogen in the system from the standpoint of abstraction by a benzamidyl radical, should be the allylic hydrogen of the unsaturated ester. This follows from a consideration of the ability of the resulting allylic radical to be stabilized through resonance. The facile formation of allylic hydroperoxides and allylic, free radical halogenations,

$$CH_2{=}CH{-}\dot{C}H{-}OCOCH_3 \longleftrightarrow \cdot CH_2{-}CH{=}CH{-}O{-}COCH_3$$

such as high temperature chlorination, testify to the relative ease of the abstraction of allylic hydrogens.

A direct experimental test of this possible explanation of the source for the unaccountable hydrogen is made possible by carrying out the addition reaction with allyl acetate in which the allylic hydrogen has been replaced with deuterium and determining if the resultant benzamide has deuterium on its nitrogen.



It has been reported[6] that attempts to reduce acrylic acid, its esters, or its salts directly in a manner suitable for the preparation of allyl-1-d_2 acetate failed due to accompanying polymerization. The deuterated ester was obtained by the addition of methyl acrylate to anthracene followed by reduction with lithium aluminum deuteride, acetylation, and pyrolysis.

In the present study the synthesis of allyl-1-d_2 acetate was achieved by reducing acrylyl chloride with lithium aluminum deuteride and acetylating the resulting deuterated allyl alcohol.

Since both allyl alcohol and allyl acetate can undergo an acid catalyzed oxotropic rearrangement,[7] resulting in an equal distribution of deuterium between the α and γ carbon atoms, it was necessary to maintain a neutral or basic medium throughout the reaction sequence. Accordingly, the lithium aluminum deuteride reduction complex was hydrolyzed with a calculated amount of water and 15% sodium hydroxide solution according to the procedure described by Amundsen and Nelson,[8] and the acetylation was carried out in the presence of pyridine after the method of Levine and Kuna who have used it to successfully acetylate allylic alcohols without isomerization.[9]

$$\rangle C{=}\overset{|}{C}{-}CD_2{-}OH \overset{H_3O^+}{\rightleftharpoons} HO{-}\overset{|}{C}{-}\overset{|}{C}{=}CD_2$$

A sample of the allyl-1-d_2 acetate thus prepared was brominated with *N*-bromobenzamide; a 2:1 molar ratio of *N*-bromoamide was used. An infrared spectrum of the recovered benzamide did not indicate the presence of deuterium, demonstrating that the allylic hydrogens are not an important source of the hydrogen found to replace the bromine of the brominating agent. At the present time we are unable to offer a satisfactory explanation of the hydrogen source.

In order to check the ability of the infrared method to determine deuterium bound to benzamide nitrogen, a sample of benzamide-*N*,*N*-d_2 was prepared by hydrolyzing sodium benzamide with pure deuterium oxide. The infrared spectrum, Fig. 1, shows a broad N—D absorption band[10] at 3.9–4.3 μ which is absent in the infrared spectrum of ordinary benzamide.

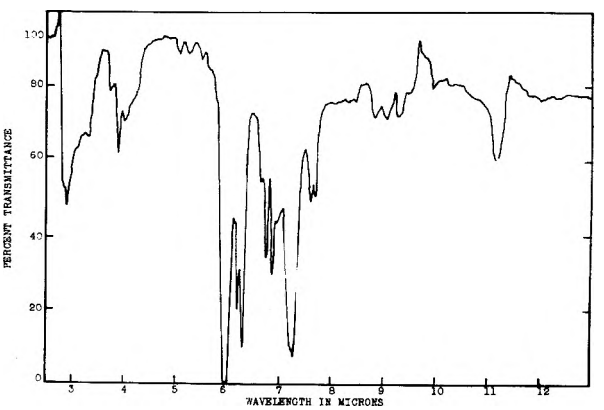


Fig. 1. Infrared spectrum of benzamide-*N*,*N*-d_2 chloroform solution

EXPERIMENTAL[11]

Materials. Lithium aluminum hydride was obtained from Metal Hydrides Inc., Beverly, Mass., and was 98% pure. Carbon tetrachloride was reagent grade material refluxed for 24 hr. with 15% sodium hydroxide, washed with water, dried in contact with calcium chloride, and distilled from

(6) P. D. Bartlett and F. A. Tate, *J. Am. Chem. Soc.*, **75**, 91 (1953).

(7) E. A. Braude, *Quart. Revs.*, **4**, 404 (1950).

(8) L. A. Amundsen and L. S. Nelson, *J. Am. Chem. Soc.*, **73**, 242 (1950).

(9) P. A. Levine and M. Kuna, *J. Biol. Chem.*, **118**, 315 (1937).

(10) H. M. Randall, N. Fuson, R. G. Fowler, and J. R. Daugle, *Infrared Determination of Organic Structures*, D. Van Nostrand Co., Inc., Toronto, Canada, 1949, p. 6.

(11) Melting points and boiling points are uncorrected. Infrared measurements were made on a Perkin-Elmer, Model 21, double beam infrared recording spectrophotometer fitted with a sodium chloride prism. The microanalyses were performed by Micro Tech Laboratories, Skokie, Ill.

phosphorous pentoxide. Allyl acetate was commercial material purified by fractional distillation in an efficient column.

Acrylyl chloride[12] and sodium benzamide[13] were prepared by methods described in the literature. *N*-Bromobenzamide was prepared according to the procedure of Hauser and Renfrow[14] and after two recrystallizations from a chloroform hexane mixture, melted at 129–130° (Literature value[14] m.p. 129–130°). Iodometric analysis indicated the *N*-bromobenzamide to be 99.8% pure.

Reaction of N-bromobenzamide with allyl acetate. A mixture of 250 ml. of carbon tetrachloride, 30 g. (0.30 mole) of allyl acetate, and 30.3 g. (0.15 mole) of *N*-bromobenzamide was refluxed gently under a nitrogen atmosphere until a negative starch-iodide test indicated the reaction to be complete (3.5 hr.). The crystalline deposit that formed on chilling was collected on a filter and washed with cold carbon tetrachloride. Extraction of this solid (m.p. 121–123°) with boiling water effected a separation into a water insoluble portion, 1.8 g., and 7.2 g. of pure benzamide which deposited from the extract on cooling. Recrystallization of the water insoluble fraction from benzene gave *N*-phenyl-*N'*-benzoylurea, m.p. 201–202°, identified *via* its infrared spectra ($CHCl_3$) and a mixed melting point with an authentic sample.[15]

Anal. Calcd. for $C_{14}H_{12}N_2O_2$: C, 70.0; H, 5.04; N, 11.7. Found: C, 70.18; H, 5.10; N, 11.49.

The combined carbon tetrachloride filtrate and washings were concentrated in vacuo to *ca.* 100 ml. and diluted with 100 ml. of cold petroleum ether, b.p. 30–60°. An orange, gummy solid precipitated which weighed 7.5 g. before recrystallization from hot water (Norite) gave 5.0 g. of pure benzamide, making the over-all yield of benzamide 12.7 g. (70%). The solvents were removed from the carbon tetrachloride-petroleum ether filtrate and the light orange residual oil was distilled through a small Vigreux column. Three fractions were collected: (*a*) b.p. 77–90° (6 mm.), 2.0 g., n_D^{20} 1.5112; (*b*) b.p. 90–94° (6 mm.), 5.7 g., n_D^{20} 1.5080; (*c*) b.p. 94–95° (6 mm.), 7.9 g., n_D^{20} 1.5107. Decomposition of the distilland with evolution of hydrogen bromide forced the discontinuation of the distillation. A black, resinous glassy material weighing 8.4 g. remained in the distillation flask. Fractions (*b*) and (*c*) were combined and redistilled to give 11.2 g. (57.4%) of 2,3-dibromopropyl acetate, b.p. 94–95° (6 mm.), n_D^{20} 1.5102 (Literature[16] values, b.p. 100–101° (5 mm.), n_D^{20} 1.5064).

Anal. Calcd. for $C_5H_8Br_2O_2$: Br, 61.47. Found: Br, 61.66.

The infrared spectrum was in agreement with that obtained for a sample of 2,3-dibromopropyl acetate prepared by the direct bromination of allyl acetate with bromine.

Allyl-1-d_2 alcohol. A slurry of 6 g. (0.14 mole) of lithium aluminum deuteride in 300 ml. of dry ether was prepared under a nitrogen atmosphere and then chilled in an ice bath. A solution of 20 g. (0.22 mole) of acrylyl chloride in 100 ml. of ether was added to the stirred hydride slurry at a rate permitting the reaction temperature to be maintained below 5°. After the acid chloride addition the mixture was stirred at room temperature for 2 hr. and again chilled in an ice bath. The reduction complex was then hydrolyzed by adding 7 ml. of water, 7 ml. of 15% sodium hydroxide, and 7 ml. of water, dropwise and in that order. The granular precipitate that formed was removed by filtration and thoroughly washed with dry ether. The combined filtrate and washings was dried with sodium sulfate, concentrated by distillation through a helice packed column to *ca.* 60 ml. and dried again with sodium sulfate. Thirty ml. of *n*-butyl ether was added for a distillation chaser, and the solution was fractionally distilled using a semi-micro, glass helice packed column. After a solvent forerun, three fractions were collected: (*a*) b.p. 45–80°, 0.58 g.; (*b*) b.p. 80–95°, 1.17 g.; (*c*) b.p. 95–98°, 5.90 g. The infrared spectrum of fraction (c) (see Fig. 2) is similar to that of allyl acetate except for

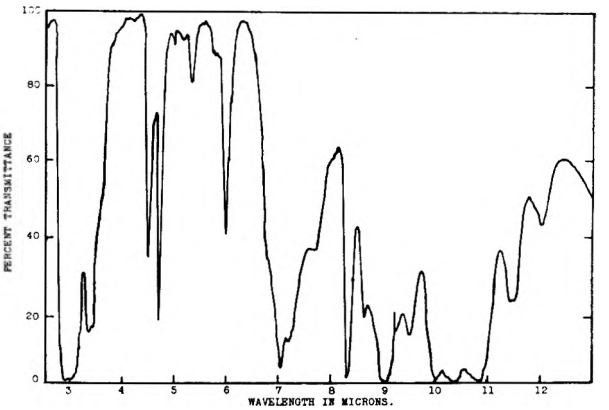


Fig. 2. Infrared spectrum of allyl-1-d_2 alcohol

the two absorption bands at 4.45–4.80μ (C—D)[17] which are absent in the spectrum of ordinary allyl acetate.

Allyl-1-d_2 acetate. Fractions (*b*) and (*c*) from the allyl-1-d_2 alcohol synthesis were combined and treated with an ice cold mixture of 15 ml. of pyridine and 12 g. of acetic anhydride. The mixture was allowed to stand at room temperature for 20 hr.; poured into a precooled solution of 10 ml. of conc. hydrochloric acid in 50 ml. of water contained in a separatory funnel, and extracted with four 20-ml. portions of pentane. The pentane extract was immediately washed with dilute sodium bicarbonate solution and dried over sodium sulfate. *n*-Butyl alcohol was added as a chaser and the solution was distilled using a semi-micro glass helice packed column. After a low-boiling forerun, a fraction boiling at 101–104° was accepted as allyl-1-d_2 acetate (literature value, b.p. allyl acetate, 102–104°). The yield was 7.8 g. (65%). The infrared spectrum (see Fig. 3) shows absorption at 4.4–4.8μ (C—D).[17]

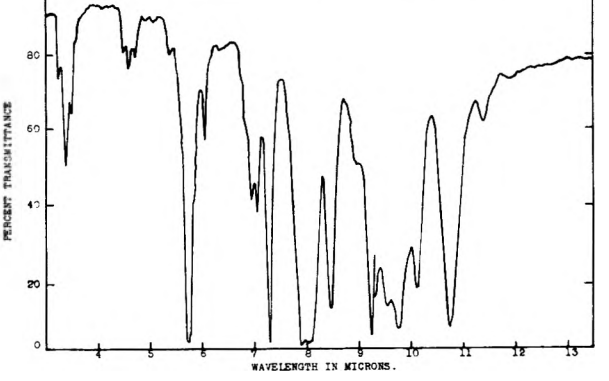


Fig. 3. Infrared spectrum of allyl-1-d_2 acetate. Carbon tetrachloride solution

Reaction of N-bromobenzamide with allyl-1-d_2. A small, all-glass apparatus was provided with a nitrogen atmosphere and charged with 25 ml. of carbon tetrachloride, 2.5 g. (0.0125 mole) of *N*-bromobenzamide and 2.5 g. (0.025 mole)

(12) G. G. Stemple, R. P. Cross, and R. P. Mariella, *J. Am Chem. Soc.*, **72**, 2299 (1950).

(13) A. W. Titherley, *J. Chem. Soc.*, **71**, 468 (1897).

(14) C. R. Hauser and W. B. Renfrow, *J. Am. Chem. Soc.*, **59**, 121 (1937).

(15) B. Kuhn, *Ber.*, **17**, 2881 (1884).

(16) V. P. Golender, *Sbornik State Obshcheĭ Khim.*, **2**, 1261 (1953); *Chem. Abstr.*, **48**, 9914 (1954).

(17) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley and Sons, Inc., N. Y., 1943, p. 171.

of allyl-1-d_2 acetate. The mixture was heated at gentle reflux for 90 min.; at which time a starch iodide test indicated complete reaction of the *N*-bromobenzamide. On being set aside overnight in a refrigerator, 0.89 g. of crude benzamide (m.p. 115–120°) deposited from solution. A single recrystallization from benzene (Norite) gave 0.6 g. (39.8%) of pure benzamide, m.p. 127°. The infrared spectrum ($CHCl_3$) was identical with that of nondeuterated benzamide and showed no absorption at 4.2μ.

Benzamide-N,N-d_2. A mixture of 0.9 g. of sodium benzamide and 3 ml. of deuterium oxide (99.8% isotropically pure) was warmed until a clear solution was obtained. The solution was protected from atmospheric moisture and allowed to crystallize. The benzamide-*N,N*-d_2 which deposited was isolated by filtration and dried *in vacuo*, m.p. 123–124°. One recrystallization from benzene gave 0.38 g. (50%) benzamide-*N,N*-d_2, m.p. 127°. Infrared spectrum (see Fig. 1) shows absorption at 3.9–4.3 μ, N—D,[17] absent in the spectrum of ordinary benzamide. It is very likely that benzamide-*N,N*-d_2 rather than *N*-deuterobenzamide was formed in this preparation since the work of Brodskii[18] some years ago showed that amide hydrogen atoms exchange readily with the hydrogens of water, even in the absence of a catalyst. In the present case, by-product deuterated sodium hydroxide would be expected to catalyze the exchange of all amide hydrogen atoms in benzamide. However, the use of either the mono or di deutero benzamide would not alter the conclusions arrived at in the present investigation.

EAST LANSING, MICH.

(18) A. I. Brodskii, *Trans. Faraday Soc.*, **33**, 1180 (1937)

[CONTRIBUTION FROM THE GENERAL ELECTRIC RESEARCH LABORATORY]

Solvent Effects in the Reaction of Free Radicals and Atoms. V. Effects of Solvents on the Reactivity of *t*-Butoxy Radicals

GLEN A. RUSSELL[1]

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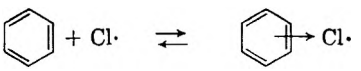
The effects of solvents upon the products of decomposition of di-*t*-butyl peroxide at 130° are considered. Quantitative data in regard to the peroxide-catalyzed reaction of chloromethanes with cyclohexane are presented. Evidence is presented supporting the displacement of a chlorine atom from 1-chloronaphthalene by a *t*-butoxy radical.

Previous papers in this series have demonstrated that aromatic solvents can drastically alter the reactivity of a chlorine atom.[2] These results have been interpreted in terms of a π-complex formed between the electrophilic chlorine atom and the electron-donating aromatic nucleus.



The complexed chlorine atom is apparently less reactive and more selective in its reactions than the free chlorine atom. Since *t*-butoxy radicals have a reactivity quite similar to chlorine atoms,[3] it was of interest to ascertain if similar solvent effects could be detected in the reactions of these radicals.

Solvent effects have been investigated in the decomposition of di-*t*-butyl peroxide in the presence of cyclohexane at 130° by measuring the fraction of *t*-butoxy radicals which enter into the decomposition reaction (1) and the hydrogen-abstraction reaction (2). From the ratio of acetone and *t*-butyl alcohol formed it is possible to calculate the ratio of k_1/k_2 provided that the products do not result from radical-radical interaction and provided that acetone and *t*-butyl alcohol are formed only in reactions 1 and 2. The former requirement will always be satisfied when the ratio of acetone and *t*-butyl alcohol is independent of *t*-butoxy radical concentration, while the latter requirement will nearly always be satisfied when the combined yield of acetone and *t*-butyl alcohol is quantitative based on the starting di-*t*-butyl peroxide. Table I presents data wherein these requirements have been met.

$$(CH_3)_3COOC(CH_3)_3 \xrightarrow{\Delta} 2(CH_3)_3CO\cdot$$

$$(CH_3)_3CO\cdot \xrightarrow{k_1} (CH_3)_2C{=}O + CH_3\cdot \quad (1)$$

$$(CH_3)_3CO\cdot + C_6H_{12} \xrightarrow{k_2} (CH_3)_3COH + C_6H_{11}\cdot \quad (2)$$

The ratio of k_1/k_2 is 0.45-.47 when cyclohexane or methylene chloride are used as solvents. The same ratio is observed when the weakly basic benzotrifluoride is used as a solvent. For more basic aromatic solvents, such as benzene, chlorobenzene or diphenyl ether, higher values of k_1/k_2 are observed although the highest value observed is only 25% greater than the value observed in an aliphatic solvent. However, the increase in the ratio of k_1/k_2 is considerably above experimental uncertainty.

The possibility that hydrogen abstraction from the aromatic solvent could occur to a significant extent is easily eliminated. Aromatic solvents cause an increase in the ratio k_1/k_2 whereas production of *t*-butyl alcohol by abstraction of a hydrogen atom from the aromatic solvent would lead to a decrease in this ratio. Moreover, estimates of the relative reactivities of cyclohexane and benzene toward a *t*-butoxy radical have been reported by Williams,

(1) Present address, Dept. of Chemistry, Iowa State College, Ames, Iowa.

(2) G. A. Russell, *J. Am. Chem. Soc.*, **79**, 2977 (1957); **80**, 4987, 4997, 5002 (1958).

(3) G. A. Russell, *J. Am. Chem. Soc.*, **79**, 3871 (1957).

TABLE I

PRODUCTS OF THE DECOMPOSITION OF DI-*t*-BUTYL PEROXIDE AT 130°

Solvent	Solvent Conc.[a]	C_6H_{12}[a]	$Me_3COOCMe_3$[a]	Products, mmol.[b] Me_3COH	Products, mmol.[b] $Me_2C{=}O$	Yield of acetone and *t*-butyl alcohol[b]	k_1/k_2[c]
C_6H_{12}	7.84	7.84	0.0926	5.30	0.310	103	0.46
C_6H_{12}	7.84	7.84	.0463	5.25	.305	102	.45
CH_2Cl_2	7.95	2.98	.0934	4.77[d]	.745	101	.47
C_6H_6	5.81	3.00	.0936	4.65	.849	101	.55
C_6H_5Cl	4.45	3.04	.0954	4.60	.940	101	.60
$C_6H_5CF_3$	4.05	2.94	.0924	4.85	.750	103	.47
$C_6H_5OC_6H_5$	3.28	3.04	.0954	4.30	.788	94	.56
1-Chloronaphthalene	3.40	3.16	.0990	4.27[e]	.338	85	—

[a] Mole/liter. [b] On the basis of 2.725 mmol. of di-*t*-butyl peroxide. [c] $\frac{k_1}{k_2[C_6H_{12}]} = \frac{\text{acetone}}{t\text{-butyl alcohol}}$. [d] Sum of *t*-butyl alcohol, *t*-butyl chloride and isobutylene, see Table II. [e] 3.54 mmol. *t*-butyl alcohol, 0.355 mmol. *t*-butyl chloride, 0.370 mmol. isobutylene.

Oberright, and Brooks.[4] At 135° these workers found that a hydrogen atom of benzene was only about 1/700 as reactive as a hydrogen atom of cyclohexane. For the experiments summarized in Table I the concentration of aromatic hydrogen atoms was usually less than the concentration of cyclohexane hydrogen atoms and thus it can be safely assumed that only about 1 part per 1000 of the *t*-butyl alcohol could have been formed from the interaction of *t*-butoxy radicals with the aromatic solvent.

Aromatic solvents appear to favor the decomposition of *t*-butoxy radicals relative to hydrogen abstraction from cyclohexane. The relative effectiveness of aromatic solvents of $C_6H_5OC_6H_5$, C_6H_5Cl, $C_6H_6 > C_6H_5CF_3$ is qualitatively in agreement with the results observed in the photochemical chlorination of branched-chain hydrocarbons.[2] However, the solvent effect in the reactions of *t*-butoxy radicals at 130° is considerably less than the solvent effect noted in photochlorinations at 20-55°.[2] There are several possible explanations to the differences in the magnitude of the solvent effect observed in these reactions. The temperature employed in the present work (130°) may be so high that the aromatic hydrocarbon–*t*-butoxy radical π-complex is extensively dissociated. Moreover, the driving force for the formation of this complex may be considerably less for a *t*-butoxy radical than a chlorine atom since the desire of a *t*-butoxy radical for an electron is considerably less than that of a chlorine atom. Expressed in terms of electron affinity the reaction of a chlorine atom with an electron is exothermic to the extent of 88 kcal./mole while the similar reaction for an alkoxy radical is exothermic only to the extent of about 50 kcal./mole.[5] Because of this a *t*-butoxy radical may be expected to form a weaker π-complex with benzene than a chlorine atom. Finally, a solvent may affect both reactions 1 and 2 to the same degree and thus partially obscure an experimental demonstration of the solvent effect from a study of competitive reaction rates.

Two experimental values for k_1/k_2 in cyclohexane have been previously reported, 0.855 (135°)[6] and 0.435 (135°).[4] Using a difference in energy of activation for reactions 1 and 2 of 6.5 kcal./mole[6] the ratio of k_1/k_2 is calculated to be 0.77 (130°)[6] and 0.39 (130°).[4] The experimentally determined value of 0.46 reported in the present work is intermediate between the two previously determined values but is much closer to the lowest of these values.

The decomposition of di-*t*-butyl peroxide in the presence of mixtures of cyclohexane and chloroform or carbon tetrachloride were also quantitatively investigated. Here the decomposition is complicated by the occurrence of a chain reaction between the chloromethane and cyclohexane.[7]

$$CCl_4 + C_6H_{12} \xrightarrow{\text{peroxide}} CHCl_3 + C_6H_{11}Cl$$

Table II summarizes the products formed in the reaction of the chloromethanes and cyclohexane at 130°.

Kinetic chain lengths for the chlorination reaction were about 16 for carbon tetrachloride, 1 for chloroform and <0.15 for methylene chloride. Undoubtedly this is in indication of the reactivity of the carbon-chlorine bonds in these molecules toward an alkyl radical and results from the relative stability of the chloroalkyl radicals of $CCl_3\cdot > CHCl_2\cdot > CH_2Cl\cdot$.

In the reaction of carbon tetrachloride with cyclohexane all products more volatile than chlorocyclohexane were analyzed. The material balance

(4) A. L. Williams, E. A. Oberright, and J. W. Brooks, *J. Am. Chem. Soc.*, 78, 1170 (1956).

(5) H. O. Prichard, *Chem. Revs.*, 52, 529 (1953) reports the electron affinity of a hydroxyl radical to be 50 kcal./mole.

(6) J. H. T. Brook, *Trans. Faraday Soc.*, 53, 327 (1957).

(7) J. P. West and L. Schmerling, *J. Am. Chem. Soc.*, 72, 3525 (1950).

TABLE II

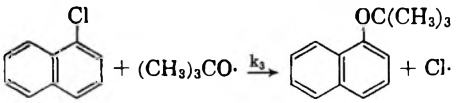
PRODUCTS OF THE REACTION OF CHLOROMETHANES AND CYCLOHEXANE AT 130°

Reactants	Quantities, mmole		
CH_2Cl_2	—	—	93.0
$CHCl_3$	—	74.4	—
CCl_4	67.0	—	—
C_6H_{12}	34.8	34.8	34.8
$Me_3COOCMe_3$	1.09	1.09	1.09
Products			
CH_3Cl	0.29	0.30	0.30
CH_2Cl_2	0.07	2.50	93.
$CHCl_3$	35.5	72.0	0.15
CCl_4	31.3	—	—
C_6H_{12}	8.3	30.5	33.7
$C_6H_{11}Cl$	18.6	1.10	<0.10
Me_3COH	0.58	0.67	1.12
Me_3CCl	.20	.27	.05
$Me_2C{=}CH_2$	.70	.81	.74
Me_2CO	.29	.27	.30

indicates that 17.1 mmol. of chlorine and 7.9 mmol. of C_6 fragments are unaccounted for, while an excess of hydrogen (on the basis of chlorocyclohexane found) of 17.6 mmol. was found in the volatile products. These results suggest that 8–9 mmol. of a dichlorocyclohexane was formed in addition to the 18.6 mmol. of chlorocyclohexane.

Significant amounts of *t*-butyl chloride were found in the decomposition of di-*t*-butyl peroxide in the presence of chloromethane–cyclohexane mixtures. Isobutylene was also formed although it could not be detected in the absence of the chloroalkane. This suggests that hydrogen chloride is formed in the presence of the chloroalkane and that in its presence *t*-butyl alcohol is in part dehydrated and in part converted to *t*-butyl chloride. In a trial experiment it was found that at 130° chlorocyclohexane did not bring about the dehydration of the alcohol or the formation of a detectable amount of *t*-butyl chloride. Possibly, the *t*-butoxy radical can abstract a chlorine atom from the chloromethane to yield *t*-butyl hypochlorite which would thermally decompose yielding a chlorine atom.

Isobutylene and *t*-butyl chloride were also formed in the decomposition of di-*t*-butyl peroxide in the presence of 1-chloronaphthalene but not in the presence of chlorobenzene. Moreover, the combined yield of acetone and *t*-butyl alcohol accounted for only 85% of the di-*t*-butyl peroxide employed in the presence of 1-chloronaphthalene whereas these products accounted for 101% of the peroxide in the presence of chlorobenzene. These results suggest that *t*-butoxy radicals can react with 1-chloronaphthalene to yield chlorine atoms.



(3)

Similar reactions, not involving alkoxy radicals, have been described by Miller and Walling.[8] Chloronaphthalene is apparently much more reactive than chlorobenzene in this reaction, a fact consistent with the greater reactivity of naphthalene derivatives than benzene derivatives in most aromatic substitutions. From the amount of *t*-butyl chloride formed in the presence of 1-chloronaphthalene (see Table I) it is calculated that the ratio of k_3/k_2 is 0.08. If 0.36 mmol. of *t*-butoxynaphthalene is formed, as indicated by the formation of 0.36 mmol. of *t*-butyl chloride, then the yield of di-*t*-butyl peroxide fragments in the experiment summarized in Table I accounts for 94% of the peroxide used. It now seems valid to calculate a value for the ratio k_1/k_2 in the presence of chloronaphthalene on the basis of acetone, *t*-butyl alcohol, *t*-butyl chloride, and isobutylene formed. This calculation indicates a value of 0.25 for k_1/k_2, whereas on the basis of basicity of solvent we might have expected aromatic solvents to have solvent effects in the order chloronaphthalene >diphenyl ether>benzene>chlorobenzene>benzotrifluoride.[2] However, 1-chloronaphthalene may effect the products of the reaction in a more profound manner than has been indicated. The *t*-butylnaphthyl ether may be cleared by hydrogen chloride to yield the *t*-butyl chloride observed. Moreover, the possibility exists that *t*-butoxy radicals may abstract hydrogen atoms from the naphthalene nucleus or add to the nucleus to give an unstable intermediate capable of decomposition to *t*-butyl alcohol

EXPERIMENTAL

A standard solution of di-*t*-butyl peroxide in Phillips reagent grade cyclohexane was weighed into a volumetric flask and diluted with a weighed amount of purified solvent. An aliquot of this solution was added to an ampoule prepared from a 1 ml. Mohr pipette calibrated in 0.01 ml. divisions. The solution was degassed and the ampoule sealed at reduced pressure. The concentration of reactants at 130° was obtained from their known concentrations at 25° by applying a correction for the observed volume change observed between 25 and 130° by using the calibrated reaction ampoule.

The ampoule was held at 130° in an oil-bath for 48 hr. This period represents approximately 10 half-lives for the peroxide and should have resulted in the decomposition of 99.9% of the peroxide. After this period the ampoule was opened at liquid nitrogen temperature and a sample injected into a Perkin-Elmer model 154B Vapor Fractometer.

The ratio of acetone, *t*-butyl alcohol, *t*-butyl chloride, isobutylene, and cyclohexane was determined from the appropriate peak areas using experimentally determined calibration curves. Usually it was assumed that the quantity of cyclohexane in the reactants and products was essentially constant. In experiments employing carbon tetrachloride or chloroform this assumption was not valid and analysis was based on the fact that the quantity of carbon tetrachloride or chloroform in the reactants should be very nearly equal to the sum of the quantities of carbon tetrachloride, chloroform, and methylene chloride in the products.

SCHENECTADY, N. Y.

(8) B. Miller and C. Walling, *J. Am. Chem. Soc.*, **79**, 4187 (1957).

[CONTRIBUTION FROM THE INSTITUTE OF ORGANIC CHEMISTRY, THE UNIVERSITY OF CHICAGO]

Reactions of Atoms and Free Radicals in Solution. XL. Reaction of Grignard Reagents with 1-Bromooctane in the Presence of Cobaltous Bromide

M. S. KHARASCH,* J. K. HAMBLING, AND T. P. RUDY

Received September 10, 1958

The reaction of Grignard reagents with 1-bromooctane in the presence of cobaltous bromide has been employed to study the interaction of octyl radicals with radicals of differing reactivities. On the basis of yields of octenes and octane, the radicals investigated can be arranged in the following order of decreasing reactivity: methyl, isopropyl, *tert*-butyl. Phenylmagnesium bromide reacts to give an approximately equimolar mixture of octene and octane, which suggests that phenyl radicals do not participate in this reaction. The C_8 olefins produced in these reactions consist of 1- and 2-octene. Formation of the latter may be due to isomerization of 1-octene.

Alkyl free radicals in solution may react in different ways. (A) They may attack the solvent. (B) They may donate a hydrogen atom to another component of the reaction system (which may be another free radical). Such a reaction between two like free radicals is termed disproportionation. (C) They may combine with other free radicals including those of their own kind.

It has been shown that short-lived free radicals differ greatly in their relative reactivities, and an ordered series has been proposed.[1] The free methyl radical is so highly reactive that in most systems it will abstract a hydrogen or halogen atom from a donor molecule. Thus, this radical is termed an oxidant. On the other hand, the *tert*-butyl radical is far less reactive in this sense and may be considered a reductant in view of its tendency to donate a hydrogen atom to another component of the reaction system. Intermediate in reactivity is the isopropyl radical, which may act as either oxidant or reductant.

The present study was undertaken to explore the possibility of comparing free radical reactivities on a more quantitative basis. If two different radicals, R· and R′·, could be caused to interact (reaction B, above), the nature of the reaction products should indicate relative oxidizing or reducing tendencies. In the case of alkyl radicals, an oxidant would be expected to abstract a hydrogen atom from a reductant, leading to the formation of a saturated hydrocarbon derived from the oxidant and an olefin derived from the reductant. Furthermore, various free radicals might be compared on the basis of reaction with a suitable standard free radical.

A convenient method of generating free radicals for this purpose is the reaction of Grignard reagents with alkyl halides in the presence of cobaltous bromide (or other suitable transition metal salt). The course of this reaction has been represented in the following manner.[2]

$$RMgX + CoX_2 \longrightarrow RCoX + MgX_2 \quad (1)$$

$$RCoX \longrightarrow R\cdot + CoX \quad (2)$$

$$CoX + R'X \longrightarrow R'\cdot + CoX_2 \quad (3)$$

Wilds and McCormack[3] have proposed an alternate path involving metallic cobalt as the reactive intermediate rather than univalent cobalt (as CoX).

$$2RMgX + CoX_2 \longrightarrow CoR_2 + 2MgX_2 \quad (4)$$

$$CoR_2 \longrightarrow Co + 2R\cdot \quad (5)$$

$$Co + 2R'X \longrightarrow CoX_2 + 2R'\cdot \quad (6)$$

Of the many possible reactions which the free radicals R· and R′· may undergo, only the following interactions are dealt with in the present study.

$$2R\cdot \longrightarrow R_{(+H)} + R_{(-H)} \quad (7)$$

$$2R'\cdot \longrightarrow R'_{(+H)} + R'_{(-H)} \quad (8)$$

$$R\cdot + R'\cdot \longrightarrow R_{(+H)} + R'_{(-H)} \quad (9a)$$

$$R\cdot + R'\cdot \longrightarrow R'_{(+H)} + R_{(-H)} \quad (9b)$$

Reactions 7 and 8 lead to formation of equimolar amounts of paraffin and olefin by disproportionation of R· and of R′·. The yields of products from reaction 9, however, depend on the relative reactivities of the two radicals. If R· is the stronger oxidant, Reaction 9a will predominate. Thus there will be formed more paraffin than olefin derived from R· and less paraffin than olefin derived from R′·. The converse will be true if R′· is the stronger oxidant, and Reaction 9b will predominate.[4] It is recognized, of course, that paraffins may be formed by radical attack on the solvent. Furthermore, polymerization may reduce the apparent yield of olefin.[5] These side reactions, however, apparently are relatively unimportant in the case of

* Deceased.

(1) M. S. Kharasch, M. Zimmermann, W. Zimmt, and W. Nudenberg, *J. Org. Chem.*, **18**, 1045 (1953).

(2) M. S. Kharasch and O. Reinmuth, *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, New York, 1954, p. 123.

(3) A. L. Wilds, and W. B. McCormack, *J. Org. Chem.*, **14**, 45 (1949).

(4) The authors are grateful for an alternative explanation, suggested by a referee, that the relative importance of reactions 9a and 9b may be due to the stabilizing effects of substituents on the incipient double bond.

(5) M. S. Kharasch, D. W. Lewis, and W. B. Reynolds, *J. Am. Chem. Soc.*, **65**, 495 (1943).

TABLE I

REACTIONS OF GRIGNARD REAGENTS WITH 1-BROMOOCTANE IN THE PRESENCE OF COBALTOUS BROMIDE

Grignard Reagent	C_8 Hydrocarbons Yield, %	Octenes in C_8 Hydrocarbons, % w	1-Octene: *trans*-2-octene Mole Ratio	1-Octene Yield, %	2-Octene[a] Yield, %
CH_3MgBr	69	75.5	85:15	42	10
i-C_3H_7MgBr	84	43.4	83:17	28	8
t-C_4H_9MgBr	88	31.0	70:30	17	10
C_6H_5MgBr	56	52.3	74:26	20	9

[a] *Cis* and *trans*.

octyl radicals under the experimental conditions here reported, since the expected trends in yields have been observed.

The present investigation deals mainly with the reactions of methyl-, isopropyl-, *tert*- butyl-, and phenylmagnesium bromide with 1-bromooctane in the presence of cobaltous bromide. Attention was focussed primarily on the relative yields of octane and octenes, since these products could be most easily separated and analyzed. According to Reaction 9, a highly reactive (oxidizing) radical derived from the Grignard reagent should lead to the formation of more octene than octane, while a less reactive (reducing) radical should lead to the opposite result. Thus, the decreasing yields of octene relative to octane (Table I.) clearly indicate decreasing reactivity in the series: methyl, isopropyl, *tert*-butyl.

Gaseous products derived from these radicals correspond roughly to the observed yields of octene and octane. However, in the case of methylmagnesium bromide the mixture of gases appears to consist of ethane and ethylene in addition to the expected major product, methane. This may be attributed to the reaction of methyl radicals with the ether solvent.[6] In the case of *tert*-butylmagnesium bromide, an apparently low yield of isobutylene is obtained. This may be due to loss of the olefin by polymerization.[5]

The reaction of phenylmagnesium bromide is believed to differ from the reactions of the alkyl Grignard reagents.[7] Presumably the aryl Grignard reagent reacts with cobaltous bromide to give biphenyl and a reduced form of cobalt. Thus, the free phenyl radical is not produced, and the C_8 products (approximately equal yields of paraffin and olefin) are those to be expected of simple disproportionation of octyl radicals.

It is interesting that a relatively constant yield of 2-octene is obtained, regardless of the Grignard reagent used. Furthermore, little, if any, 3- or 4-octene is formed. Migration of a hydrogen atom during disproportionation of 1-butyl radicals has been suggested[8] to explain the formation of 2-butene in reactions similar to those employed in the present study. Although such a migration may, occur in the case of 1-octyl radicals, an alternate path to 2-octene by isomerization of 1-octene has been established. Methylmagnesium bromide reacts with 1-bromobutane in the presence of cobaltous bromide to give products[9] analogous to those obtained in the reaction of 1-bromooctane. When 1-octene is present during the reaction, extensive rearrangement to 2-octene occurs. Further study is required to establish whether this rearrangement is due to radical attack or to a polar reaction involving other components of the reaction system.

(6) M. S. Kharasch, F. Engelmann, and W. H. Urry, *J. Am. Chem. Soc.*, 66, 366 (1944).

(7) M. S. Kharasch and E. K. Fields, *J. Am. Chem. Soc.*, 63, 2316 (1941).

EXPERIMENTAL

Reagents. 1-Bromooctane (Eastman White Label) was fractionally distilled through a 100 × 1.2 cm. glass helices packed column. Only the middle cut (b.p. 91°/20 mm., n_D^{20} 1.4503) was used. 1-Bromobutane (Eastman White Label) was fractionally distilled through a 50 × 1.0 cm. tantalum spiral column, b.p. 101°, n_D^{20} 1.4384. Ethereal solutions of the Grignard reagents were prepared in the usual manner, and concentrations were determined by the acidimetric method.[10] Cobaltous bromide (City Chemical Co., anhydrous, C.P.) was used without further treatment.

Procedure. The reactions were carried out in a 1-l., three-necked flask equipped with sealed stirrer, reflux condenser, and two-way adapter with an addition tube for solids and a pressure equalized dropping funnel with gas inlet. The reaction vessel was thoroughly dried and then purged with dry nitrogen gas. A freshly prepared solution of the Grignard reagent (400 ml., 0.60 mole) was placed in the flask, followed by cobaltous bromide (3.28 g., 0.015 mole). A solution of 1-bromooctane (58 g., 0.30 mole) in an equal volume of ether was placed in the dropping funnel. The flow of nitrogen was stopped, and a gas collector containing a saturated aqueous solution of sodium chloride was connected through a calcium chloride drying tube to the reflux condenser. The solution of 1-bromooctane was added to the flask with stirring over a period of 30 min. During this period the temperature of the reaction mixture remained below 35°. Following the addition of 1-bromooctane the reaction mixture was heated under reflux for 45 min.

The mixture was allowed to cool and then was poured into a stirred mixture of crushed ice and water. Glacial acetic acid

(8) M. S. Kharasch, F. L. Lambert, and W. H. Urry *J. Org. Chem.*, 10, 298 (1945).

(9) The products obtained differ significantly from those reported by W. B. Smith (*J. Org. Chem.*, 23, 509 (1958)). He obtained an appreciable yield of *n*-pentane and apparently no 2-butene. In contrast, we obtain 2-butene in 21% yield and less than 2% of *n*-pentane.

(10) M. S. Kharaseh and O. Reinmuth, *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, New York, 1954, p. 94.

(40 ml.) was added, and the mixture was allowed to separate. The ethereal layer was separated, and the aqueous solution was extracted with ether. The combined ethereal solutions were washed successively with water, a saturated solution of sodium bicarbonate, and water. The ethereal solution was dried over anhydrous sodium sulfate and then fractionally distilled through a Heli-Grid column (97 × 1.3 cm.), a tantalum spiral column (50 × 1.0 cm.), and finally a Piros-Glover spinning band column. High-boiling fractions were molecularly distilled from a Hickman pot-still.

Analyses and molecular weight determinations of gaseous products were carried out using the apparatus and method described by Kharasch, Lewis, and Reynolds.[11]

Analysis of C_8 products. The total yield of C_8 hydrocarbons was determined by distillation (b.p. 121–125°). Bromate-bromide titration was employed to determine the ratio of octenes to octane. The ratio of 1-octene to *trans*-nonterminal octene was determined by infrared analysis based on absorption maxima at 910 $cm.^{-1}$ (1-octene) and 960 $cm.^{-1}$ (*trans*-nonterminal octene). Gas chromatography through a 13 ft. × 1/4 in. column containing 30–60 mesh firebrick impregnated with 30% w of tricresyl phosphate permitted estimation of octane, 1-octene, *trans*-2-octene, and *cis*-2-octene. Yields are reported on the basis of 1-bromooctane used.

Complete separation of C_8 products from the reaction of *tert*-butylmagnesium bromide was effected by gas chromatograpy through a 50 ft. × 1/4 in. column containing dimethylsulfolane (26% w) on firebrick.[12] At a flow rate of 70 ml./min. of helium carrier gas and a column temperature of 80° the following emergence times were observed: octane, 87.5 min.; 1-octene, 116 min.; *trans*-2-octene, 125 min.; *cis*-2-octene, 136 min. Positive identification of these constituents was accomplished by use of authentic compounds. By employing relatively large samples (80–100 μl.), it was possible to trap enough of each constituent from the effluent gas to obtain a useful infrared spectrum. On the basis of comparable examinations of mixtures containing 3- and 4-octenes it was concluded that, at most, only traces of these isomers were produced by the reactions considered here.

It should be mentioned that the products of ozonolysis of the olefins are of limited value in the assignment of structure. Even when extreme precautions[13] are taken, as much as 5% of "abnormal" reaction occurs, leading to fragments containing one fewer carbon atom than would be expected. After experiments with pure olefins this approach was abandoned.

Higher molecular weight products, being of minor interest, were not thoroughly investigated. Characterization was limited to measurement of physical properties.

Products of the reaction of methylmagnesium bromide with 1-bromooctane. Gas: *ca.* 8.0 l., mol. wt., 17.55; unsaturation, 5%. Calculated composition: methane, 90%; ethane, 5%; ethylene, 5%. C_8 hydrocarbons: 23.5 g. (69% yield); unsaturation, 75.5%; ratio 1-octene:*trans*-2-octene, 85:15; yield 1-octene, 42%; yield 2-octene, 10%. Higher molecular weight products (primarily C_{16} hydrocarbons): 10 g. (29.5% yield); unsaturation, 19.4%; n_D^{20} 1.4320; mol. wt., 200.

Products of the reaction of isopropylmagnesium bromide with 1-bromooctane. Gas: *ca.* 7.5 l.; mol. wt., 43.24; unsaturation, 47.0%. Calculated composition: propane, 53%; propylene, 47%. C_8 hydrocarbons: 27.9 g. (84% yield); unsaturation, 43.4%; ratio 1-octene:*trans*-2-octene, 83:17; yield 1-octene, 28%; yield 2-octene, 8%. Higher molecular weight products: C_{11} hydrocarbons, 2.1 g. (4.5% yield); C_{16} hydrocarbons, 2.5 g. (7.4% yield).

Products of the reaction of tert-butylmagnesium bromide with 1-bromooctane. Gas: *ca.* 6.0 l.; mol. wt., 57.7; unsaturation, 35%. Calculated composition: isobutane, 65%; isobutylene, 35%. C_8 hydrocarbons: 30.0 g. (88% yield); unsaturation, 31.0%; ratio 1-octene:*trans*-2-octene, 70:30; yield 1-octene, 17%; yield 2-octene, 10%. Higher molecular weight products (primarily C_{12} and C_{16} hydrocarbons): 4.4 g.; unsaturation, 28%.

Products of the reaction of phenylmagnesium bromide with 1-bromooctane. Benzene, 16.6 g. C_8 hydrocarbons: 19.2 g. (56% yield); unsaturation, 52.3%; ratio 1-octene:*trans*-2-octene, 74:26; yield 1-octene, 20%; yield 2-octene, 9%. Higher molecular weight products: diphenyl, 22.5 g.; octylbenzene, 4.2 g. (7% yield); C_{16} hydrocarbons, 7.2 g. (21% yield).

Reaction of methylmagnesium bromide with 1-bromobutane. This experiment differed from the general procedure in several respects. A Dry Ice reflux condenser was used, and different amounts of reagents and solvent were employed. Thus a soluton of 1-bromobutane (27.4 g., 0.2 mole) in an equal volume of ether was added to an ethereal solution of methylmagnesium bromide (0.3 mole in 100 ml. of ether) containing 1.8 g. of cobaltous bromide (0.01 mole). When the reaction was complete, a total of 4.8 l. at S.T.P. of gas (assumed to be mostly methane) had been collected. The Dry Ice condenser was replaced by a condenser which was cooled with ice water. To this condenser was attached a trap cooled to −80°. The reaction mixture was heated to the boiling point and refluxed gently for 2 hr. The trapped material (*ca.* 9.0 g.) was analyzed by gas chromatography (using the dimethylsulfolane column) and found to consist of: *n*-butane, 42%; 1-butene, 30%: *trans*-2-butene, 18%; *cis*-2-butene, 9%; *n*-pentane, *ca.* 0.6%; and a trace of ether.

The reaction mixture was distilled almost to dryness, and the distillate (90 g., primarily ether) was also analyzed by gas chromatography. Traces of butane and butenes as well as *n*-pentane (*ca.* 0.14% w) were found. The residue was decomposed with dilute hydrochloric acid and extracted with ether. The ethereal extract was worked up as described previously and fractionally distilled. The fraction with b.p. 117–125° (2.0 g.) was analyzed by gas chromatography (dimethylsulfolane column): octane, 82%; 1-octene, 4%; *trans*-2-octene, 9%; *cis*-2-octene, 4%.

Product	Amount	Yield,[a] %
Methane	4.8 l. S.T.P.	ca. 100
n-Butane	3.8 g.	33
1-Butene	2.7 g.	24
trans-2-Butene	1.6 g.	14
cis-2-Butene	0.8 g.	7
n-Pentane	<0.2 g.	<1.8
n-Octane	1.64 g.	14
1-Octene	0.08 g.	0.7
trans-2-Octene	0.18 g.	1.6
cis-2-Octene	0.08 g.	0.7

[a] All yields except that of methane calculated on the basis of 1-bromobutane.

Isomerization of 1-octene in the reaction of methylmagnesium bromide with 1-bromobutane. The foregoing experiment was repeated, the only change being the addition of 1-octene (10.0 g.) to the solution of Grignard reagent before the reaction was begun. Yields of methane and C_4 products appeared to be unchanged. The C_8 fraction (7.0 g. recovered), b.p. 119–124°, n_D^{20} 1.4110, was analyzed by gas chromatography: *n*-octane, 12%; 1-octene, 20%; *trans*-2-octene, 45%; *cis*-2-octene, 20%; and possibly traces of other octenes. If isomerization of the added 1-octene had not occurred, the recovery had been complete, the expected composition would have been: *n*-octane, 13.7%; 1-octene, 84%: *trans*-2-octene, 1.5%; *cis*-2-octene, 0.7%.

CHICAGO 37, ILL.

(11) M. S. Kharasch, D. W. Lewis, and W. B. Reynolds, *J. Am. Chem. Soc.*, 65, 493 (1943).

(12) E. M. Fredericks and F. R. Brooks, *Anal. Chem.*, 28, 297 (1956).

(13) The method involved ozonization at −80°, catalytic hydrogenation of ozonides, oxidation of resulting aldehydes to acids with silver oxide, reaction of silver salts of the acids with methyl iodide to form methyl esters, and gas chromatographic analysis of the esters.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE STATE UNIVERSITY]

Reduction of 6,7-Diphenyldibenzo[*e*,*g*] [1,4]diazocine. An Unusual Nucleophilic Aromatic Substitution[1]

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Received October 9, 1958

Treatment of the title compound (I) with most common reducing agents led to no reaction. When I was allowed to react with excess lithium aluminum hydride in boiling tetrahydrofuran for several hours, *N*-desylcarbazole (II) was isolated in 63% yield. A mechanism is proposed for the reaction which involves a nucleophilic aromatic substitution.

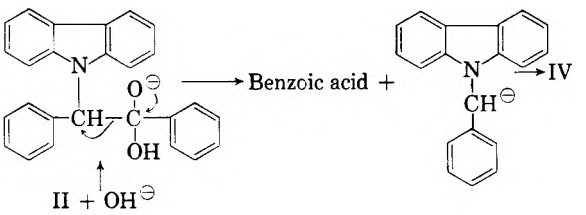
Täuber[3] prepared 6,7-diphenyldibenzo[*e*,*g*][1,4]-diazocine (I) by heating 2,2′diaminobiphenyl with benzil at 170°. We have confirmed this synthesis, and have also found that I may be more conveniently prepared by heating the same components in acetic acid. Upon acid hydrolysis the compound gave a 95% yield of benzil. The infrared spectrum of I showed no N–H stretching band, and the structure of the compound appears to be firmly established.

Compound I upon reduction with sodium amalgam in ethanol was reported[3] to yield 5,6,7,8-tetrahydro-6,7-diphenyl[*e*,*g*][1,4]diazocine (III). Täuber established the structure of III by carbon-hydrogen analysis, and by formation of a diacetyl derivative.[4] As further support for the structure assigned to III additional information has been obtained. Compound III gave the correct analysis for nitrogen, and it showed strong N-H stretching bands at 2.92 and 3.00 μ. The diacetyl derivative showed a carbonyl band at 5.98 μ.

Compound I is rather resistant to reduction, and was unaffected by low pressure catalytic hydrogenation with platinum oxide, or by treatment with zinc and alkali, sodium borohydride, stannous chloride, or lithium aluminum hydride in ether.

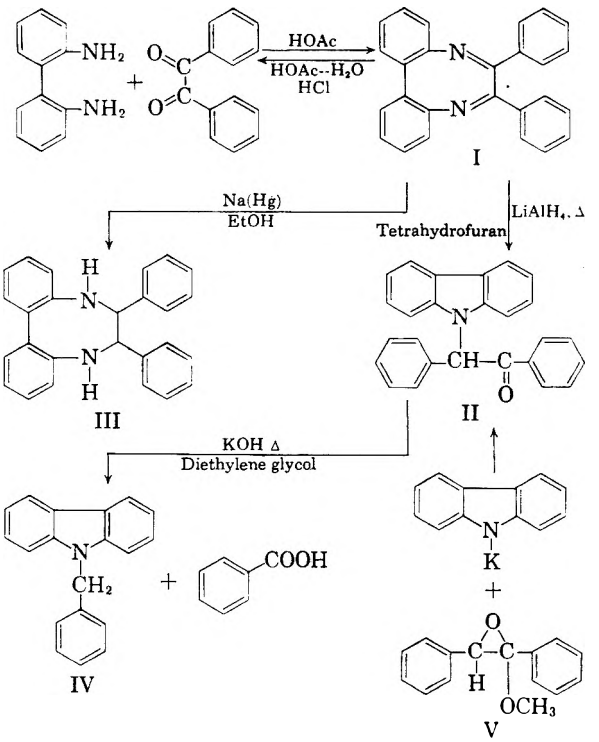
When reduction of I was carried out with lithium aluminum hydride in refluxing tetrahydrofuran for 12 hr. under a nitrogen atmosphere, a colorless crystalline substance was isolated which was identified as *N*-desylcarbazole (II). The structural assignment was indicated by elemental analysis and molecular weight. The infrared spectrum showed no N-H stretching band, but did show a carbonyl band at 5.85 μ (chloroform), about 0.1 μ lower than expected for an acetophenone. By way of analogy it was found that a synthetic sample of ethyl 9-carbazoleacetate, prepared according to Seka,[5] showed the ester carbonyl band at 5.55 μ as compared to 5.75 μ for ethyl acetate. No carbonyl derivatives of II were obtained by conventional methods.

The structure of compound II was established by degradation with potassium hydroxide in diethylene glycol. The cleavage that was expected[6] to take place was:



Compound IV and benzoic acid were isolated in yields of 45% and 33%, respectively.

It also seemed desirable to synthesize II by an unambiguous method. Attempts to condense carbazole, or various of its salts, with desyl chloride were unsuccessful. Compound II was obtained



(1) Supported in part by a research grant from the National Science Foundation.

(2) National Science Foundation Predoctoral Fellow, 1956–1959.

(3) E. Täuber, *Ber.*, **25**, 3287 (1892).

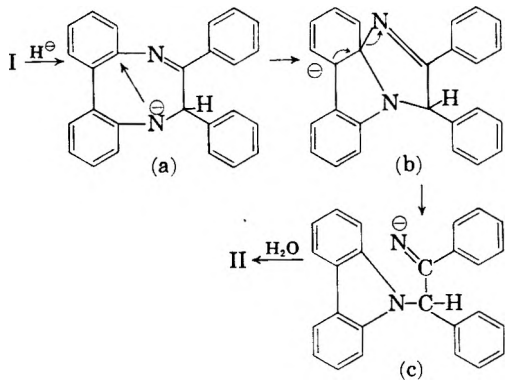
(4) E. Täuber, *Ber.*, **26**, 1703 (1893).

(5) R. Seka, *Ber.*, **57**, 1527 (1924).

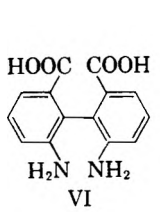
(6) D. J. Cram, J. Allinger, and A. Langemann, *Chem. & Ind. (London)*, 919 (1955).

in 21% yield by the condensation of the potassium salt of carbazole with 1,2-diphenyl-1-methoxy-1,2-epoxyethane (V).[7]

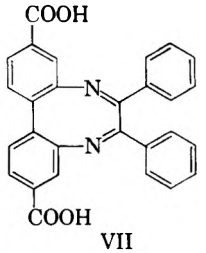
A reasonable mechanism by which compound II may have been formed from I would have the reaction initiated by attack of hydride at one of the azomethine carbons, which would yield (a). Nucleophilic attack by the amide ion on the phenyl ring would lead through (b) to (c). If no further reaction occurred, (c) would after hydrolysis yield



compound II. Ordinarily a ketimine would be expected to be reduced by lithium aluminum hydride to an amine.[8] No amine was detected in the present work, but a considerable amount of the starting material was not accounted for. The failure of II to form carbonyl derivatives under ordinary conditions suggests that this reduction may be slow, or the solubility of the salt (c) may be quite low. The solubility question is difficult to answer as the reaction is heterogeneous throughout. In structure (b), one phenyl is twisted out of the plane of the other one by an appreciable amount, yet considerable charge delocalization may still occur. This part of the reaction has an analogy in the formation of carbazole from compound VI by heating with barium oxide.[9] The structure (b) corresponds to what is normally an intermediate in nucleophilic substitution of "activated" aromatic rings.[10] It is not clear whether in this case it is an intermediate or a transition state, since the ring structure of (b) must be under some strain. Compound I probably has the eight-membered ring in a tub form, as does the formally analogous cyclooctratetraene.[11] The two rings of the biphenyl grouping are not expected to be co-planar, and in support of this geometry compound VII has been resolved into optical isomers.[12] Thus, no appreciable loss in conjugation is necessitated by the



VI



VII

formation of the multiplanar structure (b). The stabilization of charge afforded by (b) would not, however, be expected to be as great as that of an *ortho*-nitro group in the simple cases.

EXPERIMENTAL

6,7-Diphenyldibenzo[e,g][1,4]diazocine (I). A solution containing 5.0 g. of 2,2′-diaminobiphenyl[13] (prepared from the corresponding dinitro compound[14] by reduction with tin and hydrochloric acid) in 25 ml. of hot acetic acid was added to 5.76 g. of benzil in 100 ml. of hot acetic acid. The resulting solution was heated under reflux for 19 hr., and was then allowed to stand for 24 hr. The crystals were collected, and after recrystallization from acetic acid were obtained as yellow needles, m.p. 236–237° (literature,[3] m.p. 238°) wt., 7.0 g. (72%). The ultraviolet spectrum showed λ_{max} 251, ϵ 32,950 and λ_{max} 338, ϵ 2,950 (95% ethanol).

Hydrolysis of compound I. One gram of I was suspended in a solution of 25 ml. of 5*N* hydrochloric acid in 50 ml. of acetic acid. The mixture was heated under reflux in a nitrogen atmosphere for 46 hr. The solution was diluted with water, and the yellow solid was collected, m.p. 95.5–96.5°, wt. 0.56 g. (95%). No mixture melting point depression was observed with an authentic sample of benzil. The hydrolysis of I to benzil and 2,2′-diaminobiphenyl was reported by Täuber,[4] but no details or yields were given.

The action of various reducing agents on compound I. The compound proved to be rather inert to a number of common reducing agents. By appropriate isolation procedures, the bulk of the material was recovered unchanged after treatment with excess of the following reagents: sodium in ethanol, stannous chloride and hydrochloric acid, lithium aluminum hydride in ether at reflux for 2 hr., lithium aluminum hydride in tetrahydrofuran at room temperature for 72 hr., sodium borohydride in tetrahydrofuran at reflux for two days, catalytic hydrogenation with platinum oxide in tetrahydrofuran, and zinc dust in alcoholic potassium hydroxide. With tin and hydrochloric acid there was obtained a nitrogen free material, m.p. 56–76°, which was not further examined, and which probably resulted from the cleavage of I to give benzil followed by further reaction of the latter.

5,6,7,8-Tetrahydro-6,7-diphenyldibenzo[e,g][1,4]diazocine (III). With sodium amalgam in ethanol compound I was reduced to III, colorless, lustrous, granular crystals, m.p. 155–155.5° (reported,[3] m.p. 154°). The ultraviolet spectrum showed maxima at 282 and 323 mμ, with ϵ4150 and 2500 (95% ethanol).

Anal. Calcd. for $C_{26}H_{22}N_2$: N, 7.73. Found: N, 7.89.

N-Desylcarbazole (II) *from* I. A solution of 2.0 g. of I in 200 ml. of anhydrous tetrahydrofuran was added during 1 hr. to a suspension of 5.0 g. of lithium aluminum hydride in 50 ml. of tetrahydrofuran with stirring under an atmosphere of nitrogen. The resulting mixture was then heated under reflux with stirring for 18 hr. After cooling the solution, ethanol was added until the yellow color disappeared, and then water was added until the decomposition was complete. The inorganic material was removed by filtration and washed

(7) C. L. Stevens, M. L. Weiner, and R. C. Freeman, *J. Am. Chem. Soc.*, **75**, 3977 (1953).

(8) N. G. Gaylord, *Reduction with Complex Metal Hydrides*, Interscience, New York, 1956, p. 795.

(9) J. Schmidt and A. Kämpf, *Ber.*, **36**, 3745 (1903).

(10) J. F. Bunnett, E. W. Garbisch, Jr., and K. M. Pruitt, *J. Am. Chem. Soc.*, **79**, 385 (1957).

(11) I. L. Karle, *J. Chem. Phys.*, **20**, 65 (1952).

(12) F. Bell, *J. Chem. Soc.*, 1527 (1952).

(13) S. von Niementowski, *Ber.*, **34**, 3325 (1901).

(14) R. C. Fuson and E. A. Cleveland, *Org. Syntheses*, Coll. Vol. III, 339 (1955).

with tetrahydrofuran. The combined filtrates were dried with magnesium sulfate and the solvent was removed. The residue was twice crystallized from aqueous acetic acid and yielded light yellow plates, m.p. 181–182.5°, wt. 1.07 g. The inorganic salts were dissolved in dilute hydrochloric acid, combined with the acetic acid filtrates above, and the solution was extracted with chloroform. After drying the extracts the chloroform was evaporated. The residue was twice crystallized from acetic acid and gave pale yellow plates, m.p. 180.5–182.6°, wt. 0.20 g., plus filtrates (A). The total yield of pure *N*-desylearbazole was 1.27 g. (63%). An analytical sample was prepared by recrystallizing this material first from aqueous acetic acid, and then from a mixture of tetrahydrofuran and hexane, and was obtained as colorless needles, m.p. 184–184.5°. The infrared spectrum in chloroform showed a strong band at 5.85μ.

Anal. Calcd. for $C_{26}H_{19}NO$: C, 86.41; H, 5.30; N, 3.88; mol. wt., 361. Found: C, 86.29; H, 5.45; N, 3.93; mol. wt., (Rast) 342.

Filtrates (A) were neutralized with potassium hydroxide and the solution was extracted with chloroform. The chloroform extracts were dried, the solvent was evaporated, and the residue was chromatographed on alumina with chloroform-hexane. There was thus obtained 55 mg. (4%) of *N*-benzylcarbazole (IV) which was identified by mixture melting point and infrared comparison with an authentic sample.

Degradation of N-desylcarbazole. *N*-Desylcarbazole (II), 0.71 g., was dissolved in 40 ml. of diethylene glycol containing 0.11 g. of potassium hydroxide, and the resulting solution was heated under reflux for 3.5 hr. under an atmosphere of nitrogen. The cooled solution was diluted with water and the precipitated solid was collected and washed with water.

The dried solid was crystallized from petroleum ether at 0°, and gave colorless needles, m.p. 117–118°, wt. 0.23 g. (45%). This material gave no melting point depression with an authentic sample of *N*-benzylcarbazole (IV) (prepared according to Buu-Hoï and Royer[15]). The two samples also gave identical infrared spectra.

The aqueous filtrate from above was acidified and extracted with ether. The ether solution was extracted with *N* sodium hydroxide solution, and the latter was acidified and extracted with ether. The ethereal solution was dried and the solvent was evaporated which yielded a light brown crystalline solid. The solid was recrystallized from water (Norit), m.p. 122–123°. A mixture melting point with benzoic acid (m.p. 122–124°) was 123–124°. The infrared spectra of the isolated solid and benzoic acid were identical. The yield was 0.08 g. (33%).

N-Desylcarbazole (II). Several unsuccessful attempts were made to prepare this compound from carbazole itself, and from its salts as formed from potassium hydroxide, sodamide, phenyllithium, and ethyl Grignard with desyl chloride. In each case carbazole was recovered.

In a flask equipped with condenser with drying tube were placed 4.15 g. of the potassium salt of carbazole, 4.59 g. of 1,2-diphenyl-1-methoxy-1,2-epoxyethane (V),[7] and 80 ml. of dry dimethylformamide. The solution was heated under reflux 15 hr. After cooling the mixture was poured into ice water and the resulting mixture was extracted with chloroform. The chloroform solution was washed with water, dried with anhydrous magnesium sulfate, and the solvent was evaporated. The residue was adsorbed on a neutral alumina column and eluted with hexane-chloroform (4:1). A yellow oil was first eluted, followed by *N*-desylcarbazole, and then carbazole. The *N*-desylcarbazole was recrystallized twice from aqueous acetic acid forming pale yellow plates, m.p. 179–182°. The yield was 1.52 g. (21% of the theoretical). This synthetic material gave no depression in melting point when mixed with the *N*-desylcarbazole obtained from I. The ultraviolet and infrared spectra of the two samples were identical.

DETROIT 2, MICH.

(15) N. P. Buu-Hoï and R. Royer, *J. Org. Chem.*, **16**, 1198 (1951).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DE PAUL UNIVERSITY]

Compounds Related to 22-Ketocholesterol

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22-Ketocholesterol[2] (I) and one form of 3β-chloro-22-keto-5-cholestene (III) were prepared by alkylation with diisoamylcadmium of acid chlorides prepared from 3β-acetoxy-5-bisnorcholenic acid. These steroids were converted, respectively, into 6β-methoxy-3,5-cyclocholestan-22-one (methyl 22-keto-*i*-cholesteryl ether) (VIII) and 3,5-cyclocholesta-6,22-dione (*i*-cholesta-6,22-dione) (VI). Preparation of 3β-chloro-22-keto-5-cholestene (III) by chlorination of 22-ketocholesterol (I) or by rearrangement of 6β-methoxy-3,5-cyclocholestan-22-one (VIII) gave two similar isomeric products isolable because of different adsorptions on alumina. Attempted reduction of 6β-methoxy-3 5-cyclocholestan-22-one (VIII) by Wolff-Kishner procedure appeared to fail.

This study of the properties of compounds prepared from 22-ketocholesterol (I) was part of a plan to prepare side-chain labeled cholesterol. 22-Ketocholesterol (I)[2] was prepared by hydrolysis of the keto ester furnished by the reaction of 3β-acetoxy-5-bisnorcholenyl chloride with diisoamylcadmium. The 3β-chloro-22-keto-5-cholestene (III) (form B) was prepared most satisfactorily by the action of diisoamylcadmium on crude 3β-chloro-5-bisnorcholenyl chloride. Chloroketone III prepared this way contained a single isomer and was more satisfactory than chloroketone produced either from 22-ketocholesterol (I) or 6β-methoxy-3,5-cyclocholestan-22-one (VIII).

The 3β-chloro-22-keto-5-cholestene (III) prepared by action of thionyl chloride on 22-ketocholesterol (I) or from 6β-methoxy-3,5-cyclocholestan-22-one (VIII) was shown to exist as two very similar isomers. These were probably the two epimers that can exist at C-20. These isomers were separated by chromatography on alumina: A,

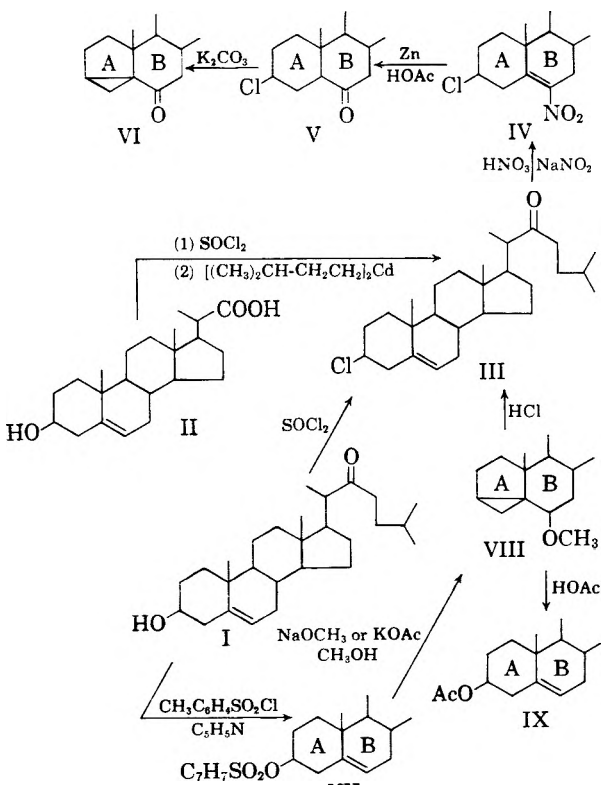
(1) Part of this work was abstracted from the Master of Science thesis of Z. F. Chmielewicz submitted to the faculty of De Paul University, 1952.

(2) W. Cole and P. L. Julian, *J. Am. Chem. Soc.*, **67**, 1369 (1945).

weakly adsorbed, m.p. 115.5–116°, $[\alpha]_D$ −50.0° and B, strongly adsorbed, m.p. 111–113°, $[\alpha]_D$ −49.6°; a mixture had m.p. 88–101°. The one isomer obtained in the alkylation of 3β-chloro-5-bisnorcholenyl chloride was form B, based on mixed melting point, and was the purest chloroketone obtained: m.p. 115.5–116°, $[\alpha]_D$ −53.2°.

3β-Chloro-22-keto-5-cholestene (III) (form B) was treated with sodium nitrite in nitric acid to produce the 3β-chloro-6-nitro-22-keto-5-cholestene (IV).[3] This product (IV) was reduced with zinc and acetic acid[3] to give the 3β-chloro-6,22-cholestadione (V). The chlorodione (V) was treated with potassium carbonate[4] to give 3,5-cyclocholesta-6,22-dione (VI). In the intermediate steps each product was chromatographed carefully on alumina to demonstrate the absence of an isomeric form.

In another sequence, 22-ketocholestrol (I) was converted to 22-ketocholesteryl *p*-toluenesulfonate (VII).[5] 6β-Methoxy-3,5-cyclocholestan-22-one (VIII) was prepared from the tosylate using sodium methoxide or potassium acetate.[6] Liquid fractions of high positive rotation appeared to be pure *i*-ether. These pure fractions were converted into 22-ketocholesteryl acetate (IX) and 3β-chloro-22-keto-5-cholestene (III). Attempts made to reduce the 22-keto group in the *i*-ether (VIII) using Wolff-Kishner procedures[7,8] failed to produce crystalline 6β-methoxy-3,5-cyclocholestane or, upon rearrangement with acetic acid, cholesteryl acetate.



EXPERIMENTAL

All melting points were uncorrected. The expression 'hexane' refers to 'Skellysolve B' (b.p. 60–70°) produced by the Skelly Oil Company, Kansas City, Mo. The alumina was Merck's 'Suitable for Chromatography.' Ultraviolet absorption spectra were taken on a Beckman Model DU spectrophotometer. Infrared spectra were taken on a Baird Associates infrared spectrophotometer. Elemental analyses were by (a) Clark Laboratories, Urbana, Illinois, (b) Micro-Tech Laboratories, Skokie, Ill. or by (c) Robert E. Meyer.

3β-Chloro-5-bisnorcholenyl chloride. Five grams of 3β-acetoxy-5-bisnorcholenic acid (The Glidden Company) was saponified to furnish 4.40 g. (99%) of hydroxy acid; m.p. 289–291°. Fernholz[9] reported m.p. 295°.

3β-Hydroxy-5-bisnorcholenic acid (II) (4.40 g.) was suspended in 50 ml. of dry ether and 100 ml. of benzene; and 6.60 g. (4.0 ml.) of thionyl chloride was swiftly added. The mixture was heated under reflux until the solution became homogeneous. The solvent was removed, an additional 50 ml. of benzene was added and was removed. A sample of the product was crystallized from benzene-hexane, m.p. 170–172°. The crude acid chloride was used for further reactions.

The acid *amide* was prepared from the acid chloride with aqueous ammonia in ethanol.[2] Recrystallization from ethanol-water gave a product having a melting point of 245–247°, $[\alpha]_D^{29}$ −21° (conc. 1.4 mg. per ml. of chloroform, α_D^{29} −0.06° in a 2-dec. tube).

Anal. Calcd. for $C_{32}H_{34}ClON$: C, 72.59; H, 9.42. Found. C, 72.65 (b); 9.49 (b).

3β-Chloro-5-cholesten-22-one (III). *A. Alkylation of 3β-chloro-5-bisnorcholenyl chloride.* Diisoamylcadmium was prepared under nitrogen with 36.5 g. of isoamyl bromide, 6.0 g. of magnesium and 24 g. of cadmium chloride in 125 ml. of ether.[2,10] A solution of 3β-chloro-5-bisnorcholenyl chloride prepared from 12.4 g. of 3β-hydroxy-5-bisnorcholenic acid (II) in 20 ml. of ether and 50 ml. of benzene was added. The mixture was stirred at 0° for 4 hr. and allowed to stand at room temperature overnight.

The reaction mixture was hydrolyzed with 10% hydrochloric acid. The organic layer was separated and washed with water and saturated sodium chloride. After drying with sodium sulfate the solvent was distilled and a residue of 12.9 g., m.p. 95–105°, was obtained. Crystallization from methanol and methanol-water gave several fractions totaling 7.73 g., m.p. 100–106°. (An additional 3.29 g. of less-pure, higher-melting product was also obtained.) To effect further purification the product was chromatographed on alumina, eluting with hexane and hexane-benzene solution, to give fractions melting at 106–111°. (Exhaustive chromatography on several fractions gave no evidence of the existence of the isomeric chloroketone.) Crystallization of this material from methanol gave 5.91 g. (39.1%) of the chloroketone, m.p. 113–115°, suitable for the subsequent reactions.

Four additional crystallizations from methanol gave the purest chloroketone obtained in this work: m.p. 115.5–116°, $[\alpha]_D^{24}$ −53.2° (39.3 mg. dissolved to 2 ml. in chloroform, α_D^{24} −1.044° in a 1 d. tube). This chloroketone was the more strongly adsorbed form B as shown by mixed melting points: mixed with A, m.p. 87–112° and mixed with B, m.p. 115–117°.

(3) *Cf.* A. Windaus and O. Dalmer, *Ber.*, **52**, 168 (1919).
(4) *Cf.* E. G. Ford, P. Chakravorty, and E. S. Wallis, *J. Am. Chem. Soc.*, **60**, 413 (1938).
(5) *Cf.* K. Freundenburg and H. Hess, *Ann.*, **148**, 128 (1926).
(6) W. Stoll, *Z. physiol. Chem.*, **207**, 147 (1932).
(7) Huang-Minlon, *J. Am. Chem. Soc.*, **68**, 248 (1946).
(8) B. Riegel and I. A. Kaye, *J. Am. Chem. Soc.*, **66**, 723 (1944).
(9) E. Fernholz, *Ann.*, **507**, 128 (1933).
(10) J. Cason and F. S. Prout, *Org. Syntheses*, Coll. Vol. III, 601 (1955).

The ultraviolet absorption spectrum shows the maximum at 285 mμ, log ε 1.88. The infrared spectrum had a peak at 5.9 microns characteristic of a ketone.[11]

The less-pure crystallization fractions (3.29 g., above) were chromatographed on alumina. Elution with ether-acetic acid (20:1) furnished an acid fraction: 1.49 g., m.p. 205–208°. Crystallization from cyclohexane gave 1.025 g., m.p. 215–217°, of 3β-chloro-5-bisnorcholenic acid; $[\alpha]_D^{28}$ −67° (10.5 mg. dissolved up to 5.0 ml. in chloroform. α_D^{28} −0.28° in a 2 dec. tube).

Anal. Calcd. for $C_{22}H_{33}O_2Cl$: C, 72.40; H, 9.11. Found: C, 71.95 (b); H, 9.24 (b).

This alkylation when attempted with the Grignard reagent gave a 19% yield of crude chloroketone.

B. Rearrangement of 6β-Methoxy-3,5-cyclocholestan-22-one (VIII). One hundred forty milligrams of 6β-methoxy-3,5-cyclocholestan-22-one (VIII) ($[\alpha]_D^{21}$ +30.1°, see below) was heated under reflux for 4 hr. with 10 ml. of dry acetone and 0.5 ml. of concentrated hydrochloric acid. The chloroketone precipitated upon dilution with water to give 101 mg. of crude product, m.p. 88–97°. This material was chromatographed on 15 g. alumina. Elution with 100 ml. of 1:9 benzene–hexane gave 48 mg. of isomer A, m.p. 100–108°, $[\alpha]_D^{25}$ −53° (chloroform). Elution with 1:4 benzene–hexane gave 22 mg. of a mixture (m.p. 80–101°) in the first 25 ml., but gave 28 mg. of isomer B, m.p. 111–113°, $[\alpha]_D^{25}$ −57° (chloroform), in the next 75 ml. Crystallization of A from alcohol gave 30 mg., m.p. 115–116.5°; and crystallization of B gave 13 mg., m.p. 112.5–114°. A mixture of the two melted at 87–97°.

Later samples of both A and B were prepared by careful chromatography of fractions of chloroketone from several runs. After chromatography and four crystallizations from ethanol the pure, weakly adsorbed A-fraction resulted as soft, short needles: m.p. 115.5–116° (softened at 113°); $[\alpha]_D^{22}$ −50.0° (58.0 mg. dissolved up to 1.96 ml. in chloroform, α_D^{22} −1.48° in 1 d. tube).

Anal. Calcd. for $C_{27}H_{43}OCl$. C, 77.36; H, 10.34. Found: C, 77.36 (b); H, 10.38 (b).

The more strongly adsorbed chloroketone, fraction B, resulted in pure heavy needles after three crystallizations from ethanol: m.p. 111–113° (softened at 109.5°); $[\alpha]_D^{22}$ −49.6° (47.0 mg. dissolved up to 1.96 ml. in chloroform, α_D^{22} −1.19° in a 1 d. tube).

Anal. Calcd. for $C_{27}H_{43}OCl$: C, 77.36; H, 10.34. Found: C, 77.07 (a); H, 10.10 (a).

A mixture of these two purified compounds had m.p. 88–101°.

C. Thionyl chloride on 22-ketocholesterol (I). 22-Ketocholesterol (I) (528 mg.) and 0.5 ml. of thionyl chloride was allowed to stand at 23° for 90 min. and heated at 40–60° for 90 min. The thionyl chloride was removed, 2 ml. of benzene was added and also removed *in vacuo*. The resulting oil was chromatographed on alumina. Elution with benzene-hexane mixtures gave three crude fractions totaling 439 mg. Fractional crystallization from alcohol led to 242 mg. of chloroketone, probably B-form, m.p. 110–116.5°. (Chloroketone prepared this way was also used to prepare the purified A- and B-forms, above.)

3β-Chloro-6-nitro-5-cholesten-22-one (IV). A suspension of 5.5 g. of 3β-chloro-5-cholesten-22-one (III) (B-isomer, prepared by alkylation of 3β-chloro-5-bisnorcholenyl chloride) in 70 ml. of glacial acetic acid was stirred while 15 ml. of fuming nitric acid (Merck, sp. gr. 1.50) was added in 20 min. After stirring for 30 min., 5.5 g. of sodium nitrite was added over a 30 min. period. After an additional hr. the mixture was poured into ice water, the solid was collected; 6.08 g. (107%); m.p. 172–180°. The chromatography of this product on 120 g. of alumina furnished 3.50 g. upon elution with benzene. Recrystallization from cyclohexane gave 2.4 g. (42%) of 3β-chloro-6-nitro-5-cholesten-22-one; m.p. 183–189°. Rechromatography of 100 mg. and crystallization from acetonitrile gave 52 mg. of pure product: m.p. 192–192.5°; $[\alpha]_D^{26}$ −52.0° (39.5 mg. dissolved up to 2 ml. in chloroform, α_D^{26} −1.027° in a 1 d. tube).

Anal. Calcd. for $C_{27}H_{42}ClO_3N$: C, 69.87; H, 9.12. Found: C, 69.88 (b); H, 8.98 (b).

The ultraviolet spectrum showed a maximum at 260 mμ; log ε 3.39. The infrared spectrum indicated the presence of a keto (5.9μ) and a nitro group (6.6μ).

3β-Chlorocholestane-6,22-dione (V). 3β-Chloro-6-nitro-5-cholesten-22-one (IV) (2.3 g.) in 55 ml. of glacial acetic acid was stirred while 4.3 g. of zinc dust was added over a 90 min. period. The mixture was stirred while heating under reflux for 2 hr. After filtering to remove the zinc, 20 ml. of water was added. The product which solidified upon cooling was collected; 1.40 g. (65%); m.p. 168–179° (darkens at 160°). After two chromatographs on alumina (eluting with 1:1 hexane–benzene) and crystallization from methanol, the purified chlorodione was obtained: m.p. 184.5–186°; $[\alpha]_D^{25}$ −14.3° (42 mg. dissolved up to 2 ml. in chloroform, α_D^{26} −0.301 in a 1 d. tube).

Anal. Calcd. for $C_{27}H_{43}O_2Cl$: C, 74.53; H, 9.96. Found. C, 74.67 (b); H, 10.04 (b).

The ultraviolet spectrum showed a maximum absorption at 290 mμ (log ε 1.98), characteristic of a ketone and no peak near 260 mμ as would be expected if the nitro group had persisted. The infrared spectrum showed an intensified band at 5.9μ (i.e., a ketone). No band at 6.6μ characteristic of the nitro group was evident.

3,5-Cyclocholestane-6,22-dione (VI). A mixture of 165 mg. of 3β-chlorocholestan-6,22-dione (V), 650 mg. of potassium carbonate, 30 ml. of 95% alcohol, and 1.5 ml. of water was heated under reflux for 2 hr. Water was added to precipitate the product which was then extracted with chloroform. After drying the chloroform solution with sodium sulfate and removing the solvent, 140 mg. (97%) of the *i*-dione was obtained; m.p. 127–130°. Crystallization from methanol gave 125 mg. (86.5%) of product: m.p. 128.5–130°; $[\alpha]_D^{27}$ +17.3° (36.5 mg. dissolved up to 2 ml. in chloroform; α_D^{26} +0.327° in a 1 d. tube).

Anal. Calcd. for $C_{27}H_{42}O_2$: C, 81.35; H, 10.62. Found: C, 81.52 (b); H, 10.66 (b).

The ultraviolet absorption spectrum showed a maximum at 282.5 mμ (log ε 2.14), indicative of the keto group. The infrared spectrum revealed a carbonyl band at 6μ, slightly displaced from 5.9μ expected for the carbonyl group.

22-Ketocholesteryl p-toluenesulfonate (VII). 22-Ketocholesterol (I) was prepared from 3β-acetoxy-5-bisnorcholenic acid in 72% yield using the three-step procedure of Cole and Julian.[2] This sterol (2.077 g.), 1.98 g. *p*-toluenesulfonyl chloride and 5 ml. of pyridine were mixed and allowed to stand 22 hr. at room temperature. The mixture was diluted with 35 ml. of water, was precipitated, and was collected: 2.84 g., m.p. 140–143°. After two crystallizations from acetone-hexane 1.289 g. (45.7%) resulted; m.p. 143–144.5°; $[\alpha]_D^{26}$ −52.0° (42.4 mg. dissolved up to 1.96 ml. in chloroform, α_D^{26} −1.139° in a 1 d. tube).

Anal. Calcd. for $C_{34}H_{50}O_4S$: C, 73.60; H, 9.08; S, 5.78. Found: C, 73.42 (a); H, 9.16 (a); S, 5.62 (c).

6β-Methoxy-3,5-cyclocholestan-22-one (VIII). *A. Sodium methoxide method.* Sodium (0.25 g.) was dissolved in 25 ml. of methanol and then 536 mg. of 22-ketocholesteryl tosylate (VII) was added. The mixture was heated under reflux for 4.5 hr., was diluted with water, and extracted with ether. After washing the ether and drying with sodium sulfate, the solvent was removed furnishing 395 mg. of crude oil. This oil was chromatographed on alumina. Elution with 1:1 hexane–benzene gave 361 mg. of oil (88.4%) that appeared homogeneous; $[\alpha]_D^{29}$ +32° (12.4 mg. dissolved up to 1.96 ml. with chloroform, α_D^{29} +0.20° in a 1 d. tube).

Anal. Calcd. for $C_{28}H_{46}O_2$: C, 81.10; H, 11.18. Found: C, 81.51 (a); H, 11.35 (a).

(11) H. M. Randall, N. Fuson, R. G. Fowler, and J. R. Dangl, *Infrared Determination of Organic Structures*, D. Van Nostrand Co., Inc., New York, New York, 1949.

B. Potassium acetate method. A mixture of 1.049 g. of 22-ketocholesteryl tosylate (VII), 1.5 g. of fused potassium acetate and 50 ml. of methanol was heated under reflux for 4.5 hr. After working up as described for procedure *A*, above, the crude oil was chromatographed on alumina. Elution with 1:4 benzene–hexane furnished 605 mg. (77%) of the *i*-ether as an oil, $[\alpha]_D$ +26° to +30° (chloroform). Further elution with 1:1 benzene–hexane and benzene gave 128 mg. of oil that was probably the normal ether, $[\alpha]_D$ −29° (chloroform).

22-Ketocholesteryl acetate (IX). A sample of 6β-methoxy-3,5-cyclocholestan-22-one (107 mg., $[\alpha]_D$ +26°) and 10 ml. of glacial acetic acid were heated under reflux for 5 hr. The mixture was diluted with water to give 108 mg. of material having m.p. 144–150°. Crystallization from ethanol gave 71 mg.; m.p. 150.5–152.5°; $[\alpha]_D^{31}$ −61° (chloroform). There was no depression upon mixing with an authentic sample of 22-ketocholesteryl acetate.

Attempted conversion of 6β-methoxy-3,5-cyclocholestan-22-one to 6β-methoxy-3,5-cyclocholestane. Two grams of sodium was dissolved in 10 ml. of methanol and 15 ml. of 85% hydrazine hydrate and 1.041 g. of the keto *i*-ether ($[\alpha]_D^{21}$ +30.1°) in 20 ml. of methanol were sealed in a tube.[8] The mixture was heated at 200° ± 10° for 12 hr. The product was extracted with ether-hexane, the solvent was removed, and the resulting oil was chromatographed on alumina. Elution with hexane gave 167 mg. of oil, $[\alpha]_D^{21}$ +43° (chloroform). (An additional 812 mg. of oil was obtained in subsequent elutions.)

The first eluate (167 mg., above) was heated under reflux for 5 hr. with 15 ml. of acetic acid. The 156 mg. of precipitate recovered was chromatographed on alumina and eluted with hexane. One fraction of 91 mg. had a specific rotation, $[\alpha]_D^{27}$ −52° (chloroform) and a following fraction of 36 mg. had a rotation of $[\alpha]_D^{25}$ −47°. Both fractions were oils and their structure is uncertain, since cholesteryl acetate has the m.p. 115–116° and $[\alpha]_D$ −47.4°.[12]

Essentially the same results were obtained when the Huang-Minlon procedure was used.[7]

Stability of the *i*-ether structure was shown by subjecting 1.0 g. of 6β-methoxy-3,5-cyclocholestane to the reduction conditions of Huang-Minlon.[7] Chromatography and crystallization from acetone-methanol furnished 485 mg. of purified starting material, m.p. 78–79°, $[\alpha]_D^{30}$ +54.0° (chloroform). Stoll[8] reported m.p. 79°, $[\alpha]_D$ +51.8°.

Acknowledgment. The authors wish to thank Drs. Wayne Cole and Byron Riegel for their helpful suggestions given during the course of this work.

CHICAGO 14, ILL.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX S.A.]

Steroids. CXIII.[1] 6-Methyl Estrogens

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17-Ethylenedioxy-6α,7α-oxidoestrone acetate (IV) was transformed into 6β-methyl-7α-hydroxyestrone (VI) and thence by collidine treatment of its 3-benzoate-7-mesylate (VIII) into 6-methyl-6-dehydroestrone (X). Catalytic hydrogenation provided 6β-methylestrone (XIII) while reduction with sodium borohydride led to 6β-methylestradiol (XV). Introduction of a 6β-methyl group into estrone or estradiol was found to be associated with a drastic decrease in estrogenic activity.

Introduction of a methyl group in position 6 of steroids belonging to the androgenic, progestational, and cortical hormone series[3] usually results in an increase in biological activity. The only group of hormones which have so far not been investigated in this respect are the estrogens and the present paper deals with the preparation of some 6-methylated estrogenic hormones.

The most commonly employed route to 6-methyl steroids has been the conversion of a Δ^5-olefin to the corresponding 5α,6α-epoxide followed by opening with a methylmagnesium Grignard reagent.[3,4] The ready availability of 6-dehydroestrone (I)[5] and 6-dehydroestradiol (II)[6] led us to employ the same path, the key intermediate being, 17-ethylenedioxy-6α,7α-oxidoestrone 3-acetate (IV); its preparation (I→II→III→IV) and stereochemistry (by transformation to 7α-hydroxyestrone) have already been reported in an earlier paper from this Laboratory.[7] Treatment of the ketal-epoxide IV with methylmagnesium bromide provided 17-ethylenedioxy-6β-methyl-7α-hydroxyestrone (V),[8] while cleavage of the ketal to 6β-methyl-7α-hydroxyestrone (VI) was accomplished

(1) Paper CXII, J. A. Zderic, D. Chávez, H. J. Ringold, and C. Djerassi, in press.

(2) This material represents part of the professional thesis submitted by Srta. Esperanza Velarde to the Facultad de Química, Universidad Motolinia.

(3) For leading references see: (a) H. J. Ringold, E. Batres, and G. Rosenkranz, *J. Org. Chem.*, **22**, 99 (1957); A. Bowers and H. J. Ringold, *J. Am. Chem. Soc.*, **80**, 3091 (1958). (b) G. Cooley, B. Ellis, D. N. Kirk, and V. Petrow, *J. Chem. Soc.*, 4112 (1957) and earlier papers. (c) J. A. Campbell, J. C. Babcock, and J. A. Hogg, *J. Am. Chem. Soc.*, **80**, 4717 (1958) and earlier papers.

(4) M. I. Ushakov and O. S. Madaeva, *J. Gen. Chem. (U.S.S.R.)*, **9**, 436 (1939); L. F. Fieser and J. Rigaudy, *J. Am. Chem. Soc.*, **73**, 4560 (1951); R. B. Turner, *J. Am. Chem. Soc.*, **74**, 5362 (1952).

(5) S. Kaufmann, J. Pataki, G. Rosenkranz, J. Romo, and C. Djerassi, *J. Am. Chem. Soc.*, **72**, 4531 (1950).

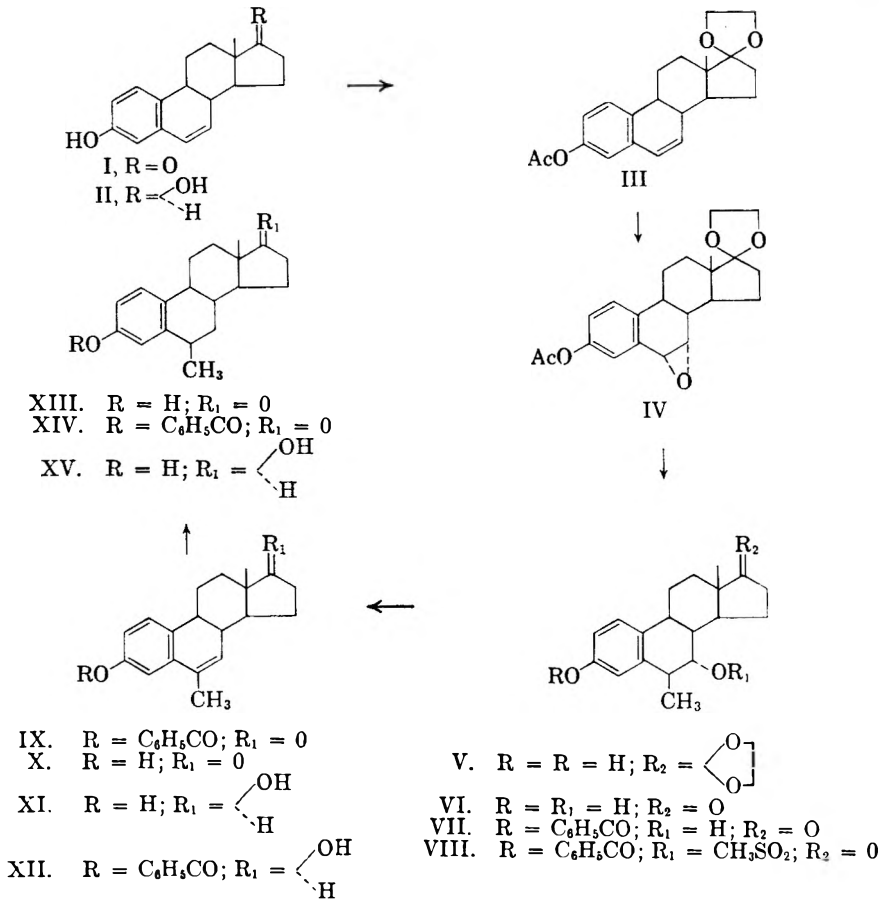
(6) C. Djerassi, G. Rosenkranz, J. Romo, S. Kaufmann, and J. Pataki, *J. Am. Chem. Soc.*, **72**, 4534 (1950).

(7) J. Iriarte, H. J. Ringold and C. Djerassi, *J. Am. Chem. Soc.*, **80**, 6105 (1958).

(8) The product of normal diaxial opening (see A. Fürst and P. Plattner, 12th Internat. Congress Pure and Appl. Chem., New York 1951, Abstracts, p. 405), which is still further favored because of benzylic activation.

with *p*-toluenesulfonic acid in acetone solution.[9] The 7α-hydroxy group was removed by converting 6β-methyl-7α-hydroxyestrone (VI) *via* its 3-benzoate VII to the 3-benzoate-7-mesylate VIII and heating the latter with γ-collidine. The resulting 6-methyl-6-dehydroestrone benzoate (IX) was saponified to 6-methyl-6-dehydroestrone (X), which exhibited the characteristic triple ultraviolet absorption maxima at 222, 262, and 305 mμ associated with the 6-dehydroestrogen chromophore.[5,6,10] Reduction of X with sodium borohydride provided 6-methyl-6-dehydroestradiol (XI) which was characterized further as the 3-monobenzoate XII.

Hydrogenation of 6-methyl-6-dehydroestrone (X) proceeded smoothly to yield 6β-methylestrone (XIII), the β-orientation being assigned to the methyl group by assuming hydrogenation from the less hindered α-side,[11] while further reduction with sodium borohydride led to 6β-methylestradiol (XV). Estrogenic assay[12] (by injection) in mice using uterine weight increase as the criterion and estrone as the standard indicated that XIII and XV possessed only about $\frac{1}{500}$ the estrogenic activity of estrone.



EXPERIMENTAL[13]

17-Ethylenedioxy-6β-methyl-7α-hydroxyestrone (*V*). To a solution of 2.0 g. of 17-ethylenedioxy-6α,7α-oxidoestrone 3-acetate (IV)[7] in 200 cc. of dry ether and 10 cc. of dry benzene was added 20 cc. of an ethereal solution of methylmagnesium bromide (Arapahoe Chemicals, Inc., Boulder, Colo.) and the mixture was heated under reflux for 30 min. After pouring into dilute hydrochloric acid solution, the organic solution was dried, evaporated, and the residue recrystallized from ethyl acetate to give an average yield of 60% of satisfactory material, m.p. 226–229°. The analytical sample of V crystallized from ethyl acetate as colorless crystals, m.p. 235–237°, $[\alpha]_D$ ±0°, λ_{max}^{EtOH} 280 mμ, log ϵ 3.32.

Anal. Calcd. for $C_{21}H_{28}O_4$: C, 73.23; H, 8.19; O, 18.58. Found: C, 72.62; H, 8.11; O, 18.64.

6β-Methyl-7α-hydroxyestrone (*VI*) *and derivatives.* A solution of 1.38 g. of the ketal V and 100 mg. of *p*-toluenesulfonic acid in 100 cc. of acetone and 30 cc. of water was heated under reflux for 30 min. and then poured into aqueous so-

(9) G. Rosenkranz, J. Pataki and C. Djerassi, *J. Org. Chem.*, **17**, 290 (1952).

(10) It is interesting to note that the methyl substituent had essentially no effect upon the position of the three maxima.

(11) That this assumption is also valid in the presence of an aromatic ring A is evidenced by the course of the hydrogenation of 7-ketoestrone enol acetate [ref. 7 and W. H. Pearlman and O. Wintersteiner, *J. Biol. Chem.*, **132**, 605 (1940)].

(12) We are indebted to Dr. R. I. Dorfman, Worcester Foundation for Experimental Biology, Shrewsbury, Mass., for the bioassays.

(13) Melting points are uncorrected. Unless noted otherwise all rotations were measured in dioxane solution. We are indebted to Dr. L. Throop and staff for all rotation and spectral measurements.

dium bicarbonate solution. Extraction with ethyl acetate and concentration afforded 1.22 g. of crystals, m.p. 206–208°, raised upon further recrystallization to m.p. 218–220°, $[\alpha]_D$ +110°, λ_{max}^{EtOH} 280 mμ, log ε 3.41.

Anal. Calcd. for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 76.17; H, 7.85.

The *3-monobenzoate VII* was prepared by adding dropwise 0.6 cc. of benzoyl chloride to 0.38 g. of 6β-methyl-7α-hydroxyestrone (VI) in 30 cc. of cold 5% aqueous potassium hydroxide and shaking vigorously. Extraction with ethyl acetate, thorough washing with sodium bicarbonate solution and water, drying, and concentration yielded the monobenzoate (0.37 g.) m.p. 220–223°, which was used in the next step. The analytical sample exhibited m.p. 230–232°, $[\alpha]_D$ +101°.

Anal. Calcd. for $C_{26}H_{28}O_4$: C, 77.20; H, 6.98; O, 15.82. Found: C, 77.28; H, 6.91; O, 15.88.

To a solution of 0.36 g. of the benzoate VII in 10 cc. of pyridine was added dropwise at 0° 1 cc. of methanesulfonyl chloride and 10 cc. of pyridine and after standing at room temperature overnight, the mixture was diluted with ether and washed well with dilute sulfuric acid, bicarbonate solution, and water. The dry ether solution was concentrated to incipient crystallization and after chilling, 0.20 g. of *6β-methyl-7α-hydroxyestrone 3-benzoate 7-mesylate* (VIII), m.p. 148–150° (dec.), was collected. Decolorization with Norit in hexane–benzene solution followed by recrystallization from chloroform furnished the analytical specimen, m.p. 156–158° (dec.), $[\alpha]_D$ +79° (chloroform).

Anal. Calcd. for $C_{27}H_{30}O_6S$: C, 67.20; H, 6.27; O, 19.89; S, 6.64. Found: C, 67.68; H, 6.40; O, 19.61; S, 6.32.

6-Methyl-6-dehydroestrone (X). A solution of 0.77 g. of the 3-benzoate-7-mesylate VIII in 50 cc. of γ-collidine was heated under reflux for 1 hr., cooled, diluted with ether, and washed well with dilute hydrochloric acid and water. Evaporation of the dried ether solution, decolorization with Norit in hexane–benzene solution and recrystallization from methanol led to 0.48 g. of *6-methyl-6-dehydroestrone 3-benzoate* (IX), m.p. 142–145°. The analytical sample, prepared from the same solvent, showed m.p. 153–156°, $[\alpha]_D$ −57°.

Anal. Calcd. for $C_{26}H_{26}O_3$: C, 80.80; H, 6.78. Found: C, 80.89; H, 7.16.

Saponification of the benzoate IX was performed by heating it under reflux for 1 hr. with 1% methanolic potassium hydroxide solution and recrystallization from ether. The analytical specimen of *6-methyl-6-dehydroestrone* (X) exhibited m.p. 218–220°, $[\alpha]_D$ −67°, λ_{max}^{EtOH} 222, 262, and 305 mμ, log ε 4.37, 3.83 and 3.42 mμ.

Anal. Calcd. for $C_{19}H_{22}O_2$: C, 80.81; H, 7.85. Found: C, 80.30; H, 7.84.

6-Methyl-6-dehydroestradiol (XI). To a solution of 0.6 g. of 6-methyl-6-dehydroestrone (X) in 50 cc. of methanol was added 0.7 g. of sodium borohydride dissolved in 50 cc. of water. After standing for 3 hr., acetic acid was added to neutrality, the mixture was concentrated, extracted with ethyl acetate, and the crude product chromatographed on 30 g. of silica gel. Elution with benzene–ether (4:1) and recrystallization from ether–hexane gave 0.40 g. of colorless crystals, m.p. 197–199°, $[\alpha]_D$ −135°, λ_{max}^{EtOH} 221, 262, and 304 mμ, log ε 4.35, 3.86, and 3.45.

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 79.85; H, 8.32.

Schotten-Baumann benzoylation (as described above for VI) and recrystallization from ether provided *6-methyl-6-dehydroestradiol 3-monobenzoate* (XII), m.p. 169–170°, $[\alpha]_D$ −98°.

Anal. Calcd. for $C_{26}H_{28}O_3$: C, 80.38; H, 7.26; O, 12.36. Found: C, 79.81; H, 7.22; O, 12.64.

6β-Methylestrone (XIII). The hydrogenation of 0.86 g. of 6-methyl-6-dehydroestrone (X) in 80 cc. of ethyl acetate was conducted at room temperature and atmospheric pressure in the presence of an equal weight of pre-reduced 10% palladized charcoal catalyst. Hydrogen up-take (corresponding to one equivalent) ceased within 30 min. and filtration of the catalyst, evaporation of the solvent, and recrystallization from ethyl acetate provided 0.84 g. of 6β-methylestrone (XIII), m.p. 219–222°. Repeated recrystallization furnished the analytical specimen, m.p. 225–226°, $[\alpha]_D$ +121°, λ_{max}^{EtOH} 281 mμ, log ε 3.32.

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51; O, 11.25. Found: C, 79.94; H, 8.51; O, 11.27.

6β-Methylestrone benzoate (XIV) was obtained by heating a sample of XIII with benzoyl chloride in pyridine solution for 30 min. on the steam bath and recrystallization from ether; m.p. 146–150°, $[\alpha]_D$ +98°.

Anal. Calcd. for $C_{26}H_{28}O_3$: C, 80.38; H, 7.26; O, 12.36. Found: C, 80.01; H, 7.14; O, 12.58.

6β-Methylestradiol (XV). The reduction of 6β-methylestrone with sodium borohydride was performed exactly as described above for X and after recrystallization from ether–hexane yielded 78% of pure 6β-methylestradiol, m.p. 174–176°, $[\alpha]_D$ +50°, λ_{max}^{EtOH} 281 mμ, log ε 3.29.

Anal. Calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15; O, 11.17. Found: C, 79.20; H, 9.44; O, 11.59.

APT. POSTAL 2679
MEXICO, D. F.

[JOINT CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE STATE UNIVERSITY AND THE RESEARCH LABORATORIES OF CHAS. PFIZER AND CO.]

Alkaloid Studies. XXII.[1] The Alkaloids of *Vallesia dichotoma* Ruiz et Pav[2]

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In an examination of the alkaloids of *Vallesia dichotoma* there was isolated reserpine, aspidospermine, vallesin, and a new alkaloid ($C_{21-22}H_{24-26}N_2O_4$) now named dichotamine. Analytical data and spectral evidence suggest that the latter compound contains the same methoxylated *N*-acetyldihydroindole nucleus (I) as is present in aspidospermine.

In a recent publication[5] we described the isolation of a new alkaloid spegazzinine ($C_{21-22}H_{28-30}N_2O_3$) which occurs together with quebrachamine in the bark of *Aspidosperma chakensis* Spegazzini. In continuation of our studies into the alkaloids from the *Apocynaceae* plant family we have now undertaken a detailed examination of *Vallesia dichotoma* from which an alkaloid had already been isolated[6] and subsequently shown to be aspidospermine.[7]

In the present investigation all parts of the plant were separately examined by a scheme[8] used earlier with certain *Rauwolfia* alkaloids with the following results:

Reserpine. This alkaloid was isolated in approximately 0.025% yield from the benzene-soluble acetates derived from the plant stems. This represents one of the few recorded instances where this important alkaloid has been encountered in a genus other than *Rauwolfia* and it appears to be the first time that reserpine has been isolated from the genus *Vallesia*. Thus while small amounts of reserpine have been reported in one species each of the genera *Alstonia*,[9a] *Tonduzia*[9b] and *Vinca*,[9c] none has been found in *Vallesia glabra*.[10]

Aspidospermine, isolated in approximately 0.2% yield from the benzene-insoluble acetate fraction from the leaves and twigs. The identity of this compound was established by mixture melting point determination, infrared and ultraviolet spectra.[11]

Vallesin, isolated in approximately 0.04% yield from the benzene-insoluble acetate fraction from the leaves and twigs. This alkaloid was first isolated from *Vallesia glabra* and shown to be identical with desacetylformylaspidospermine.[12] It should be noted that on the basis of the formula $C_{22}H_{30}N_2O_2$ for aspidospermine,[11] the formula for vallesin should be $C_{21}H_{28}N_2O_2$ rather than $C_{20}H_{26}N_2O_2$ as reported[12] originally and our own analytical results are consistent with this view.

Dichotamine, a new alkaloid isolated in approximately 0.05% yield from the benzene-insoluble acetate fraction of the leaves and twigs. The compound has the molecular formula $C_{21-22}H_{24-26}N_2O_4$ and contains one methoxyl, one *N*-methyl (*vide infra*) and one (N- or O-) acetyl group. The ultraviolet absorption spectrum [λ_{min} 235 mμ (log ϵ 3.73), λ_{max} 255 mμ (log ϵ 4.04), λ_{infl} 280–290 mμ (log ϵ 3.43–3.29)] is almost identical with the corresponding spectrum of aspidospermine. The chromophoric system of the latter compound has been shown[13] to be that of the methoxylated *N*-acetyldihydroindole system (I) and it therefore seems likely that dichotamine also contains this chromophore thus accounting for the methoxyl and acetyl groups found in the analysis. The infrared spectrum of dichotamine shows strong absorption bands at 5.67, 6.00, and 6.67 μ and a moderate intensity band at 6.22 μ. There is no significant absorption in the 3 μ region or at 8 μ. The 6.00 μ band is attributable to the *N*-acetyl group of partial structure (I) and the 6.22 μ and 6.67 μ bands are probably due to the aromatic

(1) Paper XXI, C. Djerassi, C. Bankiewicz, A. L. Kapoor, and B. Riniker, *Tetrahedron*, 2, 168a (1958).

(2) The work at Wayne State University was supported by research grants from Chas. Pfizer and Co. and from the National Heart Institute (grant No. H-2574) of the National Institutes of Health.

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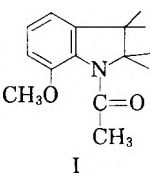
(10) W. J. McAteer, R. G. Weston and E. E. Howe, *Chem. & Ind. (London)*, 1387 (1956). According to some botanical authorities *V. glabra* and *V. dichotoma* are synonyms, but they may represent different varieties of the same species.

(11) B. Witkop, *J. Am. Chem. Soc.*, 70, 3712 (1948) and earlier references. We are greatly indebted to Dr. B. Witkop (National Institutes of Health, Bethesda) for an authentic specimen.

(12) E. Schlittler and M. Rottenberg, *Helv. Chim. Acta*, 31, 446 (1948).

(13) B. Witkop and J. B. Patrick, *J. Am. Chem. Soc.*, 76, 5603 (1954); J. R. Chalmers, H. T. Openshaw, and G. F. Smith, *J. Chem. Soc.*, 1115 (1957).

ring present in (I). In this connection it is significant that aspidospermine shows similar infrared bands in this region of the spectrum. It is interesting to speculate that the band at 5.67 μ could be attributed to a lactone ring and further that the difference in structure between dichotamine and aspidospermine might lie largely in such a lactone. The apparent molecular formulas of aspidospermine ($C_{22}H_{30}N_2O_2$) and dichotamine ($C_{22}H_{26}N_2O_4$) could be consistent with such an hypothesis. Furthermore, we have already presented evidence[5] to show that spegazzinine, which is possibly structurally related to aspidospermine, has an alcoholic hydroxyl group. A similar group in dichotamine could be involved in lactone formation. Functional group analysis points towards the presence of an *N*-methyl group although it is conceivable that this may prove to be erroneous.[14] It is pertinent to note that aspidospermine was originally believed to lack such a functional group, then was assigned one by nuclear magnetic resonance studies,[15] and finally was shown not to possess this moiety by classical degradation means.[16] Additional work is necessary to settle this point and to gain further insight into the structural features of this interesting member of the *Aspidosperma* alkaloid group. Lack of material has so far prevented further degradative study of dichotamine and since no additional supplies are anticipated in the foreseeable future, the results to date are presented in this paper.



I

The many other fractions we have obtained from *V. dichotoma* have so far yielded no crystalline material in characterizable amounts although paper chromatography indicates the presence of other alkaloids.

EXPERIMENTAL[17]

Isolation of alkaloids. Vallesia dichotoma was collected in the Department of Ica, 350 kilometers south of Lima, Peru, by Dr. Ramon Ferreyra (Universidad Nacional Mayor de San Marcos, Lima) to whom we express our thanks. The material consisted of 655 g. of stems, 1300 g. of leaves and twigs, and root which was divided into two portions: 1280 g. of root and 840 g. of low stem material, cut from the "pure" root pieces.

Leaves and twigs (1300 g.) were ground and extracted with 6 l. of boiling methanol for 6 hr., filtered, washed, and the extraction repeated. The combined extracts containing 300 g. solids were concentrated to 1 l. and 300 ml. of glacial acetic acid added. The solid residue was separated by filtration, washed with hexane and with methanol to leave 10.8 g. of a white partially crystalline solid. This non-basic material was not investigated further.

The filtrate was diluted with 4 l. of water and extracted with 4 × 1 l. hexane. The combined extracts were washed with 10% acetic acid and concentrated to dryness to give 26 g. of chlorophyll and waxes which were not further examined.

The acid aqueous phase was then extracted with 4 × 1 l. benzene, the extract washed with 10% ammonium hydroxide and concentrated to dryness under vacuum to give 2.0 g. solids. An acetic acid solution gave a positive Meyer's test. Paper chromatography showed no reserpine and chromatography on alumina gave no crystalline material.

The acid aqueous phase from above was then basified to *p*H 10.7 and extracted with 3 × 1500 ml. chloroform. Concentration to dryness under vacuum yielded 12.5 g. solid. Paper chromatography showed the presence of at least 6 components. This solid (7.25 g.) was dissolved in 500 ml. chloroform:benzene (1:1) and, after removal of a small amount of amorphous material, the solution was chromatographed on 800 g. alumina, collecting fractions of 200 ml. The first 6 fractions eluted with benzene:chloroform (1:1) contained only 69 mg. of material and were discarded.

From fractions 7–14 [benzene:chloroform (1:1)], 2.1 g. of brown, partially crystalline material was obtained. Crystallization from a small amount of acetonitrile gave 470 mg. of colorless prisms, m.p. 180–195°. Twice recrystallized from ethyl acetate and once from aqueous methanol the above material had m.p. 195–200°, $[\alpha]_D$ −92.5° (*c*, 0.58%), λ_{max}, 256 mμ (log ϵ 4.01), λ_{min} 236 mμ (log ϵ 3.68), λ_{infl} 280–290 mμ (log ϵ 3.40–3.18). These constants and the infrared spectrum of the compound are identical with those of *aspidospermine* and a mixture melting point showed no depression.

From fractions 14–21 [benzene:chloroform (1:1)], 21–28 [benzene:chloroform (1:3)], and 29 (chloroform) intractable oils, (410 mg.), (395 mg.), and (160 mg.) respectively were isolated. Fractions 30–46 (chloroform) gave 672 mg. of a yellow oil which solidified on trituration with a small amount of methanol and which was crystallized from acetonitrile to give *dichotamine* in needles, m.p. 225–249°. After many recrystallizations from ethyl acetate and from aqueous methanol dichotamine had m.p. 254–257°; $[\alpha]_D$ −105.2° (c, 0.74%); pK_a 5.4 and 10.8 in 66% dimethylformamide, mol. wt. 340; λ_{max} 255 mμ (log ϵ 4.04), λ_{min} 235 mμ (log ϵ 3.75), λ_{infl} 280–290 mμ (log ϵ 3.43–3.29); infrared bands (chloroform solution) *inter al.* at 5.67 (s), 6.00 (s), 6.22 (m) and 6.67 (s) μ.

Anal. Calcd. for $C_{22}H_{26}N_2O_4$: C, 69.09; H, 6.85; N, 7.37; OMe, 8.1; (N)-Me, 3.9; CH_3CO, 11.2; mol. wt. 382.4; for $C_{21}H_{24}N_2O_4$: C, 68.46; H, 6.57; N, 7.60; OMe, 8.42; (N)-Me, 4.08; CH_3CO, 11.69; mol. wt. 368.4. Found: C, 68.47; H, 6.68; N, 7.51; OMe, 7.15; (N)-Me, 3.22; CH_3CO, 9.11.

From fractions 22–29 [chloroform:methanol (99:1)], 30–36 [chloroform:methanol (9:1)], and 37–39 (methanol) 1.32 g. of intractable material was obtained.

From a second batch of leaves and twigs (1300 g.) 19 g. of chloroform-soluble bases were obtained by the above extraction procedure. As it was felt that some of the less polar constituents of the mixture may not have been purified sufficiently for characterization in the above chromatography on partially deactivated alumina, the material from the

(14) See B. Witkop, *J. Am. Chem. Soc.*, **71**, 2559 (1949).

(15) H. Conroy, P. R. Brook, M. K. Rout, and N. Silverman, *J. Am. Chem. Soc.*, **79**, 1763 (1957).

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(17) All melting points were determined with a Kofler block. Rotations and infrared spectra were measured in chloroform and ultraviolet spectra in 95% ethanol. Unless otherwise stated, alumina used in chromatography was of chromatographic grade and was partially deactivated by shaking a benzene slurry of 100 g. of alumina with 3 ml. of 10% aqueous acetic acid. We are grateful to Mrs. D. Phillips for all spectroscopic determinations and to Mr. G. M. Maciak (Lilly Research Laboratories) and to Dr. A. Bernhardt (Mulheim, Germany) for microanalytical determinations.

second extraction (7.25 g.) was chromatographed on 800 g. of undeactivated Merck acid washed alumina, collecting fractions of 500 ml. Fractions 1–22 [benzene:chloroform (1:1)] and 23–25 [benzene:chloroform (1:2)] and 25–34 [benzene:chloroform (1:3)] gave 0.27 g., 0.03 g., and 0.34 g. respectively of intractable material.

Fractions 35–46 (chloroform) gave 1.06 g. of a crystalline brown solid. Recrystallized from ether 0.32 g. of *vallesin* was obtained in colorless needles, m.p. 153–156° not raised by further crystallization from hexane or by sublimation; $[\alpha]_D$ −92°, (*c*, 0.12 in chloroform); λ_{max} 259 mμ (log ε 4.11), infrared bands (chloroform) *inter al.* at 5.96 (vs), 6.02 (vs), 6.13 (s), 6.2 (vs), 6.66 (vs) and 6.76 (vs) μ.

Anal. Calcd. for $C_{21}H_{28}N_2O_2$: C, 74.08; H, 8.29; N, 8.23; O, 9.40; OMe, 9.11; (N)-Me, 4.42. Found: C, 73.97; H, 8.18; N, 8.21; O, 9.55; OMe, 8.72; (N)-Me, 1.49.

Fractions 47–51 [chloroform:methanol (97:3)] gave 2.14 g. of a brown semi-solid compound which upon trituration with ether gave 1.18 g. of a cream-colored crystalline compound. Recrystallized from hexane:benzene this material yielded aspidospermine, m.p. 206–208°, characterized by mixture melting point, infrared and ultraviolet spectra.

Fractions 51–62 [chloroform:methanol (95:5)], 63–67 [chloroform:methanol (9:1)], 68–75 [chloroform:methanol (4:1)], 76–82 [chloroform:methanol (7:3)] and 83–96 [chloroform:methanol (2:3)] provided respectively 0.67 g., 0.47 g., 0.21 g., 0.20 g., and 0.37 g. of brown amorphous solid from which no crystalline material could be obtained. It therefore seems likely that dichotamine present in the original mixture is too strongly adsorbed on undeactivated alumina to permit a satisfactory isolation and purification.

Stems. Using an extraction procedure exactly similar to that described for the leaves and twigs, 655 g. of ground stems gave 67 g. of total solid extract, which was processed as described above to give the following fractions: (1) A non-basic extract of hexane solubles (discarded). (2) Benzene-soluble acetates (1.6 g.). (3) Chloroform-soluble bases (2.2 g.). The paper chromatographic behavior of this fraction showed that it had a similar composition to the corresponding fraction from the leaves and twigs.

The benzene-soluble acetates were crystallized from 40 ml. of methanol giving 315 mg. of crude *reserpine*. After washing with hexane, the crude reserpine was recrystallized from methanol:benzene to give 115 mg. of still impure reserpine, m.p. 253–255° (dec.). The infrared spectrum and paper chromatogram were characteristic of authentic reserpine.

The benzene-soluble acetates were chromatographed on alumina but no crystalline fractions were obtained.

Stems taken from directly above the roots, (837 g.) were ground, extracted with methanol and processed as above to give the following fractions: (1) Non-basic hexane extract (5.7 g.) (not investigated). (2) Benzene-soluble acetates (0.80 g.). (3) Chloroform-soluble bases (5.5 g.). (4) Chloroform and water-insoluble bases (4.6 g.) (not investigated).

The benzene-soluble acetates showed no reserpine by paper chromatography.

The chloroform-soluble bases showed 6 components by paper chromatography but none of them appeared to be identical with those of the benzene-insoluble acetates from the previous stem extraction. Careful chromatography of this fraction on alumina, followed by counter-current partition of some of the chromatographic fractions gave only traces of crystalline material in amounts insufficient to characterize.

Roots (1220 g.) were ground, extracted with 2 × 6l. of hot methanol, and the extract (150 g.) was processed as previously described to give the following fractions: (1) Non-basic extract of hexane-solubles (9.2 g.) (not investigated). (2) Benzene-soluble acetates (1.05 g.). (3) Chloroform-soluble bases (8.55 g.).

The benzene-soluble acetates when chromatographed on paper showed 9 components but only traces of reserpine.

The chloroform-soluble bases showed 4 or more components when chromatographed on paper, but careful chromatography on alumina gave only intractable resins.

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[CONTRIBUTION FROM THE INDIAN ASSOCIATION FOR THE CULTIVATION OF SCIENCE]

Studies on the Ultraviolet Absorption Spectra of Coumarins and Chromones. II. Hydroxy Derivatives[1]

KALYANMAY SEN AND P. BAGCHI

Received August 12, 1958

Study of the ultraviolet absorption spectra of coumarins and chromones, substituted by hydroxy groups in the aromatic as well as in the heterocyclic nucleus in different positions shows bathochromic shift in the position of one or more of the principal bands.

In a previous communication[2] it has been shown that a methyl group substituting different positions in coumarin and chromone fails to cause any significant bathochromic shift of the main absorption bands. This was considered to be due to the weak auxochromic property of the methyl group.

The subject of the present investigation is a systematic survey of the absorption characteristics of coumarins and chromones having hydroxyl groups at different positions of the coumarin and chromone molecule.

The absorption spectra of some similar coumarins and chromones have been reported.[3–5]

The compounds studied have been listed in Tables I and II. Absorption was measured with a Beckmann Model DU quartz spectrophotometer

(1) Taken from the thesis submitted by Kalyanmay Sen for the degree of Doctor of Philosophy (Science) of the University of Calcutta, April 1957.

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using ethanol as the solvent at a concentration of about 5–6 mg. per liter in the region 220–360 mμ. Beyond this range no interesting features were, in general, observed. Preparation of the compounds following methods given in the literature is described under Experimental.

Results and discusssion. The absorption spectra of the hydroxycoumarins and hydroxychromones studied are given in Figures 1, 2, and 3.

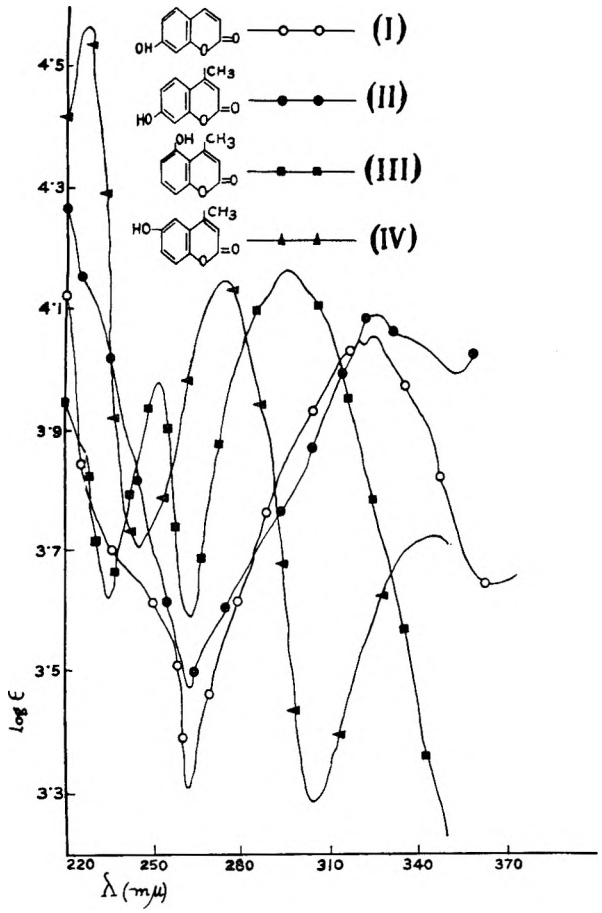

Fig. 1. Ultraviolet absorption spectra of I, 7-Hydroxycoumarin —○—○—; II, 7-Hydroxy-4-methylcoumarin —●—●—; III, 5-Hydroxy-4-methylcoumarin —■—■—■—; IV, 6-Hydroxy-4-methycoumarin —▲—▲—

It will be observed that the absorption spectrum of 6-hydroxy-4-methylcoumarin resembles those of coumarin and its methyl derivatives[2] quite closely. There is the characteristic minimum at 244 mμ(log ε = 3.71), the maximum at 275 mμ (log ε = 4.15), and the second minimum at 305 mμ. In addition there is to be found another very intense maximum at 227 mμ (log ε = 4.56) which is not observed in the spectra of coumarin and its methyl derivatives. This is perhaps the E band[6] shifted bathochromically due to the presence of the hydroxyl group in the aromatic nucleus. In the case of coumarin and its methyl derivatives this band presumably lies below 220 mμ. The band at

(6) E. A. Braude, *Ann. Repts.*, **42**, 105 (1945).

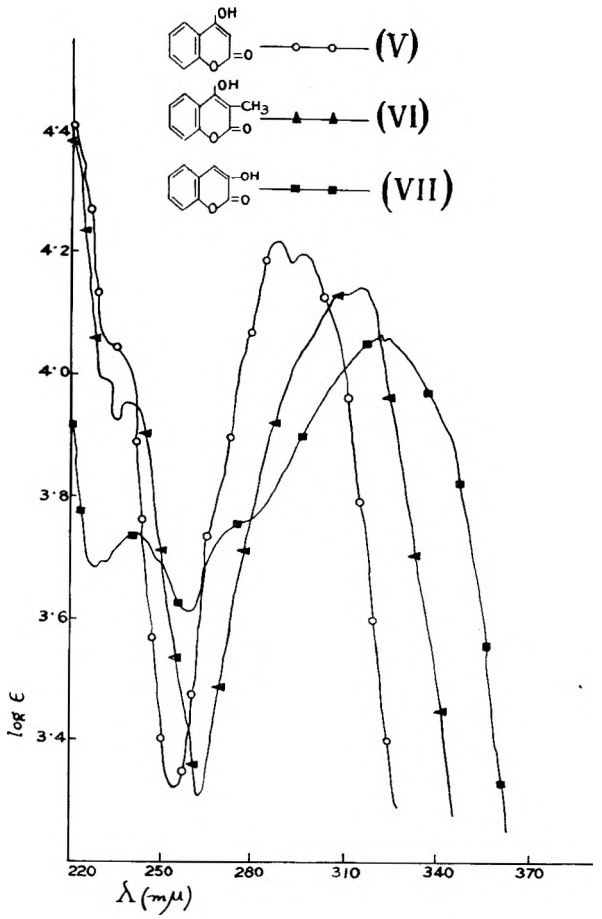

Fig. 2. Ultraviolet absorption spectra of V, 4-Hydroxycoumarin —○—○—; VI 4-Hydroxy-3-methylcoumarin —▲—▲—; VII, 3-Hydroxycoumarin —■—■—

275 mμ is presumably the K band and the low intensity one at 346 mμ the B band, which is shifted bathochromically compared to those in the spectra of coumarin and its methyl derivatives.

The spectra of 7-hydroxycoumarin and 7-hydroxy-4-methylcoumarin are very similar but are quite distinct from those of coumarin and its methyl derivatives. In both the first minimum lies around 261 mμ. In both the K and B bands have merged giving rise to one band. This contention is supported by the observation of twin peaks in the spectrum of 7-hydroxycoumarin. The presence of 4-methyl group in 7-hydroxy-4-methylcoumarin does not cause any significant change in the spectrum. A well-defined inflection at 240 mμ is observed in the spectrum of 7-hydroxycoumarin. The spectrum of the 4-methyl derivative shows a less distinct inflection at 228 mμ.

The spectrum of 5-hydroxy-4-methylcoumarin may be considered to fall in the class of the spectra of 7-hydroxycoumarin and its 4-methyl homolog. In this case the inflections observed in the spectra of 7-hydroxycoumarin and its 4-methyl homolog in the region 225–240 mμ has become resolved into a well defined band with maximum at 251 mμ (which we do not consider to be the E band because

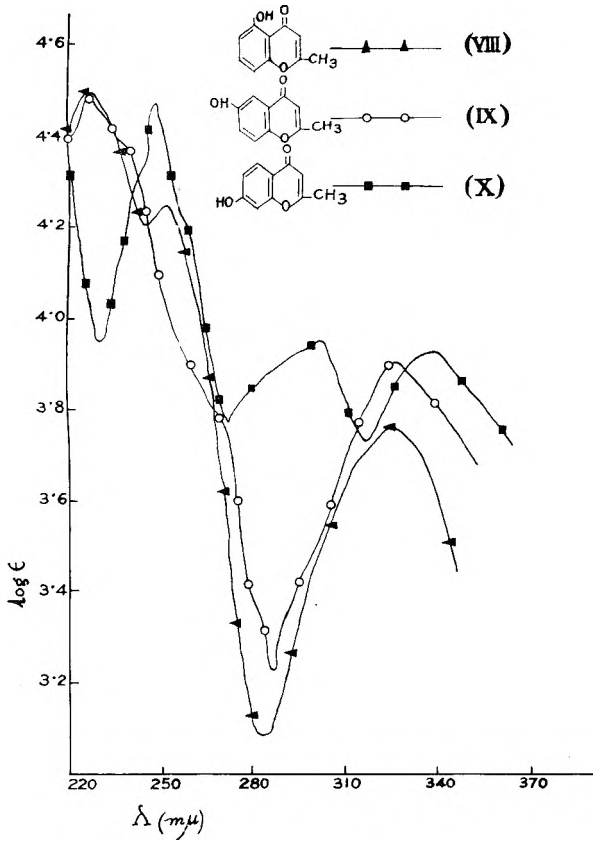

Fig. 3. Ultraviolet absorption spectra of VIII, 5-Hydroxy-2-methylchromone —▲—▲—; IX, 6-Hydroxy-2-methylchromone —○—○—; X, 7-Hydroxy-2-methylchromone —■—■—

of its low intensity). We believe that this band originates from some other structural feature of the molecule. The minimum at 262 mμ is observed. The second maximum occurs at a rather shorter wave length, λ_{max} 296 mμ, after which the absorption falls off.

The absorption spectra of hydroxycoumarins in which the hydroxyl groups occur in the heterocyclic nucleus *viz.*, 4-hydroxycoumarin, 4-hydroxy-3-methylcoumarin, and 3-hydroxycoumarin are plotted in Figure 2. It will be observed that the three curves are of similar nature, the characteristic minimum around 260 mμ is present in each case. At lower wave lengths the curves show the following features.

The curve for 4-hydroxycoumarins shows a distinct inflection at 231 mμ which develops into a wave with a short crest having λ_{max} at 293 mμ in the curve for 4-hydroxy-3-methylcoumarin. The resolution is still more pronounced in the case of 3-hydroxycoumarin where a well defined band with λ_{max} 241 mμ (log ϵ = 3.74) is observed. The other interesting fact about these curves is the occurrence of another intense band between the wave lengths 280 mμ and 325 mμ. These bands invariably show a twin crest and are presumably formed due to the merger of the K and B bands. On comparing the curves of 4-hydroxycoumarin and 4-hydroxy-3-methylcoumarin, it is found that this band is shifted bathochromically in case of the methyl derivative. The K-B band of 3-hydroxycoumarin is shifted still further, its λ_{max} occurring around 322 mμ. Beyond 325 mμ the absorption of all these three compounds rapidly falls off.

In Figure 3 are plotted the absorption curves of 5-hydroxy-, 6-hydroxy-, and 7-hydroxy-2-methylchromone. It will be observed that the curves for 5-hydroxy-2-methylchromone and 6-hydroxy-2-methylchromone are very similar in nature, the most pronounced feature being an intense maximum at 226 mμ (log ϵ = 4.49, E band) followed by a wave with a short crest in the case of the former with λ_{max} 252 mμ. There is a sharp minimum in both these cases between 284 and 286 mμ followed by a maximum around 326 mμ.

On comparing the spectra of the above compounds with those of chromone and its methyl derivatives, it will be observed that the curves are of similar nature both showing considerable amount of absorption in the region 220–250 mμ. The absorption then falls off giving rise to minima. The minima in the case of the two hydroxy compounds are shifted by about 10–15 mμ toward the higher wave length. The λ_{max} for the K-B bands for the hydroxychromones are also shifted bathochromically by about 20–30 mμ.

The absorption curve of 7-hydroxy-2-methylchromone would appear at first sight to be quite different from those of the other two hydroxychromones studied. This compound shows a sharp minimum at 230 mμ, a region in which the other two compounds show an intense maximum. It shows a sharp and intense maximum at 249 mμ (log ϵ = 4.47). It may be mentioned that 5-hydroxycoumarin also shows a λ_{max} at 252 mμ. It appears likely to us that the band at 249 mμ in the case of 7-hydroxy-2-methylchromone is the E band shifted bathochromically to a considerable extent. The band at 302 mμ in the case of 7-hydroxy-2-methylchromone very likely corresponds with the band at 252 mμ of 5-hydroxy-2-methylchromone. The third band of 7-hydroxy-2-methylchromone with λ_{max} at 340 mμ is evidently the K-B band shifted bathochromically by about 14 mμ.

Conclusions. The introduction of a hydroxyl group into the coumarin and the chromone molecule modifies the absorption characteristics causing in general bathochromic shift of the principal absorption bands.

Comparison of the spectra of 7-hydroxy- and 7-hydroxy-4-methylcoumarin, and of 4-hydroxy- and 4-hydroxy-3-methylcoumarin would reveal that the methyl group causes a bathochromic shift only in the case of the latter pair.

The absorption spectra of hydroxycoumarins differ from those of hydroxychromones in the following respects. The hydroxychromones show con-

siderable amount of absorption around 250 mμ, log ε being invariably greater than 4.1, while log ε in the case of hydroxycoumarins in this region is never greater than 3.75. The minima in the case of hydroxycoumarins have been found to lie between 255–262 mμ, whereas the minima in the case of chromone have been found to occur above 280 mμ.

Limaye and Kelkar[7] obtained both 5-hydroxy-4-methylcoumarin and 5-hydroxy-2-methylchromone from 2,6-dihydroxyacetophenone by the Kostanecki-Robinson reaction. The absorption curves of these compounds corroborate the structures assigned to these by the workers.

EXPERIMENTAL

All melting points are uncorrected. The compounds were repeatedly crystallized from the solvents noted under respective headings until sharp and constant melting points were obtained.

7-Hydroxycoumarin (I)[8] was crystallized from dilute ethanol; m.p. 226°; lit.,[8] 227–228°.

Anal. Calcd. for $C_9H_6O_3$: C, 66.66; H, 3.70. Found: C, 66.35; H, 3.79.

7-Hydroxy-4-methylcoumarin (II)[9] was crystallized from ethanol; m.p. 185°; lit.,[9] 185°.

Anal. Calcd. for $C_{10}H_8O_3$: C, 68.18; H, 4.55. Found: C, 68.13; H, 4.66.

6-Hydroxy-4-methylcoumarin (IV)[10] was sublimed under vacuum and then crystallized from glacial acetic acid; m.p. 245°; lit.,[10] 243°.

Anal. Calcd. for $C_{10}H_8O_3$: C, 68.18; H, 4.55. Found: C, 67.63; H, 4.57.

4-Hydroxycoumarin (V). To an ice cold suspension of ethyl sodioacetoacetate (prepared from 25 ml. ester, 5 g. sodium) in benzene (100 ml.) was added a benzene (50 ml.) solution of acetylsalicoyl chloride (prepared from 15 g. aspirin, 15 ml. thionyl chloride). The reaction mixture was refluxed over water bath for 7 hr. and then cooled and decomposed with ice cold hydrochloric acid (1:1). The organic layer was evaporated and the residual oil was boiled with 20% sulfuric acid (180 ml.) for 8 hr. The precipitated 4-hydroxy-3-acetylcoumarin was crystallized twice from ethanol m.p. 138°. (Yield 55%).

Anal. Calcd. for $C_{11}H_8O_4$: C, 64.72; H, 3.92. Found: C, 64.92; H, 3.93.

The above product (5 g.) was warmed with concentrated sulfuric acid (4 ml.) for 3–4 min. and the cooled solution was poured into excess water, whereby 4-hydroxycoumarin precipitated as a crystalline solid. It was crystallized twice from water; m.p. 210°; lit.,[11] 206°. (Yield 95%).

Anal. Calcd. for $C_9H_6O_3$: C, 66.66; H, 3.70. Found: C, 66.78; H, 3.5.

4-Hydroxy-3-methylcoumarin (VI)[12] was crystallized from dilute acetic acid; m.p. 231°; lit.,[12] 230°.

Anal. Calcd. for $C_{10}H_8O_3$: C, 68.18; H, 4.55. Found: C, 68.16; H, 4.46.

3-Hydroxycoumarin (VII). 3-Acetamidocoumarin prepared according to the method of Shaw *et al.*[13] was refluxed with 3*N* hydrochloric acid under nitrogen for 2 hr. The solution was kept at 5° overnight and the product filtered, washed with water, and crystallized from water; m.p. 153–154°; lit.,[14] 153°.

Anal. Calcd. for $C_9H_6O_3$: C, 66.66; H, 3.70. Found: C, 66.33; H, 3.93.

5-Hydroxy-4-methylcoumarin (III) *and 5-hydroxy-2-methylchromone* (VIII). These were obtained by slight modification of the method described by Limaye and Kelkar.[7] The Kostanecki product (1.5 g.) obtained from 2,6-dihydroxyacetophenone (2 g.), sodium acetate (2 g.), and acetic anhydride (4 ml.) after one crystallization from dilute acetic acid was refluxed with a solution of sodium carbonate (0.81 g. in 17 ml. water) for 1 hr. The insoluble matter m.p. 85° was filtered, sublimed in vacuum, and the sublimate crystallized from petroleum ether (40–60°) giving 5-hydroxy-2-methylchromone (VIII) as pale yellow needles; m.p. 92°.

Anal. Calcd. for $C_{10}H_8O_3$: C, 68.18; H, 4.55. Found: C, 67.96; H, 4.49.

The filtrate after removal of the above chromone was acidified to obtain a solid which after vacuum-sublimation and two crystallizations from ethanol, produced 5-hydroxy-4-methylcoumarin (III); m.p. 262°; lit.,[7] 262°.

Anal. Calcd. for $C_{10}H_8O_3$: C, 68.18; H, 4.55. Found: C, 67.98; H, 4.48.

6-Hydroxy-2-methylchromone (IX) was prepared following the details given by Desai and Mavani[15] employing hydroquinone diacetate prepared according to Amin and Shah.[16] It was crystallized from glacial acetic acid; m.p. 247°; lit.,[15] 247°.

Anal. Calcd. for $C_{10}H_8O_3$: C, 68.18; H, 4.55. Found: C, 67.77; H, 4.54.

7-Hydroxy-2-methylchromone (X) was prepared according to method of Tahara.[17] It was crystallized from pyridine after preliminary purification by vacuum sublimation; m.p. 252°; lit.,[17] 250°.

Anal. Calcd. for $C_{10}H_8O_3$: C, 68.18; H, 4.55. Found; C, 68.12; H, 4.62.

CALCUTTA 32, INDIA

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[CONTRIBUTION FROM DEPARTMENT OF CHEMISTRY, NEW MEXICO HIGHLANDS UNIVERSITY AND DEPARTMENT OF CHEMISTRY, ARIZONA STATE UNIVERSITY]

Potential Purine Antagonists. XVII. Synthesis of Some 2-Methyl- and 2-Methylthio-6,8-Disubstituted Purines[1]

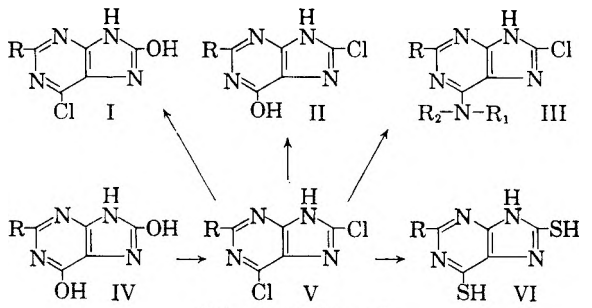
C. WAYNE NOELL[2] AND ROLAND K. ROBINS[2]

Received September 29, 1958

Urea fusion of 4,5-diamino-6-hydroxy-2-methylpyrimidine and 4,5-diamino-6-hydroxy-2-pyrimidinethiol gave 6,8-dihydroxy-2-methylpurine (IV, R = CH_3) and 6,8-dihydroxy-2-purinethiol (IV, R = SH), respectively. Methylation of IV (R = SH) gave 6,8-dihydroxy-2-methylthiopurine (IV, R = SCH_3). From IV (R = CH_3, SCH_3) were prepared 6,8-dichloro-2-methyl- and 6,8-dichloro-2-methylthiopurine (V, R = CH_3, SCH_3). Similarly, 6-hydroxy-2-methylthiopurine (VII) and 8-hydroxy-2-methylthiopurine (XIV) were converted to the corresponding 6-chloro- and 8-chloropurines, respectively. These chloropurines were further converted into additional new purine derivatives.

Renewed interest in 2-methyl- and 2-methylthiopurines has been stimulated by the discovery of 6-amino-2-methylpurine[3] and 6-amino-2-methylthiopurine[4] in natural materials. The present investigation deals with the preparation of a number of derivatives of the purine nucleus containing a 2-methyl or 2-methylthio group.

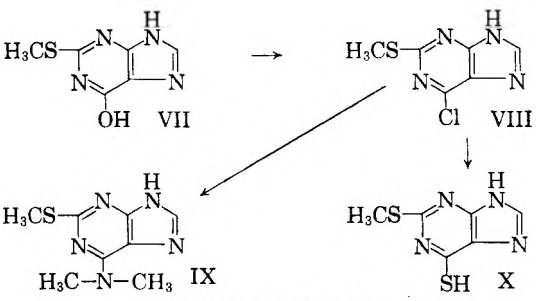
Urea fusion of 4,5-diamino-6-hydroxy-2-methylpyrimidine sulfate[5] gave 6,8-dihydroxy-2-methylpurine (IV, R = CH_3) in good yield. 6,8-Dihydroxy-2-purinethiol (IV, R = SH) was similarly prepared from 4,5-diamino-6-hydroxy-2-pyrimidinethiol[6] and urea. 6,8-Dihydroxy-2-methylthiopurine (IV, R = SCH_3) was prepared by methylation of IV, R = SH, with methyl iodide in the presence of aqueous base.



Reaction Scheme I

Chlorination of IV (R = CH_3, SCH_3) with phosphorus oxychloride and *N*,*N*-diethylaniline readily gave the corresponding 6,8-dichloropurine (V) in good yield. 2-Methyl- and 2-methylthio-6,8-purinedithiol (VI) were prepared from V (R = CH_3, SCH_3) and refluxing absolute ethanol containing thiourea.

Treatment of V with hot aqueous hydrochloric acid resulted in the preparation of the corresponding 6-chloro-8-hydroxypurine (I) while reaction of V with dilute sodium hydroxide gave the isomeric 8-chloro-6-hydroxy-2-methyl- or 8-chloro-6-hydroxy-2-methylthiopurine (II, R = CH_3, SCH_3). The structures assigned I and II were made on the basis of similar reactions noted with 6,8-dichloropurine[7] and on the similarity of ultraviolet absorption spectra of II, R = SCH_3, to 6-hydroxy-2-methylthiopurine (VII) and I, R = SCH_3, to 8-hydroxy-2-methylthiopurine (XIV). This similarity in spectra is to be expected since Mason[8] has shown there is little shift in the wave length maximum due to the presence of a chlorine atom in the purine molecule. Reaction of V with various primary and secondary amines heated on the steam bath readily gave III. This is to be expected since the "6" chlorine atom of 6,8-dichloropurine[7] has previously been shown to be most reactive in the usual nucleophilic replacement reactions. The structure of III, R = C_3H, $R_1 = R_2 = C_2H_5$, was further confirmed since the ultraviolet absorption spectra strongly resembled that of the known 6-dimethylamino-2-methylpurine.[9] Similarly, the spectra of III, R = SCH_3, $R_1 = R_2 = CH_3$, were



Reaction Scheme II

(1) This investigation was supported in part by research grant C-2845 from the National Cancer Institute of the National Institutes of Health, Public Health Service.

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(3) D. N. Brown and E. L. Smith, *Biochem. J.*, **56**, 34 (1954); H. W. Dion, D. G. Calkins, and J. J. Pfiffner, *J. Am. Chem. Soc.*, **76**, 948 (1954).

(4) F. Wilhelm and K. Bernhauer, *Chem. Ber.*, **90**, 1966 (1957).

(5) R. K. Robins, K. J. Dille, C. H. Willits, and B. E. Christensen, *J. Am. Chem. Soc.*, **75**, 265 (1953).

(6) A. Albert, D. J. Brown, and G. Cheeseman, *J. Chem. Soc.*, 474 (1951).

(7) R. K. Robins, *Potential Purine Antagonists XV . . . .*, *J. Am. Chem. Soc.*, **80**, 6671 (1958).

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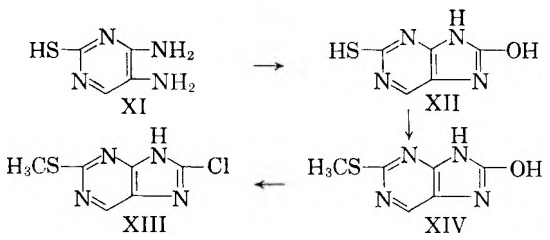
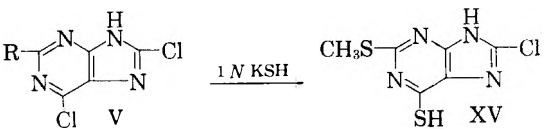
(9) R. K. Robins, J. W. Jones, and H. H. Lin, *J. Org. Chem.*, **21**, 696 (1956).



Reaction Scheme III

found similar to the spectra of 6-dimethylamino-2-methylthiopurine (IX). The preparation of IX was accomplished with dimethylamine and 6-chloro-2-methylthiopurine (VIII) which was in turn prepared from 6-hydroxy-2-methylthiopurine (VII)[10] by treatment of VII with phosphorus oxychloride and *N*,*N*-diethylaniline. 2-Methylthio-6-purinethiol (X) was prepared from 6-chloro-2-methylthiopurine (VIII) and thiourea in refluxing ethanol. The preparation of 8-hydroxy-2-methylthiopurine (XIV) was accomplished by methylation of 8-hydroxy-2-purinethiol (XII) with methyl iodide. The compound, 8-hydroxy-2-purinethiol (XII), was obtained from the thiourea fusion of 4,5-diamino-2-pyrimidinethiol (XI).[11] 8-Chloro-2-methylthiopurine (XIII) was prepared from 8-hydroxy-2-methylthiopurine (XIV) by the use of *N*,*N*-diethylaniline and phosphorus oxychloride. 6,8-Dichloro-2-methylthiopurine (V, R = SCH_3) was treated with boiling *N* potassium hydrosulfide to give a monopurinethiol, judged to be 8-chloro-2-methylthio-6-purinethiol (XV) since the ultraviolet absorption spectra of 2-methylthio-6-purinethiol (X) and that of XV at *p*H 1 and 11 were almost identical. 8-Chloro-2-methyl-6-purinethiol was similarly prepared from V, R = CH_3. The ultraviolet



absorption spectra of the 2-methyl- and 2-methylthiopurines prepared are listed in Table I.

EXPERIMENTAL[12]

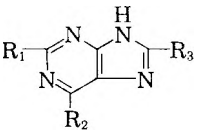
Preparation of 6,8-dihydroxy-2-methylpurine (IV, R = CH_3). 4,5-Diamino-6-hydroxy-2-methylpyrimidine sulfate[5] (100 g.) and 300 g. of urea were ground and mixed thoroughly. This mixture was heated at 160–180° for approximately 30 min. until it became semisolid. The cooled solid was dissolved in hot dilute potassium hydroxide solution. Norit was added, and the solution was filtered. The hot filtrate was acidified with glacial acetic acid, and the precipitate that formed was filtered immediately, washed with water, and dried at 110° to yield 105 g. of product. A small amount was recrystallized from a large volume of water for analysis.

Anal. Calcd. for $C_6H_6N_4O_2$: C, 43.3; H, 3.6. Found: C, 42.9; H, 4.0.

6,8-Dichloro-2-methylpurine (V, R = CH_3). Finely powdered 6,8-dihydroxy-2-methylpurine (IV, R = CH_3) (80 g.)

TABLE I

ULTRAVIOLET ABSORPTION SPECTRA OF SOME 2-METHYL- AND 2-METHYLTHIOPURINES



R_1	R_2	R_3	λ_{max} *p*H 1 (Mμ)	ε	λ_{max} *p*H 11 (Mμ)	ε
CH_3	OH	OH	255	6,140	273	6,300
CH_3	Cl	Cl	235	6,770	283	11,100
			275	14,000		
CH_3	SH	SH	270	13,400	270	23,900
			360	23,000	335	43,600
CH_3	Cl	OH	255	14,400	273	14,400
CH_3	OH	Cl	255	15,200	265	14,400
CH_3	$N(C_2H_5)_2$	Cl	240	7,180	283	14,300
			275	14,300		
CH_3	$N<^{(CH_2)_2CH_3}_{(CH_2)_2CH_3}$	Cl	275	11,800	279	11,200
CH_3	SH	Cl	230	10,000	236	14,000
			332	20,800	319	18,000
SCH_3	OH	OH	265	10,700	224	17,000
			298	7,500	283	11,200
SCH_3	Cl	Cl	230	22,100	242	25,400
			260	12,200		
			310	9,160	307.5	9,850
SCH_3	Cl	OH	264	13,800	240	16,200
			309	8,600	308	11,900
SCH_3	OH	Cl	265	17,200	227	21,400
					277	15,400
SCH_3	SH	Cl	230	17,900	243	16,800
			265	10,600	263	17,000
			340	19,600	325	17,900
SCH_3	SH	SH	275	23,600	227	23,600
			310	12,600	268	28,500
			370	31,000	345	32,400
SCH_3	$N(CH_3)_2$	Cl	257	20,400	240	25,600
			296	19,600	292	17,300
	H					
SCH_3	N(*o*-ClC_6H_4)	Cl	258	17,900	255	22,500
			318	15,300	330	24,100
SCH_3	H	OH	245	19,500	238	16,400
			270	12,200		
			308	5,100	305	10,200
SCH_3	H	Cl	240	20,000	242	26,000
			308	6,800	305	11,000
SCH_3	Cl	H	230	16,800	243	20,200
			259	11,000		
			307	5,100	305	6,600
SCH_3	$N(CH_3)_2$	H	255	26,900	240	31,600
			293	21,800	292	19,600
SCH_3	SH	H	242	11,100	238	12,700
			268	10,300	263	13,800
			338	16,600	318	15,600
SCH_3	OH	H	265	16,000	270	11,200
SH	OH	OH	265	11,000	225	28,500
			297	7,700	283	11,800
SH	H	OH	251	19,100	250	24,200
			285	25,200	260	25,200
					320	25,200

(10) G. B. Elion, W. H. Lange, and G. H. Hitchings, *J. Am. Chem. Soc.*, 78, 217 (1956).

(11) D. J. Brown, *J. Appl. Chem.* (*London*), 2, 239 (1952).

(12) All melting points are uncorrected and were taken on a Fisher-Johns melting point apparatus, unless otherwise indicated.

was covered with 1500 ml. of phosphorus oxychloride and 250 ml. of *N,N*-diethylaniline. This mixture was then refluxed 6 hr.; the excess phosphorus oxychloride was removed under reduced pressure, and the residue was poured on chopped ice. The mixture was then allowed to stand 10 min., and the cold solution was extracted with 6 × 1000 ml. portions of ether. The combined ether extract was washed with 3 × 400 ml. portions of ice water and then dried over anhydrous sodium sulfate. Upon removal of the ether by distillation, 59 g. of 6,8-dichloro-2-methylpurine was obtained, m.p. 196–199°. Recrystallization from toluene yielded white crystals, m.p. 205–206°.

Anal. Calcd. for $C_6H_4N_4Cl_2$: C, 35.4; H, 2.0; N, 27.6. Found: C, 35.7; H, 1.9; N, 27.5.

6-Chloro-8-hydroxy-2-methylpurine (I, R = CH_3). 6,8-Dichloro-2-methylpurine (V, R = CH_3) (4 g.) was placed in 75 ml. of 3*N* hydrochloric acid solution, and the mixture was refluxed for 12 hr. The solution was then cooled and filtered, and the precipitate was washed with water and dried at 110° to yield 1.5 g. of product. A small portion was recrystallized from water for analysis, m.p. >300°.

Anal. Calcd. for $C_6H_5N_4ClO$: C, 38.9; H, 2.7. Found: C, 38.6; H, 3.0.

8-Chloro-6-hydroxy-2-methylpurine (II, R = CH_3). 6,8-Dichloro-2-methylpurine (V, R = CH_3) (10 g.) was covered with 100 ml. of 2*N* sodium hydroxide, and the solution was refluxed for 2 hr. The hot basic solution was then treated with Norit and filtered, and the warm filtrate was acidified with glacial acetic acid. The mixture was allowed to stand 3 days; then it was filtered. The precipitate was washed with water and dried at 110° to yield 3.1 g. of product. A small portion was recrystallized from water for analysis, m.p. >300°.

Anal. Calcd. for $C_6H_5N_4ClO$: C, 38.9; H, 2.7; N, 30.2. Found: C, 38.5; H, 2.9; N, 30.1.

8-Chloro-2-methyl-6-purinethiol. 6,8-Dichloro-2-methylpurine (V, R = CH_3) (3 g.) was added to 50 ml. of a *N* potassium sulfide solution, and the mixture was refluxed for 4 hr. The hot solution was treated with Norit and filtered, and the filtrate was acidified with glacial acetic acid. The mixture was cooled, and the orange needles were filtered and washed with water. The yield was 1.9 g. A small sample was further purified by reprecipitation.

Anal. Calcd. for $C_6H_5N_4ClS$: C, 35.9; H, 2.4. Found: C, 35.9; H, 2.9.

2-Methyl-6,8-purinedithiol (VI, R = CH_3). 6,8-Dichloro-2-methylpurine (V, R = CH_3) (8 g.) was covered with 200 ml. of absolute ethanol, and 7 g. of thiourea was added. This mixture was refluxed for 4 hr. and then allowed to cool to room temperature. The precipitate was filtered, washed with alcohol, and dried at 110°. The product obtained (7.9 g.) was purified by reprecipitation with glacial acetic acid from a boiling basic solution.

Anal. Calcd. for $C_6H_6N_4S_2$: C, 36.4; H, 3.0; N, 28.2. Found: C, 36.4; H, 3.5; N, 28.4.

Preparation of some 8-chloro-2-methyl-6-substituted aminopurines (III). *8-Chloro-6-diethylamino-2-methylpurine hydrochloride* (III, R = CH_3, R_1, R_2 = C_2H_5). 6,8-Dichloro-2-methylpurine (V, R = CH_3) (2 g.) was covered with 60 ml. of absolute ethanol, and 1.9 g. of diethylamine was added. The mixture was evaporated to dryness on the steam bath. Benzene (60 ml.) was added, and heating was continued until the volume had decreased to approximately 20 ml. The solution was then cooled, and the precipitate was filtered and dried at 110° for 2 hr. to yield 3.0 g. Recrystallization from benzenemethanol gave a pure product, m.p. 163–165°.

Anal. Calcd. for $C_{10}H_{14}N_5Cl \cdot HCl$: C, 43.5; H, 5.4; N, 25.3. Found: C, 43.6; H, 5.3; N, 25.0.

8-Chloro-6-di-n-propylamino-2-methylpurine hydrochloride (III, R = CH_3, R_1, R_2 = C_3H_7). 6,8-Dichloro-2-methylpurine (V, R = CH_3) (2 g.) was covered with 60 ml. of absolute ethanol, and 1.2 g. of di-*n*-propylamine was added. The isolation and purification of this compound is identical to that of the 6-diethylamino derivative (IX). Yield of product was 2.3 g., m.p. 163–165°.

Anal. Calcd. for $C_{12}H_{18}N_5Cl \cdot HCl$: C, 47.3; H, 5.9. Found: 47.1; H, 6.3.

6,8-Dihydroxy-2-purinethiol (IV, R = SH). 4,5-Diamino-6-hydroxy-2-pyrimidinethiol[6] (190 g.) was thoroughly mixed with 380 g. of urea, and the mixture was heated at 160–180°. Heating was continued approximately 30 min. until the liquid melt became quite viscous and difficult to stir. Then 3000 ml. of hot water and sufficient potassium hydroxide were added to dissolve all the solid material. Norit was added to the hot solution, which was then filtered. The filtrate was acidified with concentrated hydrochloric acid. The precipitate that formed was filtered from the hot solution, and the product was washed with water, then acetone, to yield 225 g. This product was shown by ultraviolet absorption spectra to be above 95% pure. An analytically pure sample was obtained by reprecipitation of the crude product from a boiling basic solution with hydrochloric acid.

Anal. Calcd. for $C_5H_4N_4O_2S$: C, 32.6; H, 2.2; N, 30.4. Found: C, 32.5; H, 2.1; N, 30.4.

6,8-Dihydroxy-2-methylthiopurine (IV, R = SCH_3). To 3000 ml. of hot water were added 200 g. of 6,8-dihydroxy-2-purinethiol and sufficient potassium hydroxide to dissolve all solid material. The solution was then cooled to 25° and stirred mechanically while 152 g. of methyl iodide was added. Vigorous stirring was continued for 45 min., after which time, the solution was heated to 50°, treated with charcoal, and filtered. The filtrate was acidified with glacial acetic acid, and the precipitate that formed was filtered immediately. Two more reprecipitations gave 205 g. of pure product, m.p. > 300°.

Anal. Calcd. for $C_6H_6N_4O_2S \cdot H_2O$: C, 33.1; H, 4.1; N, 26.0. Found: C, 33.2; H, 3.9; N, 26.2.

6,8-Dichloro-2-methylthiopurine (V, R = SCH_3). 6,8-Dihydroxy-2-methylthiopurine (IV, R = SCH_3) (150 g.), finely powdered, was added to 1500 ml. of phosphorus oxychloride. *N,N*-Diethylaniline (300 ml.) was then added, and the mixture was refluxed for 5 hr. The excess phosphorus oxychloride was removed under reduced pressure with a steam bath as the source of heat. The residue was poured on ice, with manual stirring, and the solution was allowed to stand 10 min. This cold aqueous solution was extracted with 6 × 1000 ml. portions of ether. The combined ether extract was washed with 3 × 400 ml. portions of ice water, and the ethereal solution was dried overnight over anhydrous sodium sulfate. Upon removal of the ether by distillation, 109 g. of product, m.p. 224–227°, was obtained. Recrystallization from a toluene-benzene mixture yielded a product, m.p. 230°.

Anal. Calcd. for $C_6H_4N_4Cl_2S$: C, 30.6; H, 1.7; N, 23.8. Found: C, 30.9; H, 2.2; N, 23.9.

8-Chloro-6-hydroxy-2-methylthiopurine (II, R = SCH_3). 6,8-Dichloro-2-methylthiopurine (V, R = SCH_3) (10 g.) was dissolved in 100 ml. of 2*N* sodium hydroxide, and the solution was refluxed for 2 hr. The solution was then filtered, and the filtrate was cooled to room temperature. After acidification with glacial acetic acid, the mixture was allowed to stand for 1 hr., and the precipitate was filtered, washed with water, and dried at 110° to yield 8.5 g. of product. Recrystallization from water gave an analytically pure sample, m.p. > 300°.

Anal. Calcd. for $C_6H_5N_4ClOS$: C, 33.2; H, 2.3; N, 25.8. Found: C, 33.1; H, 2.3; N, 25.5.

6-Chloro-8-hydroxy-2-methylthiopurine (I, R = SCH_3). 6,8-Dichloro-2-methylthiopurine (V, R = SCH_3) (10 g.) was covered with 100 ml. of 2*N* hydrochloric acid solution, and the mixture was refluxed for 4 hr. The mixture was allowed to cool to room temperature, and the colorless precipitate was filtered and washed with water to yield 7.5 g. of product. A small portion was recrystallized from water for analysis, m.p. > 300°.

Anal. Calcd. for $C_6H_5N_4ClOS$: C, 33.2; H, 2.3. Found: C, 33.1; H, 2.2.

8-Chloro-2-methylthio-6-purinethiol (XV). 6,8-Dichloro-2-methylthiopurine (V, R = SCH_3) (3 g.) was covered with 40 ml. of *N* potassium sulfide solution, and the mixture was refluxed for 4 hr. The hot solution was then treated with charcoal and filtered, and the warm filtrate was acidified with glacial acetic acid. The mixture was filtered after standing for 30 min., and the product was washed with water and dried at 110° to yield 2.7 g. of yellow needles. Purification for analysis was afforded by reprecipitation with glacial acetic acid from a hot dilute sodium hydroxide solution.

Anal. Calcd. for $C_6H_5N_4S_2Cl$: C, 30.9; H, 3.0. Found: C, 30.8; H, 2.9.

2-Methylthio-6,8-purinedithiol (VI, R = SCH_3). 6,8-Dichloro-2-methylthiopurine (V, R = SCH_3) (10 g.) was covered with 350 ml. of absolute ethanol, and 7.5 g. of thiourea was added. This mixture was then refluxed for 4 hr. and allowed to stand at room temperature for 2 hr. The yellow precipitate was filtered, washed with ethanol, and dried at 110° to yield 6.5 g. of product. A small portion of product was recrystallized from *N,N*-dimethylformamide and water.

Anal. Calcd. for $C_6H_6N_4S_3$: C, 31.3; H, 2.6; N, 24.3. Found: C, 31.6; H, 2.9; N, 24.7.

Preparation of some 8-chloro-2-methylthio-6-substituted aminopurines (III, R = SCH_3). *8-Chloro-6-dimethylamino-2-methylthiopurine* (III, R = SCH_3, R_1, R_2 = CH_3). 6,8-Dichloro-2-methylthiopurine (V, R = SCH_3) (3 g.) was covered with 15 ml. of water, and then 15 ml. of dimethylamine solution (25% in water) was added. This mixture was heated on the steam bath for 3 hr. and allowed to cool in a refrigerator. The precipitate was filtered, washed with water, and dried to yield 3 g. of product. For purification the amine was recrystallized from *N,N*-dimethylformamide and ethanol. The melting point of the product was 291°.

Anal. Calcd. for $C_8H_{10}N_5ClS$: C, 39.4; H, 4.1; N, 28.8. Found: C, 39.8; H, 4.3; N, 29.0.

8-Chloro-6-o-chloroanilino-2-methylthiopurine (III, R = SCH_3, R_1 = H, R_2 = *o*-ClC_6H_4). 6,8-Dichloro-2-methylthiopurine (V, R = SCH_3) (3 g.) was covered with 50 ml. of absolute ethanol, and 1.7 g. of *o*-chloroaniline was added. The mixture was placed on the steam bath for 3 hr., then cooled. The precipitate that had formed was filtered and washed with a small portion of ethanol to yield 3.2 g. of product. Recrystallization from ethanol gave a pure sample, m.p. 282°.

Anal. Calcd. for $C_{12}H_9N_5Cl_2S$: C, 44.2; H, 2.8. Found: C, 44.6; H, 3.3.

8-Hydroxy-2-purinethiol (XII). 4,5-Diamino-2-pyrimidinethiol (XI)[7] (21 g.) was finely ground and thoroughly mixed with 42 g. of urea, and the mixture was heated at 160–180° on a hot plate. After the mixture had become a melt, heating was continued until it became too viscous to stir manually. The solid mass was then dissolved in hot dilute sodium hydroxide, and the solution was treated with Norit and filtered. The hot filtrate was acidified with glacial acetic acid. The precipitate that formed was filtered immediately and washed with water. After drying overnight at 130°, 18 g. of product was obtained. Two more reprecipitations gave a pure sample, m.p. > 300°.

Anal. Calcd. for $C_5H_4N_4OS$: C, 35.8; H, 2.4. Found: C, 35.4; H, 2.3.

8-Hydroxy-2-methylthiopurine (XIV). 8-Hydroxy-2-purinethiol (XII) (50 g.) was added to 600 ml. of water, and the mixture was stirred mechanically. An adequate amount of sodium hydroxide was added to dissolve all solid material; then 41.3 g. of methyl iodide was added. The mixture was vigorously stirred for 30 min., and then the temperature was finally raised to 70°. The hot solution was treated with charcoal and filtered, and the hot filtrate was acidified with glacial acetic acid. The precipitate that formed was filtered immediately, washed with water, and dried at 110° to yield 42 g. of product. The product was recrystallized from water for analysis.

Anal. Calcd. for $C_6H_6N_4OS$: C, 39.5; H, 3.3; N, 30.8. Found: C, 39.1; H, 3.4; N, 30.2.

8-Chloro-2-methylthiopurine (XIII). 8-Hydroxy-2-methylthiopurine (XIV) (20 g.) was covered with 300 ml. of phosphorus oxychloride, and 30 ml. of *N,N*-diethylaniline was added. This mixture was refluxed for 5 hr., and the excess phosphorus oxychloride was removed under reduced pressure with a steam bath as the source of heat. The residue was poured on ice, with stirring, and the solution was allowed to stand 10 min. The cold aqueous mixture was extracted with 6 × 500 ml. portions of ether. The combined ether extract was then washed with 3 × 200 ml. portions of water and placed over anhydrous sodium sulfate to dry. After the ether was removed by distillation, 9.9 g. of chloro compound was obtained. Recrystallization from a toluene-methanol mixture yielded a product, m.p. 208°.

Anal. Calcd. for $C_6H_5N_4ClS$: C, 36.1; H, 2.5; N, 28.1. Found: C, 36.1; N, 2.8; N, 28.0.

6-Chloro-2-methylthiopurine (VIII). 6-Hydroxy-2-methylthiopurine (VII)[10] (20 g.) was covered with 300 ml. of phosphorus oxychloride, and 30 ml. of *N,N*-diethylaniline was added. The mixture was refluxed for 1.5 hr. The excess phosphorus oxychloride was then removed by vacuum distillation with a steam bath as the source of heat. The residue was poured over chopped ice, with stirring, and allowed to stand 10 min. The aqueous mixture was extracted with 6 × 8000 ml. portions of ether. The combined ether extract was washed with 4 × 400 ml. portions of water, and the ether was removed by distillation. The wet chloro compound was first dried under vacuum and then at 80° for 2 hr. to yield 12 g. of yellow needles. Recrystallization from ethanol gave a product, m.p. 274° (dec.).

Anal. Calcd. for $C_6H_5N_5ClS$: C, 36.0; H, 2.5; N, 28.1. Found: C, 36.0; H, 3.0; N, 27.9.

2-Methylthio-6-purinethiol (X). 6-Chloro-2-methylthiopurine (VIII) (1 g.) was covered with 50 ml. of absolute ethanol, and 1 g. of thiourea was added. This mixture was refluxed for 5 hr. and then allowed to cool to room temperature. The yellow precipitate was filtered, washed with ethanol, and dried at 110° to yield 0.7 g. of product. A pure sample was obtained by reprecipitation with glacial acetic acid from a dilute sodium hydroxide solution.

Anal. Calcd. for $C_6H_6N_4S_2$: C, 36.4; H, 3.0; N, 28.3. Found: C, 36.6; H, 3.2; N, 28.9.

6-Dimethylamino-2-methylthiopurine hydrochloride (IX). 6-Chloro-2-methylthiopurine (VIII) (1 g.) was covered with 30 ml. of water, and 10 ml. of dimethylamine solution (25% in water) was added. This mixture was heated on the steam bath until the final volume was approximately 15 ml. The mixture was then allowed to cool, and the precipitate was filtered and dried at 110° for 2 hr. to yield 1.1 g. of product, m.p. 297–299°. Recrystallization from methanol did not change the melting point.

Anal. Calcd. for $C_8H_{11}N_5S$·HCl: C, 45.9; H, 5.3. Found: 45.5; H, 5.4.

TEMPE, ARIZ.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, BERKELEY]

4-Oxo-5,6-dihydro-4*H*-pyrido[3,2,1-*jk*]carbazole and Its Aralkylidene Derivatives

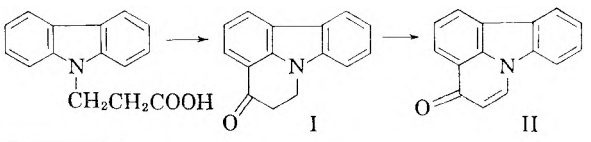
HENRY RAPOPORT AND DOROTHY M. BOWMAN

Received September 15, 1958

4-Oxo-5,6-dihydro-4H-pyrido[3,2,1-*jk*]carbazole (I) was prepared by cyclization of 9-carbazolepropionic acid with anhydrous hydrogen fluoride, in a copper pressure vessel. Condensation of I with several aldehydes in the presence of piperidine led to aralkylidene derivatives which isomerized to the corresponding 4-quinolines on heating with alkali.

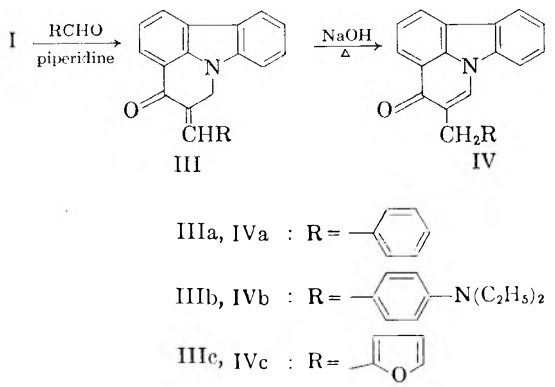
As part of a study of fused ring compounds and the effect of ring strain on aromatic properties and interactions,[1-3] a series of indoles was required for which 4-oxo-5,6-dihydro-4H-pyrido[3,2,1-*jk*]carbazole (I) appeared to be a very attractive intermediate. A convenient synthesis of this compound is described in this paper. Also, the chemistry of some of its α-ylidene derivatives was studied in view of the interesting isomerism recently observed with similar compounds.[4,5]

The synthesis of the pyridocarbazole I from 9-carbazolepropionitrile by fusion with a mixture of aluminum chloride, sodium chloride, and potassium chloride has been reported.[6] However, since others were unable to repeat this cyclization,[7] it was not investigated further. Instead, the cyclization of 9-carbazolepropionic acid, which appeared to offer a more promising path to I, was undertaken. 9-Carbazolepropionic acid was readily prepared by hydrolysis of 9-carbazolepropionitrile, itself easily available from cyanoethylation of carbazole.[8] Hydrolysis with hydrochloric acid has been reported,[7] but was found to be unsatisfactory due to the very low solubility of the nitrile in concentrated hydrochloric acid. Alkaline hydrolysis, using aqueous ethanol as the solvent, proceeded rapidly to give 9-carbazolepropionic acid in quantitative yield.



Three catalysts were investigated for the ring-closure of the acid to the pyridocarbazole I. Polyphosphoric acid, which had been used successfully in the synthesis of 1-ketolilolidine,[4] gave only polymeric material. Trifluoroacetic anhydride[9] gave a small yield of impure ketone. Anhydrous hydrogen fluoride gave the most promising results, but the yield was still low under the reaction conditions usually used,[10] *i.e.*, allowing the reaction mixture to stand at room temperature until all the hydrogen fluoride had evaporated. By carrying out the reaction in a copper pressure vessel, which had the advantage of lengthening the reaction time and of maintaining a high concentration of hydrogen fluoride,[11] the yield of ketone I was raised from 12% to 49%, making I available in quantity.

The condensation of the pyridocarbazole I with various aldehydes was then considered. Benzylidene and *p*-diethylaminobenzylidene derivatives of I have been isolated and have been reported to exist as cis-trans isomers.[6] However, it seems more likely that this isomerism is due to migration of the benzylidene double bond of III into the ring to form the quinolone derivative IV, as has been reported for the derivatives of dihydro-4-quinolone[5] and of 1-ketolilolidine.[4] In order to investi-



(1) H. Rapoport and J. Z. Pasky, *J. Am. Chem. Soc.*, **78**, 3788 (1956).

(2) H. Rapoport and G. Smolinsky, *J. Am. Chem. Soc.*, **79**, 5831 (1957).

(3) H. Rapoport and G. Smolinsky, *J. Am. Chem. Soc.*, **80**, 2910 (1958).

(4) H. Rapoport and J. R. Tretter, *J. Org. Chem.*, **23**, 248 (1958).

(5) P. I. Ittyerah and F. G. Mann, *J. Chem. Soc.*, 467 (1958).

(6) I. G. Farbenindustrie A.-G., French Patent **806,715** (1936).

(7) P. A. S. Smith and T. Y. Yu, *J. Am. Chem. Soc.*, **74**, 1096 (1952).

(8) F. C. Whitmore, H. S. Mosher, R. R. Adams, R. B. Taylor, E. C. Chapin, C. Weisel, and W. Yanke, *J. Am. Chem. Soc.*, **66**, 725 (1944).

(9) R. J. Ferrier and J. M. Tedder, *J. Chem. Soc.*, 1435 (1957).

(10) W. S. Johnson, *Org. Reactions*, **2**, 157 (1944).

(11) A more complex apparatus for refluxing hydrogen fluoride under pressure to attain a higher reaction temperature has been described by L. F. Fieser and E. B. Hershberg, *J. Am. Chem. Soc.*, **62**, 49 (1940).

gate this isomerization with the present compounds, various aralkylidene derivatives of I were prepared. As a model compound containing the quinolone chromophore present in IV, 4-oxo-4H-pyrido-[3,2,1-*jk*]carbazole (II) was prepared by catalytic dehydrogenation of the parent ketone I.

When I was condensed with benzaldehyde, using sodium hydroxide as the catalyst, the product was yellow and melted at 215°, the melting point reported for one of the isomers.[6] Its ultraviolet spectrum (Fig. 1) was very similar to that of II,

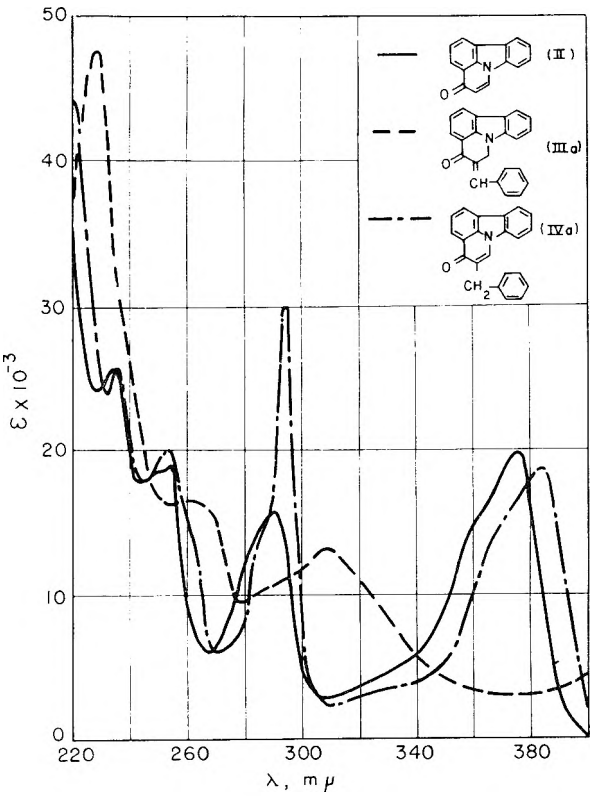
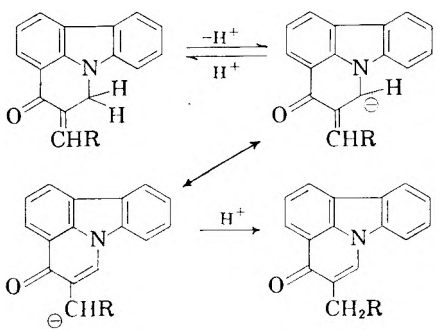


Fig. 1. Ultraviolet absorption spectra in methanol of 4-oxo-4H-pyrido 3,2,1-*jk* carbazole (II) ———, 4-oxo-5-benzylidene-5,6-dihydro-4H-pyrido 3,2,1-*jk*-carbazole (IIIa) — — —, and 4-oxo-5-benzyl-4H-pyrido 3,2,1-*jk* carbazole (IVa) — - —

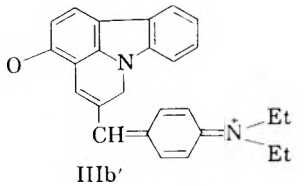
indicating that the compound has the quinolone structure IVa. When piperidine was used as the catalyst for the condensation, the product isolated was orange, and melted at 151°, the melting point reported (148°) for the other isomer.[6] Its spectrum is entirely different from that of the yellow isomer, and it is undoubtedly the expected benzylidene derivative (IIIa). Refluxing the lower-melting orange isomer in alcoholic sodium hydroxide for a few minutes converted it quantitatively to the higher-melting, yellow isomer. When *p*-diethylaminobenzaldehyde or furfural was used instead of benzaldehyde, the same condensation product was obtained with either piperidine or a cold solution of sodium hydroxide as the catalyst. The products were red-orange, and have ultraviolet spectra similar to that of the benzylidene derivative, IIIa. They can therefore be assigned the structures IIIb and IIIc, respectively, with the double bond exocyclic. When these compounds were heated with alcoholic potassium hydroxide, they were converted to lower-melting, yellow isomers having spectra similar to those of the quinolones, II and IVa. The yellow compounds can therefore be assigned structures IVb and IVc, respectively, in which the double bond has migrated into the ring. The isomerization of the furfurylidene derivative (IIIc) to the quinolone (IVc) was also accomplished by refluxing with potassium carbonate in ethanol. Thus, the isomerization on heating takes place whenever a catalyst of sufficient alkalinity is present.

It is interesting that the melting points give no indication of isomer identity; in one instance the quinolone is the higher melting, but in two it is the lower melting. The ultraviolet spectra are the best means of identification, as seen in Fig. 1. When both isomers are available, the color appears to be a reliable guide; the aralkylidene derivatives are always redder than the quinolones. For the three series in which this isomerization has been observed, the quinolones are almost colorless to pale yellow, while the aralkylidenes are orange to red.

The mechanism of the isomerization can be pictured as proceeding by abstraction of a proton by the base, and subsequent return of the proton to the position that leaves the more stable double bond. This would lead to the prediction that the position of equilibrium would be greatly affected by

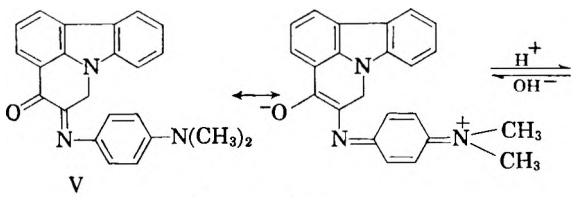


any factors which would stabilize the double bond in one of the two positions. The fact that the benzylidene derivative (IIIa) of I can be isolated, while those of 1-ketolilolidine[4] and of 1,2,3,4-tetrahydro-4-oxoquinoline[5] cannot, shows the effect of conjugation on the isomerization. For the latter two compounds, formation of the quinolone adds significantly to the conjugation of the aromatic system, and therefore occurs with great ease. Compound IIIa, with the stable carbazole system already present, can gain less by formation of the quinolone (IVa) and therefore has less tendency to isomerize. Similarly, IIIb, in which the aralkylidene structure is stabilized by contributions from the resonance form IIIb′, isomerizes less readily than does IIIa.

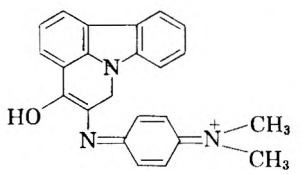


IIIb'

p-Dimethylaminonitrosobenzene was also condensed with I. With sodium hydroxide, piperidine, or potassium carbonate as the catalyst, in refluxing methanol, the product was always the same very deep red compound. This was recovered unchanged on refluxing with potassium hydroxide in ethanol, with potassium *t*-butoxide in *t*-butyl alcohol, or with hydrochloric acid in ethanol. Structure V, with the exocyclic double bond, seems most likely



V



VI

for this compound. If the double bond had migrated into the ring the compound would be expected to be yellow, as is 3-*p*-dimethylaminoanilino-1,4-dihydro-1-methyl-4-oxoquinoline,[5] although comparisons between different ring systems are not necessarily valid. The ultraviolet spectrum does not parallel that of either the aralkylidene derivatives (III) or the quinoline derivatives (IV), but is more similar to the former. In addition, the infrared spectrum did not show an N—H band. The color of V did change to yellow-green in acid, but returned to the original red when the solution was made alkaline. This change can be accounted for by a structure such as VI for the salt. The failure of V to isomerize is not surprising since there would be considerable resonance stabilization of the exocyclic double bond.

EXPERIMENTAL[12]

9-Carbazolepropionic acid. Two hundred g. of 9-carbazolepropionitrile, prepared as described,[8] was mixed with 600 cc. of 95% ethanol and 300 cc. of 3*N* potassium hydroxide, and the solution was heated under reflux in a nitrogen atmosphere for 22 hr. The solution was concentrated until the temperature in the boiling flask reached 98°, diluted with 600 cc. of water, and filtered at 80°. Acidification of the filtrate with 3*N* hydrochloric acid gave a precipitate (241 g.), which was crystallized in 20-g. portions by solution in 500 cc. of benzene, distillation of 50 cc. of the solvent, hot filtration, concentration to 300 cc. and finally cooling to room temperature. After a second recrystallization, the colorless crystals melted at 173–174° (reported[7] m.p. 169–170°).

4-Oxo-5,6-dihydro-4H-pyrido[3,2,1-jk]carbazole (I). A pressure bomb was constructed from a piece of 3 in. o.d. copper pipe, 0.087 in. thick and 6½ in. long, with a copper bottom welded in. The top of the bomb had an exterior threaded band. A Teflon O-ring was set in a groove at the top of the bomb, and a polished copper plate was tightly held against the Teflon ring by a threaded brass head. Ten g. of 9-carbazolepropionic acid and 200 g. of anhydrous hydrogen fluoride were placed in the bomb, and the head was closed tightly so that there was no visible leakage of hydrogen fluoride. The bomb was allowed to stand at room temperature for 48 hr., with occasional shaking, then it was cooled in an ice bath, the top was removed, and the hydrogen fluoride was evaporated rapidly in a stream of nitrogen, the last traces being removed by warming in a water bath. The contents of the bomb were washed out with 100 cc. of boric acid solution and 200 cc. of chloroform, followed by several additional small portions of chloroform. The washings were combined, the layers were separated, and the chloroform phase was washed with 500 cc., then 300 cc., of 0.5*N* sodium hydroxide, followed by 300 cc. of water. The combined aqueous solutions were washed with chloroform, which was added to the original chloroform solution. Acidification of the alkaline solution with acetic acid gave 2 g. of red solid, from which 1.5 g. of unreacted 9-carbazolepropionic acid was recovered on recrystallization. The chloroform solution was dried over sodium sulfate and evaporated to dryness, leaving a dark oil, which was dissolved in hot methanol, filtered, and cooled thoroughly, to give 4 g. (49% yield) of yellow crystals melting at 98–100° (reported[6] m.p. 98°), having an infrared peak at 5.92 μ (KBr pellet). Ultraviolet spectrum: λ_{max} 225 mμ (ϵ 64,700), 293 (14,300), 320 (6330), 289 (7970).

4-Oxo-4H-pyrido[3,2,1-jk]carbazole (II). A solution of 1 g. of 4-oxo-5,6-dihydro-4H-pyrido[3,2,1-*jk*]carbazole (I) in 10 cc. of *p*-cymene was boiled with 15 mg. of 5% palladium on charcoal for 3 hr., at the end of which time hydrogen evolution had stopped. The mixture was cooled to 50° and filtered, using ether to wash the catalyst. The filtrate was evaporated to dryness, and the residue was recrystallized from methanol, then sublimed, to give 480 mg. (49%) of pale yellow crystals, m.p. 177–178°. Ultraviolet spectrum: λ_{max} 217 mμ (ϵ 38,300), 234 (25,600), 254 (19,000), 290 (16,000), 375 (20,000).

Anal. Calcd. for $C_{15}H_9NO$: C, 82.2; H, 4.1; N, 6.4. Found: C, 82.2; H, 4.2; N, 6.3.

Aralkylidene derivatives (III) *of 4-oxo-5,6-dihydro-4H-pyrido[3,2,1-jk]carbazole* (I). One g. of I was dissolved in 50 cc. of refluxing absolute ethanol containing 0.3 cc. of piperidine, and 1 g. of the aldehyde was added. The solution was boiled in a nitrogen atmosphere for 4 hr., then allowed to stand overnight to complete crystallization. The product was recrystallized from a rather large volume of absolute ethanol and dried at 60°/1 mm. for several hours. In this manner the following were prepared:

4-Oxo-5-benzylidene-4,5-dihydro-4H-pyrido[3,2,1-jk]carbazole (IIIa), m.p. 150–151° (reported[6] 148°). Ultraviolet spectrum, 228 mμ (ϵ 47,600), 261 (16,600), 308 (13,300).

4-Oxo-5-p-diethylaminobenzylidene-4,5-dihydro-4H-pyrido-[3,2,1-jk]carbazole (IIIb), m.p. 185–186° (reported[6] m.p. 182°). Ultraviolet spectrum: λ_{max} 229 mμ (ϵ 27,200), 261 (9550), 293 (8750).

4-Oxo-5-furfurylidene-4,5-dihydro-4H-pyrido[3,2,1-jk]-carbazole (IIIc), m.p. 208–208.4°. Ultraviolet spectrum, λ_{max} 228 mμ (ϵ 21,200), 263 (8800), 346 (9350).

Anal. Calcd. for $C_{20}H_{13}NO_2$: C, 80.3; H, 4.4; N, 4.7. Found: C, 80.4; H, 4.6; N, 4.8.

Compounds IIIb and IIIc were also formed when 1 g. of sodium hydroxide dissolved in 10 cc. of 50% ethanol was

(12) All melting points are corrected, and those above 200° were taken in evacuated capillaries. Microanalyses were performed by the Microchemical Laboratory, University of California, Berkeley. Ultraviolet spectra were taken in methanol.

added to a solution of 1 g. of I and 1 g. of the aldehyde in 50 cc. of ethanol, and the resulting solution stirred at room temperature for 2 hr. The product precipitated during this time, and was removed by filtration and washed with ethanol. Under these reaction conditions, benzaldehyde formed the quinolone, isomerization being too rapid to permit isolation of IIIa.

Isomerization of aralkylidene derivatives IIIa,b,c. One hundred mg. of the arylidene derivative was heated under reflux with 20 cc. of a *N* solution of potassium hydroxide in absolute ethanol, for 10 min. As the more soluble quinolone was formed, all of the solid went into solution. Concentration to 10 cc. and cooling gave the crystalline product in quantitative yield. It was recrystallized several times from methanol and dried at 60°/1 mm. for several hours. By this procedure the following were prepared:

4-Oxo-5-benzyl-4H-pyrido[3,2,1-jk]carbazole (IVa), m.p. 214–215° (reported[6] m.p. 215°). Ultraviolet spectrum: λ_{max} 218 mμ (ε 44,500), 236 (25,800), 253 (20,100), 294 (20,900), 384 (18,900). This compound was also formed when benzaldehyde was stirred with I at room temperature, with sodium hydroxide as the catalyst, under the conditions reported above.

4-Oxo-5-p-diethylaminobenzyl-4H-pyrido[3,2,1-jk]carbazole (IVb), m.p. 114.5–115°, unchanged on further recrystallization (reported[6] m.p. 144°). Ultraviolet spectrum, λ_{max} 218 mμ (ε 38,400), 237 (25,000), 243 (23,500), 250 (25,300), 293 (20,900), 384 (15,000).

Anal. Calcd. for $C_{36}H_{24}N_2O$: C, 82.1; H, 6.3; N, 7.4. Found: C, 82.5; H, 6.6; N, 7.4.

4-Oxo-5-furfuryl-4H-pyrido[3,2,1-jk]carbazole (IVc), m.p. 156–156.4°. Ultraviolet spectrum, λ_{max} 213 mμ (ε 40,700), 237 (26,600), 251 (20,600), 294 (18,700), 383 (15,300).

Anal. Calcd. for $C_{20}H_{13}NO_2$: C, 80.3; H, 4.4; N, 4.7. Found: C, 79.7; H, 4.6; N, 4.7.

4-Oxo-5-p-dimethylaminophenylimino-5,6-dihydro-4H-pyrido[3,2,1-jk]carbazole (V). A solution of 0.3 g. of 4-oxo-5,6-dihydro[3,2,1-*jk*]carbazole (I) in 10 cc. of methanol containing 2 cc. of 10% sodium hydroxide solution (or 0.1 cc. of piperidine, or saturated with potassium carbonate) was boiled while a solution of 0.3 g. of *p*-dimethylaminonitrosobenzene in 10 cc. of methanol was added dropwise over 5 min. The solution was boiled for a few minutes longer, filtered, and allowed to cool. Very dark red needles formed, which were recrystallized three times from absolute ethanol and dried at 120°/5 mm., m.p. 180.5–181°. Ultraviolet spectrum: λ_{max} 225 mμ (ε 35,300), 294 (27,900).

Anal. Calcd. for $C_{23}H_{19}N_3O$: C, 78.2; H, 5.4; N, 11.9. Found: C, 78.4; H, 5.5; N, 12.1.

This compound was recovered unchanged when it was allowed to stand with alcoholic hydrochloric acid, or boiled with potassium hydroxide in ethanol, or boiled with potassium *t*-butoxide in *t*-butyl alcohol.

BERKELEY, CALIF.

[CONTRIBUTION FROM THE ENTOMOLOGY RESEARCH DIVISION, AGRICULTURAL RESEARCH SERVICE, U. S. DEPARTMENT OF AGRICULTURE]

Syntheses of Compounds with the Methylenedioxyphenyl Group

S. I. GERTLER, B. H. ALEXANDER, AND M. BEROZA

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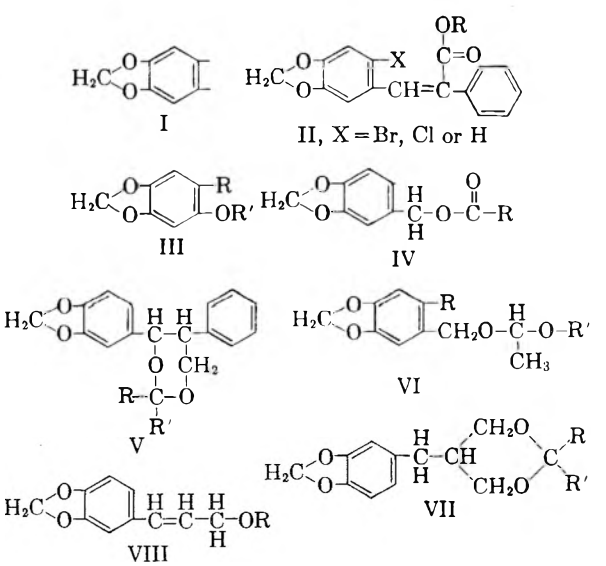
Since the development of several insecticidal substances with the methylenedioxyphenyl group, a variety of new compounds embodying this group has been prepared for insecticidal study. The preparation of these compounds as well as their intermediates is described.

Since a number of compounds with the methylenedioxyphenyl structure I have shown insecticidal or synergistic (with pyrethrins) activity,[1] several other compounds containing this group were prepared for similar testing. Such compounds include types II and III that had not previously been described. The synthesis of the other new methylenedioxyphenyl compounds (IV–VIII) was also undertaken to determine the effect of lengthening the side chain or the inclusion of ring compounds (*m*-dioxanes) on insecticidal activity.



Most of the preparations proceeded smoothly and in good yields to give the expected products. The high yield of 6-nitrosesamol (III, R = NO_2, R′ = H) obtained from the hydrolysis of its acetate

(1) Yuh-Lin Chen and W. F. Barthel, U. S. Dept. Agr., ARS-33-23, 10 pp. (1956); E. K. Harvill, *Contrib. Boyce Thompson Inst.*, **10**, 143 (1939); M. E. Synerholm, U. S. Patent 2,458,656 (1949); Y. Inoue, Y. Katsuda, A. Nishimura, K. Kitagana, and M. Ohno, *Botyu-Kagaku*, **16**, 153 (1951); M. Beroza, *J. Agr. Food Chem.*, **4**, 49 (1956); M. Beroza and W. F. Barthel, *J. Agr. Food Chem.*, **5**, 855 (1957); H. L. Haller, F. B. LaForge, and W. N. Sullivan, *J. Econ. Entomol.*, **35**, 247 (1942); H. L. Haller, F. B. LaForge, and W. N. Sullivan, *J. Org. Chem.*, **7**, 185 (1942); P. G. Piquett, B. H. Alexander, and W. F. Barthel, *J. Econ. Entomol.*, **51**, 39 (1958).

(III, R = NO_2, R′ = $COCH_3$) was unanticipated, since we had previously shown that the saponification of the corresponding acetate of 6-bromosesamol (III, R = Br, R′ = $COCH_3$) yielded only polymeric substances.[2] The excellent yield of the 6-nitrosesamol is understandable when it is noted that hydrogen bonding of the hydroxyl group is possible with the nitro but not with the bromo group.

The ease of preparing II (X = H)[3] made possible the preparation of similar compounds (II, X = halogen). This substitution in position 6 was suggested by the considerable insecticidal activity of the 6-halopiperonyl chrysanthemumates[4] in contrast to the unsubstituted piperonyl chrysanthemumate which was far less active. Introducing the halogen atom into the 6-position of the methylenedioxyphenyl compounds generally increased the activity. The new acetals (VI) were prepared essentially as described by Beroza.[1]

Attempts to isolate the diol intermediate necessary for the preparation of V often resulted in partial dehydration due to the instability of the diol in the acidic medium whence it came.

EXPERIMENTAL

3,4-Methylenedioxyphenyl-1-piperidinecarboxylate [III, R = H, R′ = $CON(CH_2)_4CH_2$] was prepared in the usual way by refluxing a mixture of sesamol (20.7 g.), benzene (100 ml.), pyridine (15 ml.), and 1-piperidinecarbonyl chloride (22.2 g.) for 1 hr.; m.p. 89° (95% alcohol); b.p. 144°/0.1 mm.; yield 32%.

Anal. Calcd. for $C_{14}H_{17}NO_3$: N, 5.67%. Found: N, 5.69%.

4,5-Methylenedioxy-2-nitrophenyl acetate (III, R = NO_2, R′ = $COCH_3$) was prepared by the nitration of 3,4-methylenedioxyphenyl acetate, the preparation of which was reported by Beroza.[1] A solution of 3,4-methylenedioxyphenyl acetate (388 g.) in glacial acetic acid (335 ml.) was added dropwise, with stirring, over a period of 3 hr. to a solution of concentrated nitric acid (255 ml.) and glacial acetic acid (500 ml.) maintained below 5°. The mixture was then poured into a mixture of ice (500 g.) and 10% sodium hydroxide (800 ml.). Precipitation occurred and the mixture was filtered. The yellow crystals were washed free of solvent with cold water and then dried; yield 67%, m.p. 104–105° (alcohol).

Anal. Calcd. for $C_9H_7NO_6$: N, 6.22%. Found: N, 6.24%.

4,5-Methylenedioxy-2-nitrophenol (III, R = NO_2, R′ = H) was obtained by the sodium methylate saponification of the acetate in the usual way,[4] with this exception: After treatment with sodium methylate the mixture contained the phenol and its sodium salt. It was poured into water and, while it was stirred, concentrated hydrochloric acid was added to a *p*H of 2. After standing overnight at 25°, the desired product was filtered off; crude yield 99%; m.p. 93–94° (alcohol).

Anal. Calcd. for $C_7H_5NO_5$: C, 45.92%; H, 2.75%; N, 7.65%. Found: C, 46.18%; H, 2.99%; N, 7.75%.

4,5-Methylenedioxy-2-nitrophenyl propionate (III, R = NO_2, R′ = COC_2H_5) was prepared in the usual manner by reacting propionyl chloride with the phenol in the presence of pyridine and benzene; yield 86%; m.p. 94–95° (benzene–petroleum ether, 60–70°).

Anal. Calcd. for $C_{10}H_9NO_6$: N, 5.87%. Found: N, 5.80%.

4,5-Methylenedioxy-2-nitrophenyl chrysanthemumate (III, R = NO_2, R′ = COC_9H_{15}) was prepared in the same manner as the propionate from synthetic chrysanthemumoyl chloride; yield 85%; m.p. 85–86° (alcohol).

Anal. Calcd. for $C_{17}H_{19}NO_2$: N, 4.20%. Found: N, 4.48%.

4,5-Methylenedioxy-2-nitrophenyl benzoate (III, R = NO_2, R′ = COC_6H_5) was made in the same manner as the other esters; yield 78%; m.p. 141–142° (alcohol).

Anal. Calcd. for $C_{14}H_9NO_6$: N, 4.88%. Found: N, 5.24%.

4,5-Methylenedioxy-2-nitrophenyl-1-naphthoate (III, R = NO_2, R′ = $COC_{10}H_7$) was prepared in the same manner as the other esters; yield 28%; m.p. 129–130° (alcohol).

Anal. Calcd. for $C_{18}H_{11}NO_6$: N, 4.15%. Found: N, 3.86%.

3-(3,4-Methylenedioxyphenyl)-2-propen-1-yl chrysanthemumate (VIII, R = COC_9H_{15}) was prepared as above from 3-(3,4-methylenedioxyphenyl)propanol and synthetic chrysanthemumoyl chloride; yield 94%; b.p. 185–190°/0.1 mm.; $n_D^{25°}$ 1.5528.

Anal. Calcd. for $C_{20}H_{24}O_4$: C, 73.14%; H, 7.37%. Found: C, 73.39%; H, 7.26%.

3-(3,4-Methylenedioxyphenyl)propyl chrysanthemumate [VIII (*dihydro*), R = COC_9H_{15}] was prepared as above; yield 89%; b.p. 170–173°/0.3 mm.; $n_D^{25°}$ 1.5210.

Anal. Calcd. for $C_{20}H_{26}O_4$: C, 73.00%; H, 7.93%. Found: C, 73.29%; H, 8.08%.

3-(3,4-Methylenedioxyphenyl)-2-propen-1-yl 3,5-dinitrobenzoate [VIII, R = $COC_6H_3(NO_2)_2$] was prepared as above; yield nearly quantitative, m.p. 148–149° (alcohol).

Anal. Calcd. for $C_{17}H_{12}N_2O_8$: C, 54.84%; H, 3.25%; N, 7.53%. Found: C, 55.06%; H, 3.27%; N, 7.73%.

3-(3,4-Methylenedioxyphenyl)propyl 3,5-dinitrobenzoate [VIII (*dihydro*), R = $COC_6H_3(NO_2)_2$] was prepared as above; yield nearly quantitative; m.p. 125–126° (alcohol).

Anal. Calcd. for $C_{17}H_{14}N_2O_8$: C, 54.55%; H, 3.77%; N, 7.49%. Found: C, 54.79%; H, 3.88%; N, 7.35%.

2,2-Dimethyl-5-piperonyl-m-dioxane (VII, R = R′ = CH_3) was prepared from 2-piperonyl-1,3-propanediol and acetone by the procedure of Prill, Hartzell, and Arthur,[5] except that 85% phosphoric acid was used as catalyst instead of *p*-toluenesulfonic acid. The intermediate diol was made by the lithium aluminum hydride reduction of piperonylmalonic ester and melted at 92–93° (benzene); yield of *m*-dioxane 66%; m.p. 81–82° (alcohol).

Anal. Calcd. for $C_{14}H_{18}O_4$: C, 67.18%; H, 7.25%. Found: C, 66.73%; H, 6.92%.

2-Methyl-5-piperonyl-m-dioxane (VII, R = H, R′ = CH_3) was prepared from 2-piperonyl-1,3-propanediol and acetaldehyde; yield 54%; b.p. 137–146°/1 mm.; m.p. 76–78° (alcohol).

Anal. Calcd. for $C_{13}H_{16}O_4$: C, 66.08%; H, 6.83%. Found: C, 66.24%; H, 6.85%.

2-Ethyl-5-piperonyl-m-dioxane (VII, R = H, R′ = C_2H_5) was prepared from 2-piperonyl-1,3-propanediol and propionaldehyde; yield 64%; b.p. 140–153°/0.8 mm.; m.p. 66–67° (alcohol).

Anal. Calcd. for $C_{14}H_{18}O_4$: C, 67.18%; H, 7.25%. Found: C, 67.01%; H, 7.28%.

2-Ethyl-2-methyl-5-piperonyl-m-dioxane (VII, R = CH_3, R′ = C_2H_5) was prepared from 2-piperonyl-1,3-propanediol and 2-butanone; yield 40%; b.p. 151–158°/0.8 mm.; $n_D^{25°}$ 1.5251.

Anal. Calcd. for $C_{15}H_{20}O_4$: C, 68.16%; H, 7.63%. Found: C, 67.91%; H, 7.74%.

2-Methyl-4-(3,4-methylenedioxyphenyl)-5-phenyl-m-dioxane (V, R = H, R′ = CH_3) was prepared from 1-(3,4-methylene-

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dioxyphenyl)-2-phenyl-1,3-propanediol and acetaldehyde. This diol was prepared by the lithium aluminum hydride reduction of the methyl ester of the acetate of *beta*-(3,4-methylenedioxyphenyl)tropic acid, the preparation of which has been reported by Alexander and Barthel.[3] The procedure for making the *m*-dioxane is the same as described above; yield 60%; b.p. 200–225°/0.8 mm.; m.p. 109–111° (alcohol).

Anal. Calcd. for $C_{18}H_{18}O_4$: C, 72.47%; H, 6.08%. Found: C, 71.60%; H, 6.18%.

2,2-Dimethyl-4-(3,4-methylenedioxyphenyl)-5-phenyl-m-dioxane (V, $R = R' = CH_3$) was prepared as described above from 1-(3,4-methylenedioxyphenyl)-2-phenyl-1,3-propanediol and acetone; yield 80%; m.p. 137–139° (alcohol).

Anal. Calcd. for $C_{19}H_{20}O_4$: C, 73.06%; H, 6.45%. Found: C, 73.00%; H, 6.31%.

4-[1-(2-Ethylhexyloxy)ethoxy]methyl-1,2-methylenedioxybenzene [VI, $R = H$, $R' = CH_2CH(C_2H_5)C_4H_9$] and the other acetals, described below, were prepared from piperonyl alcohol and the vinyl ether of R′ according to the procedure reported by Beroza.[1] Because these acetals were somewhat unstable at high temperatures, they were distilled rapidly. Rapid distillation necessitated superheating, so that wide boiling ranges were obtained; yield 60%; b.p. 143–154°/0.8 mm.; $n_D^{25°}$ 1.4891.

Anal. Calcd. for $C_{18}H_{28}O_4$: C, 70.10%; H, 9.15%. Found: C, 69.37%; H, 8.88%.

4-(1-Ethoxyethoxy)methyl-1,2-methylenedioxybenzene (VI, $R = H$, $R' = C_2H_5$); yield 79%; b.p. 112–116°/1.1 mm.; $n_D^{25°}$ 1.5021.

Anal. Calcd. for $C_{12}H_{16}O_4$: C, 64.27%; H, 7.19%. Found: C, 63.85%; H, 7.38%.

4-[1-(2-Chloroethoxy)ethoxy]methyl-1,2-methylenedioxybenzene (VI, $R = H$, $R' = CH_2CH_2Cl$); yield 83%; b.p. 137–156°/0.7 mm.; $n_D^{25°}$ 1.5202.

Anal. Calcd. for $C_{12}H_{15}ClO_4$: Cl, 13.71%. Found: Cl, 13.67%.

4-(1-Butoxyethoxy)methyl-1,2-methylenedioxybenzene (VI, $R = H$, $R' = C_4H_9$); yield 71%; b.p. 123–132°/0.6 mm.; $n_D^{25°}$ 1.4954.

Anal. Calcd. for $C_{14}H_{20}O_4$: C, 66.64%; H, 7.99%. Found: C, 66.66%; H, 7.83%.

4-(1-Isobutoxyethoxy)methyl-1,2-methylenedioxybenzene [VI, $R = H$, $R' = CH_2CH(CH_3)_2$]; yield 63%; b.p. 116–129°/0.8 mm.; n_D^{25} 1.4938.

Anal. Calcd. for $C_{14}H_{20}O_4$: C, 66.64%; H, 7.99%. Found: C, 66.05%; H, 7.67%.

4-{1-[2-(2-Ethoxyethoxy)ethoxy]ethoxy}methyl-1,2-methylenedioxy-5-propylbenzene [VI, $R = C_3H_7$, $R' = (C_2H_4O)_2C_2H_5$] was prepared from 6-propylpiperonyl alcohol which was made by the chloromethylation of safrole[6] and then hydrogenation; yield 50%; b.p. 169–195°/0.5 mm.; n_D^{25} 1.4950.

Anal. Calcd. for $C_{19}H_{30}O_6$: C, 64.38%; H, 8.53%. Found: C, 64.54%; H, 8.53%.

4-{1-[2-(2-Ethoxyethoxy)ethoxy]ethoxy}methyl-1,2-methylenedioxy-5-propenylbenzene [VI, $R = CH{:}CHCH_3$, $R' = (C_2H_4O)_2C_2H_5$]; yield 60%; b.p. 186–209°/0.3 mm.; n_D^{25} 1.5136.

Anal. Calcd. for $C_{19}H_{28}O_6$: C, 64.75%; H, 8.01%. Found: C, 64.61%; H, 8.01%.

4-{1-[2-(2-Ethoxyethoxy)ethoxy]ethoxy}methyl-1,2-methylenedioxybenzene [VI, $R = H$, $R' = (C_2H_4O)_2C_2H_5$]; yield 70%; b.p. 172–180°/0.3 mm.; n_D^{25} 1.4941.

Anal. Calcd. for $C_{16}H_{24}O_6$: C, 61.52%; H, 7.75%. Found: C, 61.30%; H, 7.40%.

Ethyl-3-(2-chloro-4,5-methylenedioxyphenyl)-2-phenylacrylate (II, $R = C_2H_5$, X = *Cl*) was prepared from 6-chloropiperonal according to reported directions;[7] over-all yield 37%; m.p. 61–63° (alcohol).

Anal. Calcd. for $C_{18}H_{15}ClO_4$: C, 65.36%; H, 4.57%; Cl, 10.72%. Found: C, 64.93%; H, 4.53%; Cl, 10.20%.

Ethyl-3-(2-bromo-4,5-methylenedioxyphenyl)-2-phenylacrylate (II, $R = C_2H_5$, X = *Br*) was prepared as above; over-all yield 45%; m.p. 76–78° (alcohol).

Anal. Calcd. for $C_{18}H_{15}BrO_4$: C, 57.61%; H, 4.03%; Br, 21.30%. Found: C, 58.12%; H, 3.90%; Br, 21.84%.

Piperonyl octanoate [IV, $R = (CH_2)_6CH_3$] was made in the usual manner from the alcohol and acid chloride; yield 90%; b.p. 130°/0.3 mm.; n_D^{25} 1.4977.

Anal. Calcd. for $C_{16}H_{22}O_4$: C, 69.06%; H, 7.91%. Found: C, 68.97%; H, 8.20%.

Piperonyl chloroacetate (IV, $R = CH_2Cl$) was prepared as above; yield 90%; b.p. 126–127°/0.4 mm.; n_D^{25} 1.5440.

Anal. Calcd. for $C_{10}H_9ClO_4$: C, 52.51%; H, 3.94%. Found: C, 53.24%; H, 4.15%.

Piperonyl isobutyrate [IV, $R = CH(CH_3)_2$] was prepared as the above; yield 90%; b.p. 99°/0.07 mm.; n_D^{25} 1.5068.

Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64.85%; H, 6.35%. Found: C, 64.40%; H, 6.64%.

Piperonyl p-anisate (IV, $R = p\text{-}CH_3OC_6H_4$) was prepared as the above; yield 82%; b.p. 200°/0.1 mm.; m.p. 61° (benzene–petroleum ether, 60–70°).

Anal. Calcd. for $C_{16}H_{14}O_5$: C, 67.13%; H, 4.90%. Found: C, 67.27%; H, 5.17%.

Piperonyl 1-naphthoate (IV, $R = alpha\text{-}C_{10}H_7$) was prepared as the above; yield 84%; m.p. 86–87° (alcohol).

Anal. Calcd. for $C_{19}H_{14}O_4$: C, 74.51; H, 4.58%. Found: C, 74.27%; H, 4.61%.

BELTSVILLE, MD.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NEW HAMPSHIRE]

Preparation and Ring Opening of 2-Methoxy-6-methyl-2-phenyl-1-ox-6-azaspiro[2.5]octane, an Epoxyether[1]

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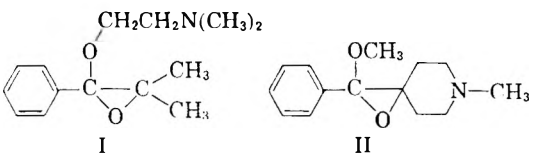
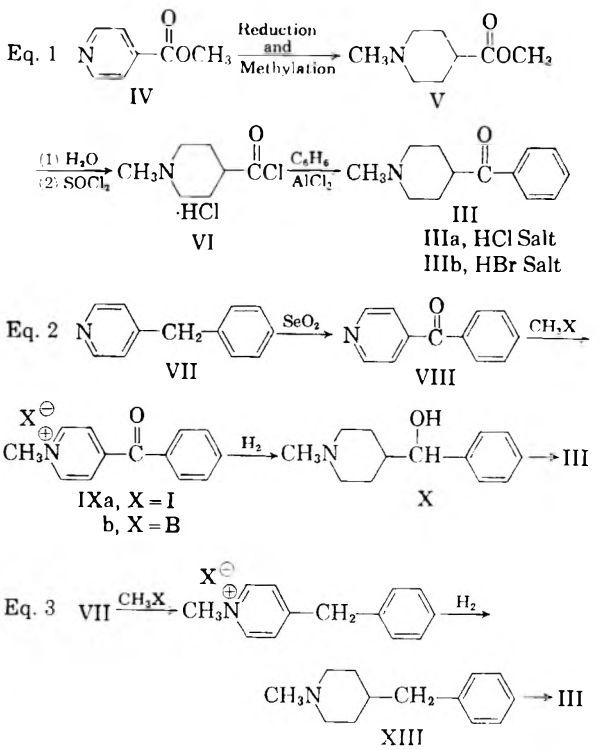
The title compound (II) was prepared by the reaction of 1-methyl-4-halo-4-piperidyl phenyl ketone hydrohalide with bases in absolute alcohol. Unlike the amino epoxyether (I) previously reported, II gave a facile reaction with acids. The reported methods of synthesis of 1-methyl-4-piperidyl phenyl ketone are evaluated, and an improved procedure is described.

The extensive research of Stevens[3a] on the chemistry of epoxyethers suggested the use of this type of compound as an intermediate in the synthesis of 4,4-disubstituted piperidines. Stevens, however, has shown that an epoxyether of an amino alcohol (I) was resistant to attack by acids due to the repulsion of the ammonium nitrogen for the attacking proton.[3b] The proposed piperidine epoxyether (II) would have the ammonium nitrogen separated from the oxirane ring by the same number of atoms as in I. Consequently, the effect of the positive charge on the ease of ring opening due to induction would be about the same in both compounds. This effect should be small, however, in comparison to the field effect which is possible with I but which should be of lesser importance with the rigid piperidine analog II. With this question of the reactivity in mind the synthesis of II was attempted.



I II

The successful use of II for the synthesis of piperidines required a convenient method of obtaining quantities of 1-methyl-4-piperidyl phenyl ketone (III). Three different synthetic routes were devised from reactions which had been reported, and each of these was investigated: (1) the Friedel-Crafts acylation of benzene with 1-methylisonipecotyl chloride hydrochloride (VI),[4] prepared from methyl isonicotinate (IV) (Equation 1), (2) the reduction of 1-methyl-4-benzoylpyridinium halide (IX) to 1-methyl-4-piperidylphenylcarbinol (X) and oxidation of X to III[5] (Equation 2), and (3) oxidation of 1-methyl-4-benzylpiperidine (XII),[4] prepared by the reduction of 1-methyl-4-benzylpyridinium halide (XI)[6] (Equation 3). Methyl 1-methylisonipecotate (V) used in the first method was prepared from methyl isonicotinate (IV) by the procedures of Lyle *et al.*[7] or Feldkamp *et al.*[8] Hydrolysis of the ester and conversion of the resulting acid to the acid chloride (VI) were achieved by standard methods, and the acylation followed the method of Villani *et al.*[4] The yields of III by this method were consistently good; how-



IV V VI III IIIa, HCl Salt IIIb, HBr Salt VII VIII IXa, X = I b, X = B X XIII

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(2) Abstracted from the theses of S. A. L., H. J. T., and G. H. W. presented to the Graduate School of the University of New Hampshire in partial fulfillment of the requirements of the degree of Doctor of Philosophy.

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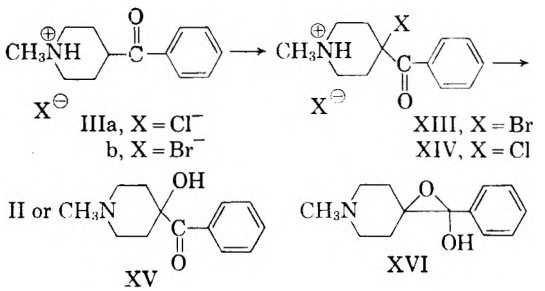
ever, the mechanical difficulty of separating the product from the aluminum salts in the last step was a disadvantage.

At the time this research was initiated 4-benzoylpyridine (VIII) was not available, and a study of method 2 required the synthesis of VIII from 4-benzylpyridine (VII). Although other oxidizing agents caused this conversion,[9,10] the most convenient procedure used selenium dioxide. Unfortunately the hydrogenation of VIII or its quaternary salts (IX) led to reduction of the carbonyl group as well as of the pyridine ring. Indeed it was found that unlike other ketonic pyridine derivatives,[11,12] the carbonyl group of VIII or IX underwent reduction before the pyridine ring. Detection of reduction reactions which had not gone to completion was easily accomplished, for the addition of base to the partially reduced reaction mixture produced a blue dye which faded on standing or on addition of more base. Although no hydrogenation procedure could be found which gave III directly from IX, a procedure for the oxidation of X was devised which led to the isolation of IIIb, thus avoiding the extraction of the base, III, from an aqueous mixture containing chromium hydroxide. This modification (Equation 2) was accepted as the best method of synthesis of III.

The successful oxidation of 4-benzylpyridine (VII) by selenium dioxide suggested the similar oxidation of 1-methyl-4-benzylpiperidine (XII) to III as a method of improving the synthesis of III (Equation 3). Villani *et al.*[4] had reported a poor yield of III from the oxidation of XII with chromic acid; however, it was found that XII was not oxidized by selenium dioxide.

The isolation of III (Equation 2) as the hydrobromide (IIIb) permitted its direct bromination to XIII. The product of the bromination was colored and did not give consistent analyses for halogen. This material apparently was the hydrobromide-perbromide, for addition of phenol to a methanolic solution of the red material caused decolorization and led to the isolation of colorless XIII.

The reactions of XIII with hydroxide or alkoxide in nonaqueous solvents led to one of two products, II or 1-methyl-4-hydroxy-4-piperidyl phenyl ketone (XV), depending on the solvent. In alcoholic medium II was consistently obtained in excellent yield, while in anhydrous ether XV resulted from the reaction of XIII with hydroxide. A consideration of the conditions of the reaction in ether precludes the formation of XV through II, and a nucleophilic attack of the hydroxide ion on the *tertiary* bromine in the 4-position seems unlikely. The epoxy-alcohol (XVI), analogous to that postulated by Stevens,[3c] appears to offer the most logical explanation for the formation of this product of heterogeneous catalysis. In the homogeneous medium, absolute alcohol, no hydroxy-ketone (XV) was obtained. This, of course, occurs since sodium hydroxide dissolved in absolute methanol is largely in the form of sodium methoxide. For this investigation II was prepared by the reaction of XIII with commercial sodium methoxide in methanol.



The structure of II was fully supported by the infrared absorption spectrum which showed no absorption indicative of a carbonyl or of an hydroxyl group. Bands characteristic of an aliphatic ether (1075 cm.$^{-1}$) and an oxirane ring (1220 and 1280 cm.$^{-1}$) were present in the spectrum of II.

For comparison, 1-methyl-4-chloro-4-piperidyl phenyl ketone hydrochloride (XIV) was prepared by the chlorination of IIIa. The base of XIV was found to be stable and resistant to reaction with sodium hydroxide in ether, but the reaction of XIV with sodium methoxide in methanol gave II.

Unlike the epoxyether (I) of Stevens, II was readily converted to the hydroxyketone (XV) by aqueous mineral acid and formed ketoesters with organic acids.[13] Attempts to prepare the picrate or methiodide of II failed, and only the corresponding derivative of the hydroxyketone (XV) was isolated. It is therefore evident that the acid resistance of I results from a shielding of the epoxy ring created by the chain containing the ammonium group assuming the conformation which places the positive nitrogen in the vicinity of the epoxide ring. The fact that the amino nitrogen of II is in a ring prevents the ammonium ion formed in acid from interfering with attack of acid on the oxirane ring.

EXPERIMENTAL

4-Benzoylpyridine (VIII). A suspension of 26 g. of selenium dioxide and 31.2 g. of 4-benzylpyridine (VII) in 125 ml. of glacial acetic acid was heated carefully until a highly exothermic reaction began. After the initial boiling ceased, the mixture was heated for 0.5 hr. The selenium was removed by filtration, and the solution was concentrated under reduced pressure. Water was added, and the reaction mixture

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was neutralized with sodium hydroxide solution. The solid which precipitated was isolated by filtration, washed with water, and dried to give 27.5 g. (81%) of 4-benzoylpyridine (VIII), m.p. 69–75°, lit.[14] m.p. 72–75°.

4-Benzoylpyridine methiodide (IXa). A solution of 32.9 g. of 4-benzoylpyridine (VIII) and 52 g. of methyl iodide in 150 ml. of dry methanol was heated under reflux for 2 hr. The solvent was removed by distillation under reduced pressure, and the residue crystallized on addition of acetone giving 56 g. (96%) of IXa, m.p. 174–176°, lit.[5] m.p. 80–180°.

Anal. Calcd. for $C_{13}H_{12}INO$: I, 39.03. Found: I, 39.08, 39.15.

4-Benzoylpyridine methobromide (IXb). To a solution of 3 g. of 4-benzoylpyridine (VIII) in 15 ml. of acetone was added 5 ml. of liquid methyl bromide, and the flask was stoppered tightly. The precipitated salt, 3.8 g. (82%), was collected by filtration. Recrystallization from acetone and drying under reduced pressure gave 4-benzoylpyridine methobromide, (IXb), m.p. 165–168°.

Anal. Calcd. for $C_{13}H_{12}BrNO$: Br, 28.73. Found Br, 28.93, 28.61.

4-Pyridylphenylcarbinol methiodide. The hydrogenation of 10.8 g. of 4-benzoylpyridine methiodide (IXa) in 200 ml. of methanol over 0.2 g. of platinum oxide was stopped after 3 hr. The catalyst was removed by filtration, and the filtrate was concentrated. The residue, after washing with anhydrous ether, partially crystallized. The solid was removed by filtration and discarded, and the filtrate was warmed, treated with ethyl acetate, and cooled to give 1.8 g. (17%) of 4-pyridylphenylcarbinol methiodide, m.p. 143–144°. The melting point of this compound was not depressed on mixing with an authentic sample prepared from 4-pyridylphenylcarbinol.[14] Solutions containing 4-pyridylphenylcarbinol methiodide turned dark blue on addition of base.

Anal. Calcd. for $C_{13}H_{14}INO$: I, 38.79. Found: I, 38.94.

Reduction of 4-benzoylpyridine (VIII). The hydrogenation of 15 g. of VIII in 100 ml. of methanol over 1.0 g. of Raney nickel catalyst at 130° and 50 atm. of pressure of hydrogen for 6 hr. gave an oily solid after evaporation of the solvent. The residue was triturated with petroleum ether extracting 2.18 g. of 4-benzylpyridine (VII). The solid remaining after the trituration was dissolved in water by the addition of acetic acid. Base was added to adjust the *p*H to approximately 6 causing the precipitation of 3.4 g. of 4-pyridylphenylcarbinol, m.p. 112–118°; lit.[14] m.p. 123–125°. The filtrate from the isolation of 4-pyridylphenylcarbinol was made strongly basic giving 8.0 g. of 4-piperidylphenylcarbinol, m.p. 154–159°; lit.[9] m.p. 166–167°. Recrystallization of the solids raised the melting points to the corresponding literature values.

4-Piperidylphenylcarbinol (2.0 g.) was converted to 2.0 g. of 1-benzoyl-4-piperidylphenylcarbinol, m.p. 103–105°, by reaction with 2 g. of benzoyl chloride in aqueous sodium hydroxide. Recrystallization from ethyl acetate gave an analytical sample of 1-benzoyl-4-piperidylphenylcarbinol, m.p. 112–114°.

Anal. Calcd. for $C_{19}H_{21}NO_2$: C, 77.25; H, 7.17; N, 4.74. Found: C, 76.70, 76.69; H, 6.97, 7.21; N, 4.70, 4.78.

1-Methyl-4-piperidylphenylcarbinol (*X*) *from 4-piperidylphenylcarbinol.* A solution of 4 g. of 4-piperidylphenylcarbinol in 7 ml. of formic acid and 4 ml. of formalin was heated at 100° for 7 hr. The reaction mixture was neutralized while cooling to give 3.95 g. (93%) of 1-methyl-4-piperidylphenylcarbinol, m.p. 149–152°. The melting point was depressed by mixing with the starting material but was not depressed by mixing with authentic 1-methyl-4-piperidylphenylcarbinol (X), m.p. 160–161°.

1-Methyl-4-piperidylphenylcarbinol (*X*) *from 4-benzoylpyridine methobromide* (IXb). A solution of 15.9 g. of 4-benzoylpyridine methobromide (IXb) in 55 ml. of water was reduced at low pressure over 0.3 g. of platinum oxide for 24 hr. The catalyst was removed by filtration, and the filtrate was neutralized with 50 ml. of 20% potassium hydroxide with cooling. The solid which separated was collected to give 11.0 g. (94% of 1-methyl-4-piperidylphenylcarbinol (X), m.p. 153–156°, lit.[5] m.p. 157–159°.

The reduction of 10 g. of IXb in 40 ml. of methanol over 0.2 g. of platinum oxide for 4 hr. gave, after removal of the catalyst and solvent, 8.8 g. (85.5%) of 1-methyl-4-piperidylphenylcarbinol hydrobromide, m.p. 133–141°.

Anal. Calcd. for $C_{13}H_{20}BrNO$: Br, 27.92. Found, Br. 27.35, 27.39.

1-Methyl-4-piperidyl phenyl ketone (III). A mixture of 32.5 g. of 1-methyl-4-piperidylphenylcarbinol (X), 13.3 g. of chromic acid anhydride, and 650 ml. of acetic acid was heated at 100° for 1 hr. The solvent was removed by distillation under reduced pressure, and the residue was diluted with 100 ml. of water and basified with 400 ml. of 25% sodium hydroxide solution. The oily layer which separated was dissolved in ether, and the aqueous layer was extracted 3 times with ether. The combined extracts were dried over potassium carbonate and fractionally distilled under reduced pressure. 1-Methyl-4-piperidyl phenyl ketone (III) (27.5 g., 85%) was collected as the fraction boiling at 190° at 21 mm.; lit.[4] b.p. 130–137° at 2 mm.

1-Methyl-4-piperidyl phenyl ketone hydrobromide (IIIb). The reaction of 33 g. of X and 13.5 g. of chromic acid anhydride in 650 ml. of glacial acetic acid was effected as above. After removal of the solvent the green residue was dissolved in chloroform, and the solution was saturated with hydrogen bromide. The chloroform was removed by distillation, and the residue was suspended in hot isopropyl alcohol and filtered. On cooling the filtrate, the hydrobromide (IIIb) precipitated yielding 29.3 g. (65%), m.p. 198–204°, lit.[16] m.p., 211–212°.

1-Methyl-4-bromo-4-piperidyl phenyl ketone hydrobromide (XIII). A solution of 25 g. of 1-methyl-4-piperidyl phenyl ketone hydrobromide (IIIb) in 90 ml. of chloroform was treated with 12 ml. of bromine. The reaction mixture was allowed to stand for 12 hr. at room temperature, and the solvent was removed under reduced pressure. The residue was dissolved in a solution containing 6.5 g. of phenol in 100 ml. of methanol, and the solution was diluted with anhydrous ether precipitating 28.0 g. (93%) of 1-methyl-4-bromo-4-piperidyl phenyl ketone hydrobromide (XIII), m.p. 155–156° (dec.).

Anal. Calcd. for $C_{13}H_{17}Br_2NO$: 1 Br, 22.1; 2 Br, 44.2. Found: Br (Volhard), 22.2, 22.4; Br (Stepanow), 44.3, 44.2.

1-Methyl-4-chloro-4-piperidyl phenyl ketone hydrochloride (XIV). 1-Methyl-4-piperidyl phenyl ketone hydrochloride (IIIa) was prepared in quantitative yield from the base (III) by precipitation from a solution of hydrogen chloride in ether. The hydrochloride (IIIa) melted at 201–205° after recrystallization from methanol chloroform. A chloroform solution of 6.4 g. of IIIa was saturated with chlorine and allowed to stand for 12 hr. The solvent was removed under reduced pressure, and the residue was dissolved in methanol and treated with phenol. After filtration, the solution was diluted with anhydrous ether precipitating 5.3 g. (73%) of 1-methyl-4-chloro-4-piperidyl phenyl ketone hydrochloride (XIV), m.p. 179–180° (dec.).

Anal. Calcd. for $C_{13}H_{17}Cl_2NO$: 1 Cl, 12.9. Found: Cl, 12.88, 12.67.

Reactions of 1-methyl-4-halo-4-piperidyl phenyl ketone hydrohalide in alcohol. (a) 1-Methyl-4-bromo-4-piperidyl phenyl ketone hydrobromide (XIII) (3.6 g.) dissolved in 50 ml. of absolute methanol was added dropwise to a refluxing solution of 3.2 g. of sodium in 100 ml. of methanol (or an equivalent amount of commercial sodium methoxide

(14) M. R. Kegelman and F. V. Brown, *J. Am. Chem. Soc.*, **75**, 4649 (1953).

(15) C. A. Grob and E. Renk, *Helv. Chim. Acta*, **37**, 1672 (1954).

in methanol). The mixture was heated for 6 hr. and allowed to stand overnight. The solvent was removed by distillation under reduced pressure, and the residue was washed with 150 ml. of ether. The ether solution was distilled under reduced pressure to give 1.9 g. (83%) of 2-methoxy-6-methyl-2-phenyl-1-ox-6-azaspiro[2.5]octane (II), $n_D^{26.5}$ 1.5170.

Anal. Calcd. for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21. Found: C, 71.59, 71.91; H, 8.10, 8.27.

(b) A similar reaction of XIII with 5.0 g. of sodium hydroxide in methanol gave an 87% yield of the epoxyether (II), b.p. 145–146° at 8 mm., $n_D^{27.5}$ 1.5165.

(c) 1-Methyl-4-chloro-4-piperidyl phenyl ketone hydrochloride (XIV) (2.8 g.) was added to a solution of 4 g. of sodium in 100 ml. of methanol, and the reaction mixture was treated as in (a). 2-Methoxy-6-methyl-2-phenyl-1-ox-6-azaspiro[2,5]octane (II) (2.0 g., 84%) was obtained as the fraction, b.p. 170–175° at 25 mm., n_D^{30} 1.5158.

Reaction of 2-methoxy-6-methyl-2-phenyl-1-ox-6-azaspiro [2,5]octane (II) with hydrochloric acid. A mixture of 2.0 g. of the epoxyether (II), 5 ml. of concentrated hydrochloric acid, and 30 ml. of water on neutralization with sodium carbonate gave 2.7 g. (100%) of 1-methyl-4-hydroxy-4-piperidyl phenyl ketone (XV), m.p. 130–131°.

Anal. Calcd. for $C_{13}H_{17}NO_2$: C, 71.22; H, 7.82. Found: C, 71.46, 71.55; H, 7.99, 7.90.

The *hydrochloride*, m.p. 170–172°, was prepared by the usual method.

Anal. Calcd. for $C_{13}H_{18}ClNO_2$: Cl, 13.74. Found, Cl, 13.62, 13.65.

Preparation of the *oxime* of XV by the usual procedure gave the derivative, m.p. 204–205°.

Anal. Calcd. for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74. Found, C, 66.78; H, 7.68.

Reactions of 1-methyl-4-bromo-4-piperidyl phenyl ketone hydrobromide (XIII) in ether. (a) The base from 1.35 g. of XIII was obtained by saturating a solution of the salt in water with sodium bicarbonate. The slightly basic mixture was extracted with two 30 ml. portions of ether. The ether extracts were dried over Drierite for 20 min. and added, after filtration, to a suspension of 1.0 g. of sodium methoxide or sodium ethoxide in 50 ml. of ether. The mixture was heated under reflux for 3 hr. and allowed to stand at room temperature for 8 hr. The insoluble salts were removed by filtration, and the solvent was distilled from the filtrate to yield 0.5–0.8 g. (62–95%) of 1-methyl-4-hydroxy-4-piperidyl phenyl ketone (XV), m.p. 130–131°.

(b) The base was obtained from 3.6 g. of the bromoketone hydrobromide (XIII) by treatment with 0.8 g. of *n*-butylamine in 150 ml. of anhydrous ether. After being stirred for 5 hr., the solution was filtered to remove the butylamine hydrobromide, and the filtrate was added to 0.4 g. of sodium hydroxide. The mixture was heated under reflux for 11 hr. and, filtered, and the filtrate was concentrated to give 1.0 g. (45.5%) of 1-methyl-4-hydroxy-4-piperidyl phenyl ketone (XV), m.p. 130–131°.

(c) To 3.6 g. of XIII in 150 ml. of anhydrous ether 1 g. of powdered sodium hydroxide was added, and the mixture was heated under reflux for 16 hr. The insoluble material was removed by filtration, and the filtrate was concentrated to give 0.25 g. (37%) of 1-methyl-4-hydroxy-4-piperidyl phenyl ketone (XV), m.p. 130–131°.

DURHAM, N. H.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NEW HAMPSHIRE]

Some Reactions of 1-Methyl-4-halo-4-piperidyl Phenyl Ketones[1]

ROBERT E. LYLE AND HENRY J. TROSCIANIEC[2]

Received July 9, 1958

Reactions of the title compounds with organometallics, hydrogen over catalysts, lithium aluminum hydride, and sodium borohydride are described. The results of these reactions show that any effect of the amine function is subtile and cannot be directly traced to the slight differences in the products from the piperidine derivatives as compared with the cyclohexane analogs.

The displacement of the halogen of an α-haloketone by nucleophiles has been shown to lead to a wide variety of products, as reviewed recently by Tchoubar.[3] The results which have been reported arise largely from a study of alicyclic or acylic α-haloketones, and there has been no investigation of the reactions of analogous heterocyclic compounds. The investigation of the reactions of 1-methyl-4-halo-4-piperidyl phenyl ketone hydrohalides (Ia and IIa), reported in the preceding paper,[4] with nucleophilic reagents was of interest, for these heterocycles contain a nucleophile as a portion of the molecule. This amino function could participate in the reaction of the α-haloketones[5]

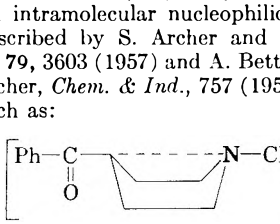
(1) This research was supported in part by a grant, H-1713, from the National Heart Institute of the National Institutes of Health, Public Health Service.

(2) Abstracted in part from the thesis of HJT submitted to the Graduate School of the University of New Hampshire in partial fulfillment of the degree of Doctor of Philosophy.

(3) B. Tchoubar, *Bull. Soc. Chim.*, 1362 (1955).

(4) R. E. Lyle, S. A. Leone, H. J. Troscianiec, and G. H. Warner, *J. Org. Chem.*, 24, 330 (1959).

(5) The amino group could participate as (a) a proton acceptor as in the footnote 8 in S. M. McElvain and R. E. Lyle, *J. Am. Chem. Soc.*, 72, 384 (1950), or (b) as a nucleophile in an intramolecular nucleophilic displacement such as that described by S. Archer and co-workers, *J. Am. Chem. Soc.*, 79, 3603 (1957) and A. Bettini, C. A. Grob, and E. Schumacher, *Chem. & Ind.*, 757 (1958), to give an intermediate such as:



or have no effect on the reactivity of Ia or IIa resulting in the formation of products analogous to those from 1-halocyclohexyl phenyl ketone.[3] The following report describes the initial investigation of this question.

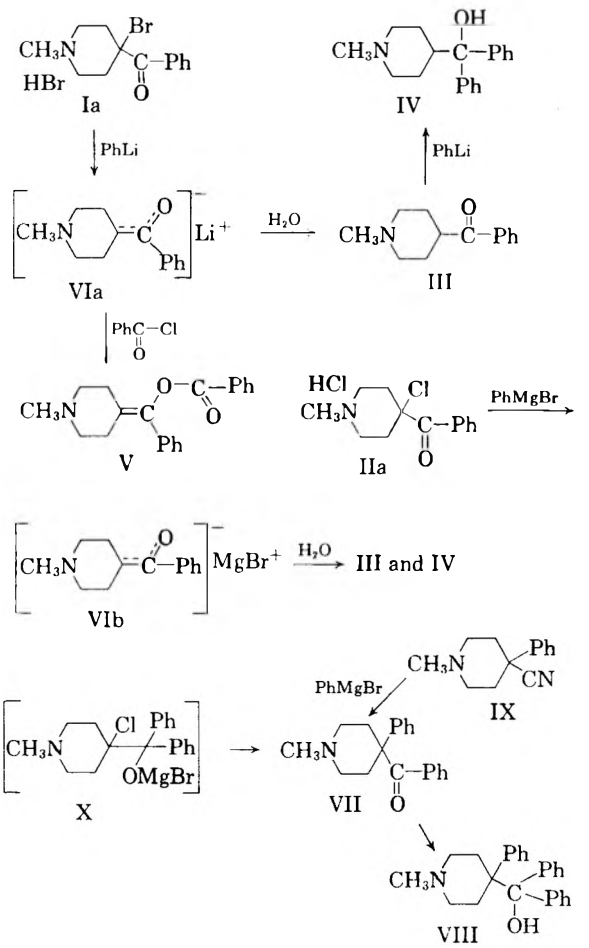
The major difference in the reactivity of the piperidine derivatives as compared with the cyclohexane analog was the failure of the former to undergo the Favorski rearrangement. Thus reactions of I or II with alkoxide, hydroxide, amines, or silver ion lead to the formation of the corresponding epoxyether, hydroxy ketone, or unsaturated ketone.[4]

Some difference in the course of the reactions of I or II with organometallics as compared with the cyclohexane analog[3,6] was also observed, for extensive metal halogen interchange occurred with the piperidine derivatives. The reaction of phenyllithium with Ia gave 1-methyl-4-piperidyl phenyl ketone (III), 30%, and 1-methyl-4-piperidyldiphenylcarbinol (IV), maximum yield 32%. That metal halogen exchange rather than addition occurred was confirmed by adding benzoyl chloride to the reaction mixture before hydrolysis to give 1-methyl-4-(α-benzoyloxybenzylidene)piperidine (V). Although V could not be purified as the hydrobromide to give an analytical sample, the picrate of V was obtained pure. The structure of V was proved by the ultraviolet and infrared absorption spectra and by hydrolysis of V to III and benzoic acid.

The method of formation of IV in this reaction was not obvious, for the reaction of phenyllithium with the enolate (VIa) was highly unlikely. Hydrolysis of the reaction mixture by slow addition to aqueous acid, rather than the reverse, gave a 65% yield of III and only 3% of the alcohol (IV). Thus, hydrolysis by addition of aqueous acid to the reaction mixture was causing the conversion of the enolate (VIa) to the ketone (III) before the excess phenyllithium was decomposed. The ketone (III) then gave IV with phenyllithium.

With the more electronegative chlorine in IIa and the less nucleophilic organometallic, the Grignard reagent, slightly different results were obtained. The reaction of II with phenylmagnesium bromide gave a complex mixture of products. From one reaction the ketonic products were isolated by distillation of the product mixture to give 36% of 1-methyl-4-piperidyl phenyl ketone (III) and 34% of 1-methyl-4-phenyl-4-piperidyl phenyl ketone (VII). The slight solubility of 1-methyl-4-phenyl-4-piperidyldiphenylcarbinol (VIII) hydrobromide in water led to its isolation in about 18% yield from several reactions. 1-Methyl-4-piperidyldiphenylcarbinol (IV) was found also in several reactions, but the amount of this compound present was dependent on the method of hydrolysis used. Thus, the yield varied considerably from reaction to reaction. The yield of VIII did not appear to be dependent on the hydrolytic procedure.

The identity of the products was established by comparison with authentic samples. The reaction of phenyllithium with VII, prepared from 1-methyl-4-phenylisonipectonitrile (IX) and phenylmagnesium bromide,[7] gave VIII.[8] The reaction of Demerol, ethyl 1-methyl-4-phenylisonipectotate, with phenylmagnesium bromide failed to give VIII.



The formation of III and IV occurred by the same course, through the intermediate VIb, as that discussed under the phenyllithium reaction. VII probably resulted from the rearrangement of the 1,2-addition product (X) of II and phenylmagnesium bromide.[3,6] The formation of VIII clearly indicated that VII was formed during the reaction proper, for the yield of VIII was unaffected by the method of hydrolysis.

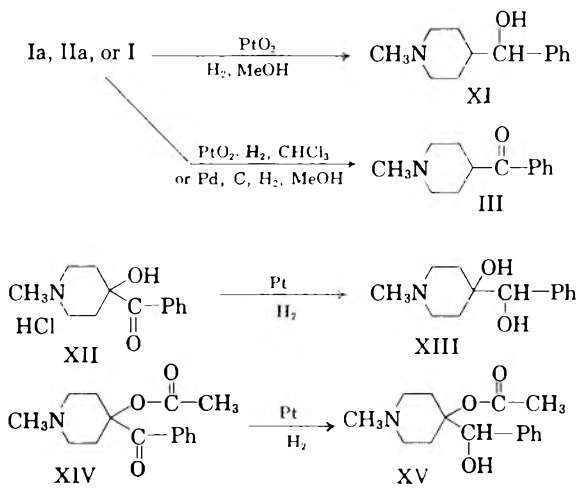
In an effort to prepare another series of piperidine derivatives for comparison with the cyclo-

(6) R. L. Huang, *J. Chem. Soc.*, 4089 (1957); G. Cauquil and J. Rouzaud, *Bull. Soc. Chim.*, 285 (1954).

(7) O. Eisleb, U. S. Patent 2,248,018, July 1, 1941.

(8) O. Schaumann, *Arch. exptl. Path. Pharmakol.*, 196, 109 (1940).

hexane analogs, the preparation of halohydrins by the reduction by several methods of the carbonyl function of the α-haloketones II, Ia, and IIa was investigated and led to interesting observations. II, Ia, and IIa on hydrogenation over platinum catalyst in methanol produced 1-methyl-4-piperidylphenylcarbinol (XI). If the catalyst were changed to palladium on charcoal or the solvent to chloroform, 1-methyl-4-piperidyl phenyl ketone (III) was formed. Since 1-methyl-4-piperidyl phenyl ketone hydrochloride (IIIa) was not affected by hydrogen over platinum catalyst under conditions effective for the reduction of the haloketones II, Ia, and IIa,[9] hydrogenolysis of the carbon-halogen bond followed by reduction of the carbonyl group did not offer an adequate explanation of these reactions. The ease of metal halogen exchange of the haloketones with organometallics suggested a similar mechanism for the catalytic hydrogenation, for a molecule of the haloketone oriented on the surface of the catalyst with the oxygen and halogen atoms adjacent to a hydrogen molecule could, by a concerted shift of electrons, form the enol (VI) and hydrogen bromide. Because of steric relationships the enol (VI) would be expected to be adsorbed on the catalyst with greater ease than the ketone (IIIa).[10] Thus, whether the carbinol (XI) or the ketone (III) is the product of the hydrogenation of the α-haloketone under a given set of conditions depends on the relative



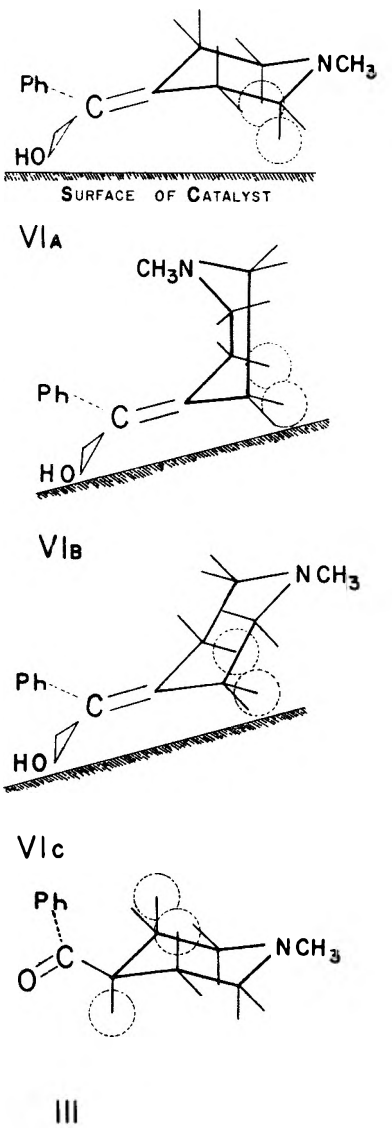
rates of ketonization or reduction of the enol VI. An analogous effect of conditions and mechanism was reported for the hydrogenation of the allylic halide, 14-bromocodeinone.[11]

Polar groups, other than halogen, on the 4-position of 1-methyl-4-piperidyl phenyl ketone were not hydrogenolyzed. Thus 1-methyl-4-hydroxy-4-piperidyl phenyl ketone hydrochloride (XII) gave 1-methyl-4-hydroxy-4-piperidylphenylcarbinol (XIII), and 1-methyl-4-acetoxy-4-piperidyl phenyl ketone (XIV) gave 1-methyl-4-acetoxy-4-piperidylphenylcarbinol (XV)[9] on hydrogenation over platinum in methanol.

The failure to produce halohydrins from I and II by catalytic reduction led to a study of the reactions of I with lithium aluminum hydride and sodium borohydride. The products isolated from

(9) S. A. Leone, Ph.D. thesis, University of New Hampshire (1958).

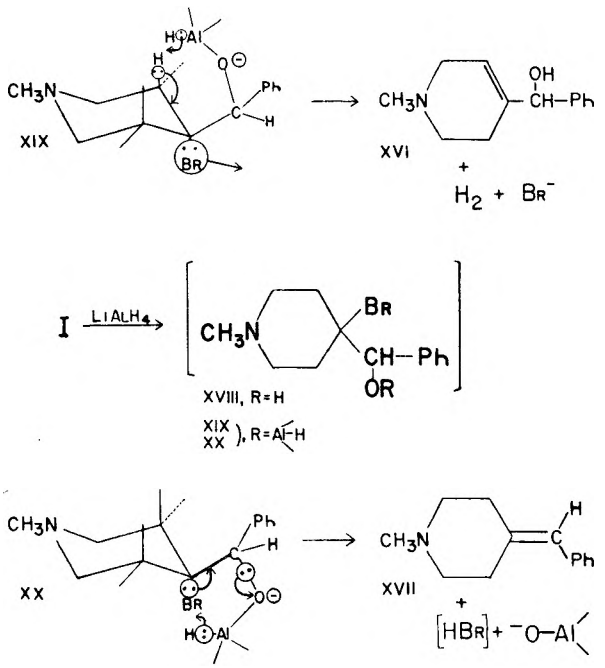
(10) The planar nature of the substituted benzylidene portion of the enol (VI) would allow adsorption on the surface of the catalyst, whereas the adsorption of the carbonyl group of the ketone (III) would be inhibited by interference of the *alpha* or *beta* axial hydrogens with the catalyst surface. The piperidine ring would be in an unfavorable



conformation for further reduction immediately after the hydrogenolysis (VIa), and rearrangement of the conformation to the boat form (VIb) [*Ann. Repts.*, **54**, 173 (1957)] or the inverted chair form (VIc) must occur before reduction to the carbinol (XI) can proceed. The necessity of these conformational changes allows time for rearrangement of the enol (VI) to the ketone (III) under some reaction conditions.

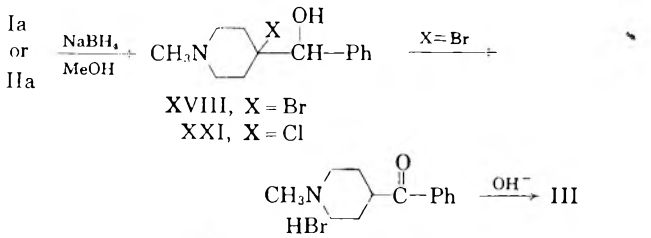
(11) H. Conroy, *J. Am. Chem. Soc.*, **77**, 5960 (1955).

the reaction of lithium aluminum hydride with I were found to be 1-methyl-1,2,3,6-tetrahydro-4-pyridylphenylcarbinol (XVI),[12] 55%, and 1-methyl-4-benzylidenepiperidine (XVII), 34%. 1-Methyl-4-piperidylphenylcarbinol (XI) was isolated in trace amounts from some reactions. A plausible mechanism for the formation of these products would be the dehydrohalogenation of the bromohydrin (XVIII) to form XVI and dehydration of XI, the hydrogenolysis product of XVIII, to form XVII during the decomposition of the reaction mixture and the isolation of the products. The formation of XVI by this route cannot be disproved; however, a consideration of the properties of XVIII, as prepared below, makes this unlikely. Certainly, XVII cannot be formed in this manner, for dehydration of XI in acid led exclusively to 1-methyl-4-benzyl-1,2,3,6-tetrahydropyridine.[12] XI is not dehydrated under other conditions. It is further evident that these products do not arise by hydrogenolysis of the carbon-halogen bond prior to reduction of the carbonyl. These



products must be formed by the reaction of lithium aluminum hydride with the bromohydrin (XVIII). In this case the decomposition of the rotational conformations (XIX and XX) of the carbinol-to-piperidine ring bond, offer a possible explanation for the formation of XVI and XVII.

The reduction of 1-methyl-4-bromo-4-piperidyl phenyl ketone hydrobromide (Ia) with sodium borohydride gave the bromohydrin (XVIII), and a similar reduction of IIa produced the chlorohydrin (XXI). Pure XVIII was stable in the solid state; however, attempted recrystallization of XVIII or the presence of impurities in solid XVIII caused the decomposition to a saltlike material. The product of the decomposition was soluble in water, and the water solution, on neutralization with base, deposited an oil. The infrared spectrum of the oil clearly showed it to be a mixture containing alcoholic and ketonic components. The oxime and picrate of the ketonic component were prepared from the mixture and were shown to be derivatives of 1-methyl-4-piperidyl phenyl ketone (III). The alcoholic component was not identified; however, the stability of the oil eliminates the possibility of the presence of 1-methyl-1,2,3,6-tetrahydro-4-pyridylphenylcarbinol (XVI)[12] in the mixture. XXI was more stable than XVIII, for the chlorohydrin could be recrystallized from acetone.



The reactions of I and II indicate a positive nature associated with the 4-halo substituent which, in conjunction with the infrared absorption data, suggest that the most favorable conformation of I and II is that in which the halogen-carbon bond is approximately parallel with the *pi* orbital of the carbon of the carbonyl group. In this orientation the transition from the α-haloketone to the overlapping *pi* orbital system of the enol (VI) or enolate (VIa or VIb) can most easily occur.

EXPERIMENTAL

Catalytic hydrogenations of 1-methyl-4-bromo-4-piperidyl phenyl ketone hydrobromide (Ia) *and the chloro analog* (IIa). (*a*) *Platinum in methanol.* A solution of 3.6 g. of Ia in 75 ml. of methanol was treated with hydrogen (3 atm.) over 0.1 g. of platinum oxide as catalyst. When the pressure remained constant, the reaction mixture was filtered, and the solvent was removed by distillation leaving an oily residue. A portion (0.2 g.) of the oil was converted to the base to give 1-methyl-4-piperidylphenylcarbinol (XI), m.p. 152–155°, which did not depress the melting point, 154–157°, of an authentic sample on mixing. The remainder of the oily hydrobromide was crystallized from methanol-ether solution to give 1.35 g. (54.5% based on total oil) of 1-methyl-4-piperidylphenylcarbinol hydrobromide, m.p. 133–136°.

(*b*) *IIa over platinum in methanol.* A solution of 2.4 g. of IIa in 50 ml. of methanol was treated as in (a) to give an oily hydrochloride which on neutralization in aqueous solution gave 1.7 g. of XI. Recrystallization from benzene gave 1.1 g. (46%) of XI, m.p. 154–156°.

(*c*) *IIa—sodium carbonate over platinum in methanol.* A solution of 1.0 g. of 1-methyl-4-chloro-4-piperidyl phenyl ketone hydrochloride (IIa) in 50 ml. of methanol was treated with 0.5 g. of sodium carbonate to free the base. The solution of II was treated as in (a) to give 0.5 g. (66.7%) of 1-methyl-4-piperidylphenylcarbinol (XI), m.p. 142–150°.

(12) A. E. Kerlin, B.S. thesis, University of New Hampshire (1956).

Recrystallization of 0.4 g. from benzene gave 0.25 g. of XI, m.p. 153–155°.

(*d*) *Ia over platinum in chloroform.* A solution of 2.0 g. of Ia in 150 ml. of chloroform over 0.1 g. of platinum oxide was treated as in (a) to give, on evaporation of the solvent, an oily residue. Crystallization of the oil from methanol ether gave 0.7 g. (45%) of 1-methyl-4-piperidyl phenyl ketone hydrobromide (IIIb), m.p. 196–204°.[4]

(*e*) *Ia over palladium-on-charcoal in methanol.* A solution of 1.0 g. of Ia in 50 ml. of methanol over 0.2 g. of catalyst was treated as in (a). Ether was added to the concentrated reaction mixture to precipitate 0.35 g. (45%) of IIIb, m.p. 201–204°.

Catalytic hydrogenation of 1-methyl-4-hydroxy-4-piperidyl phenyl ketone hydrochloride (XII). A solution of 1.0 g. of XII in 50 ml. of methanol with 0.1 g. of platinum oxide was treated as in (a). The residue was converted to the base in water, and an ether solution of the base deposited 0.8 g. of 1-methyl-4-hydroxy-4-piperidylphenylcarbinol (XIII), m.p. 142–144°.[9]

Reaction of Ia with phenyllithium. (a) A suspension of 3.6 g. (0.01 mole) of 1-methyl-4-bromo-4-piperidyl phenyl ketone hydrobromide (Ia) in 50 ml. of ether was added to a solution of 0.07 mole of phenyllithium [prepared from 1.4 g. (0.2 g. atom) of lithium and 10.05 g. (0.07 mole) of bromobenzene] in ether. The mixture was heated under reflux for 4 hr., and the reaction mixture was poured onto 75 g. of ice. The ether layer was separated, and the aqueous layer was extracted with ether. The combined ether solutions were dried over sodium carbonate, and the solvent was removed by distillation. Addition of 15 ml. of water and 3 ml. of 1:1 hydrochloric acid to the residual oil caused the precipitation of 1.0 g. (32%) of impure 1-methyl-4-piperidyldiphenylcarbinol hydrochloride (IVa), m.p. 283–287°. Recrystallization of a small sample gave pure IVa, m.p. 310–312° (dec.), lit.[13] m.p. 310–311° (dec.).

Anal. Calcd. for $C_{19}H_{23}ClNO$: Cl, 11.16. Found: Cl, 11.52.

The base was prepared from the hydrochloride above to give IV, m.p. 134–135°, which did not depress the melting point of an authentic sample on mixing.

The acidic solution which deposited IV was neutralized with sodium carbonate and extracted with ether. After drying, the ether solution was concentrated, and the residue was distilled under reduced pressure to give 0.6 g. (30%) of 1-methyl-4-piperidyl phenyl ketone (III), b.p. 154° at 4 mm. III was identified as the hydrochloride, m.p. 204–206°, and by conversion to IV, m.p. 132–134°, on reaction with phenyllithium.

Anal. Calcd. for $C_{13}H_{18}ClNO$: Cl, 14.79. Found: Cl, 14.68.

(b) The reaction above was repeated; however, the mixture was hydrolyzed by slow addition, 3 hr., to 150 ml. of 10% hydrochloric acid. The ether layer was separated and discarded. The acidic solution was neutralized with sodium carbonate and extracted with ether. The extracts were dried over sodium carbonate and concentrated to give 2.25 g. of oily residue. Addition of 20 ml. of water and 3 ml. of concentrated hydrochloric acid caused the precipitation of 0.1 g. (3%) of crude 1-methyl-4-piperidyldiphenylcarbinol hydrochloride (IVa), m.p. 295–298° (dec.).

The acidic solution was neutralized with sodium carbonate and extracted with ether. The ether was removed by distillation, and the residual oil was distilled under pressure to give 1.3 g. (65%) of 1-methyl-4-piperidyl phenyl ketone (III), b.p. 140° at 3 mm.

(c) Repetition of the above reaction and addition of 1.6 ml. of benzoyl chloride before hydrolysis gave a very exothermic reaction. The solvent was removed by distillation, and the residual oil was treated with methanol to give 1.95 g. (54%) of impure 1-methyl-4-(α-benzoyloxybenzylidene)-piperidine hydrobromide (Va), m.p. 247–253°. Recrystallization of Va from chloroform acetone raised the melting point to 255–257°. The infrared absorption spectrum of Va supported the assignment of structure and the ultraviolet absorption spectrum in 95% ethanol showed a maximum at 253 mμ, log ε = 4.424.

Anal. Calcd. for $C_{20}H_{22}BrNO_2$: C, 61.68; H, 5.71; Br, 20.58. Found: C, 60.49, 60.42; H, 5.69, 5.77; Br, 21.25.

The picrate of V was prepared in ethanol to give a derivative, m.p. 211–213°.

Anal. Calcd. for $C_{26}H_{24}N_4O_9$: C, 58.21; H, 4.51. Found: C, 58.01, 58.24; H, 4.39, 4.67.

V (0.55 g.) on heating under reflux with 20 ml. of 20% hydrochloric acid gave 0.35 g. of 1-methyl-4-piperidyl phenyl ketone (III), characterized as the picrate, m.p. 200–201°, and 0.1 g. of benzoic acid, m.p. 121–122°.

Reaction of IIa with phenylmagnesium bromide. Because of the complex mixture of products from this reaction, several runs were necessary to isolate all of the products. Each reaction used 3.5 g. (0.013 mole) of IIa and 0.14 mole of phenylmagnesium bromide (prepared from 3.6 g. of magnesium and 22 g. of bromobenzene) in ether. The reaction mixture was heated under reflux for 1 hr. and then worked up as follows:

(a) The reaction mixture was poured onto 75 g. of ice, the ether layer was separated, and the aqueous layer was extracted with additional ether. The ether extract was extracted with dilute hydrochloric acid, and the acidic extract was neutralized. The basic solution was then extracted with ether. After drying over potassium carbonate the ether solution was concentrated, and the residual oil (4.9 g.) was distilled under reduced pressure to give 3.8 g. of distillate, b.p. 160–250° at 3 mm. Redistillation gave 1.45 g. (35.7%) of impure 1-methyl-4-piperidyl phenyl ketone (III), b.p. 110–112° at 1 mm., which was converted to 1.9 g. of the hydrobromide, m.p. 202–204°. A second fraction, b.p. 140–182°, was largely 1-methyl-4-phenyl-4-piperidyl phenyl ketone (VII) contaminated with a trace of 1-methyl-4-piperidyldiphenylcarbinol (IV). The composition was shown by treating 0.15 g. of this oil with dilute hydrochloric acid to precipitate 0.03 g. of 1-methyl-4-piperidyldiphenylcarbinol hydrochloride (IVa), m.p. 313–315°. A second sample, 0.5 g., was dissolved in 20 ml. of concentrated sulfuric acid to destroy the IV present. Dilution of the acid solution, neutralization, extraction with ether, and concentration of the ether solution gave 0.3 g. of impure 1-methyl-4-piperidyl phenyl ketone picrate, m.p. 195–211°, after addition of methanolic picric acid to the residue. One recrystallization of the solid from methanol gave 0.15 g. of VII picrate, m.p. 223–225°, which showed no depression of melting point on mixing with an authentic sample.

(b) A second reaction mixture was decomposed by dropwise addition to 30 ml. of water. The voluminous inorganic precipitate was dissolved by addition of 50 ml. of 1:1 hydrochloric acid solution. Extraction of the acidic solution with ether caused the precipitation of 3.0 g. of solid. Trituration of the solid with acetone gave 1.2 g. (18.2%) of 1-methyl-4-phenyl-4-piperidyldiphenylcarbinol hydrobromide (VIII),[14] m.p. 230–235°. The 1.8 g. of material which remained in acetone could not be crystallized; however, it was assumed to be largely salts of IV. Neutralization of a solution of 0.2 g. of VIIIa in water gave 0.15 g. of the crude base, which on recrystallization from ether-petroleum ether gave 0.1 g. of 1-methyl-4-phenyl-4-piperidyldiphenylcarbinol (VIII), m.p. 122–124°.[8]

Anal. Calcd. for $C_{25}H_{27}NO$: C, 83.99; H, 7.61. Found: C, 83.91; H, 7.73.

(13) F. J. Villani, M. S. King, and D. Papa, *J. Org. Chem.*, **17**, 249 (1952).

(14) The amine hydrobromide precipitated from the solution containing both chloride and bromide ions because of the greater insolubility of the hydrobromide. Treatment of the base with hydrogen chloride gave VIII hydrochloride, m.p. 219–221° after recrystallization from acetone ether.

Anal. Calcd. for $C_{25}H_{28}ClNO$: Cl, 9.00. Found: Cl, 9.30.

Preparation of 1-methyl-4-phenyl-4-piperidyldiphenylcarbinol (VIII). An ethereal solution of 0.06 mole of phenyllithium and 1.1 g. (0.004 mole) of 1-methyl-4-phenyl-4-piperidyl phenyl ketone (VII) was heated under reflux for 12 hr. The mixture was poured into 20 ml. of concentrated hydrochloric acid and 50 g. of ice causing the precipitation of 1.3 g. (76.5%) of 1-methyl-4-phenyl-4-piperidyldiphenylcarbinol hydrobromide (VIIIa),[14] m.p. 220–225°.

Reduction of Ia with sodium borohydride. A solution of 10 g. of Ia in 50 ml. of methanol was treated with 4 g. of sodium borohydride in 30 ml. of methanol. A precipitate formed and was removed by filtration to give 1.5 g. of XVII. Removal of the solvent from the filtrate and addition of water to the residue gave an additional 4.42 g. of XVII for a total yield of 5.9 g. (76%) of XVII. The compound could not be purified by recrystallization; however, the material from the reaction mixture, m.p. 104–105°, gave the correct analytical values for carbon and hydrogen.

Anal. Calcd. for $C_{13}H_{18}BrNO$: C, 54.94; H, 6.38. Found: C, 55.16; H, 6.63.

An attempt to recrystallize a sample of XVII gave, on evaporation of the ethanol, a water soluble oil. Neutralization of the aqueous solution deposited an oil which formed an oily methiodide, a picrate (m.p. 199–201°), and an oxime (m.p. 188–190°). These melting points correspond to those of derivatives of 1-methyl-4-piperidyl phenyl ketone (III) as did the carbonyl stretching frequency (1675 cm.$^{-1}$) in the infrared absorption spectrum.[9]

Reduction of IIa with sodium borohydride. A solution of 1 g. of IIa in 7 ml. of methanol was treated with 0.3 g. of sodium borohydride. The solid which precipitated was removed by filtration to give 0.5 g. of XXI, m.p. 139–141°. Evaporation of the filtrate without heating and addition of water caused the precipitation of an additional 0.24 g. of XXI, m.p. 138–140°. The combined yield of XXI represented 85% of the starting IIa. The identity of the compound was confirmed as XXI by mixture melting point determination with an authentic sample,[9] m.p. 140.0–140.5°.

Reduction of Ia with lithium aluminum hydride. A suspension of 20.0 g. of Ia in ether was added to 4.0 g. of lithium aluminum hydride suspended in ether. After heating under reflux for 2 hr., water was added cautiously. The ether was separated from the inorganic precipitate, and the solid was washed with additional ether. Evaporation of the ether gave 11.2 g. of oily residue. Addition of petroleum ether to the oil caused the precipitation of 6.1 g. (55.5%) of 1-methyl-1,2,3,6-tetrahydro-4-pyridylphenylcarbinol (XVI), m.p. 107–108°, which gave no depression of melting point when mixed with an authentic sample.[12]

Anal. Calcd. for $C_{13}H_{17}NO$: C, 76.78; H, 8.43. Found: C, 76.83; H, 8.51.

The petroleum ether solution remaining from the isolation of XVI was concentrated, and the residue was allowed to stand for 3 weeks to remove the remaining traces of XVI by decomposition. At the end of this time the 4.55 g. of oily residue was fractionally distilled under reduced pressure to give four fractions all boiling at about 115–126° at 7 mm. weighing a total of 3.5 g. This material was shown to be 1-methyl-4-benzylidene piperidine (XVII), $\lambda_{max}^{96\% \text{ EtOH}} = 243$ mμ (log ε = 3.962), contaminated with XVI and possibly XI.[15]

Anal. Calcd. for $C_{13}H_{17}N$: C, 83.39; H, 9.16. Calcd. for $C_{13}H_{17}NO$: C, 76.78; H, 8.43. Found: C, 82.00; H, 8.70.

The reaction of 0.15 g. of impure XVI with methyliodide gave, after recrystallization from acetone, 0.06 g. of XVI methiodide, m.p. 213–215°.

Anal. Calcd. for $C_{14}H_{20}IN$: C, 51.06; H, 6.12; N, 4.26. Found: C, 51.83; H, 6.26; N, 3.71.

Hydrogen bromide was added to a sample of 1.05 g. of impure XVI to give a hydrobromide, which was recrystallized twice from acetone yielding 0.3 g. of pure XVI hydrobromide, m.p. 199–201°, $\lambda_{max}^{95\% \text{ EtOH}} = 241$ mμ (log ε = 4.163).

Anal. Calcd. for $C_{13}H_{18}BrN$: C, 58.20; H, 6.75; N, 5.22. Found: C, 58.68, 58.52; H, 6.82, 6.58; N, 4.99.

Catalytic hydrogenation of XVI methiodide. A solution of 0.3 g. of XVI methiodide in 75 ml. of methanol was reduced over Raney nickel at 100 atm. of pressure of hydrogen. After 1 hr. the reduction was stopped, and the mixture was filtered to remove the catalyst. Evaporation of the solvent and trituration of the residue with acetone gave 0.2 g. of 1-methyl-4-benzylpiperidine methiodide, m.p. 208–210°. A mixture of this methiodide with an authentic sample melted at 208–209°.

DURHAM, N. H.

(15) From several reactions an impure solid, m.p. about 115–140°, was isolated. The material could not be purified by recrystallization, but since the melting point was higher than that of XVI, the solid was thought to be 1-methyl-4-piperidylphenylcarbinol (XI).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NEW HAMPSHIRE]

A New Series of Potential Local Anesthetics

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A series of esters of 1-alkyl-4-aroyl-4-piperidinols has been prepared by the acidolysis of epoxy ethers. The esters have been screened for physiological activity and have been shown to produce local anesthesia. The irritability of the compounds precludes the usefulness of these compounds as local anesthetics.

Esters of 4-piperidinols have been shown to have pharmacological, as well as structural, similarities to the natural local anesthetic, cocaine,[2,3] and recently the esters of substituted 4-phenyl-4-piperidinols were demonstrated to be potent analgesics.[4] On the basis of Stevens' preparations

(1) Abstracted from the theses of HJT and GHW to be submitted to the Graduate School of the University of New Hampshire in partial fulfillment of the degree of Doctor of Philosophy.

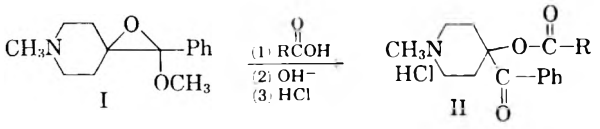
(2) S. M. McElvain, *J. Am. Chem. Soc.*, **46**, 1721 (1924).

(3) T. P. Carney, *Record Chem. Progr.*, **15**, 143 (1954).

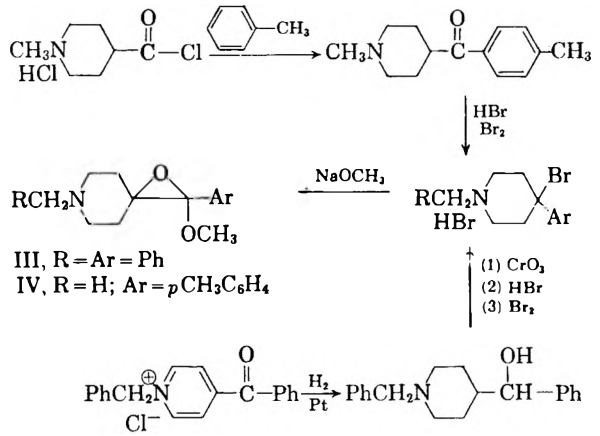
(4) R. H. X. Foster and A. J. Carman, *J. Pharmacol. Exptl. Therap.*, **91**, 195 (1947). K. A. Jensen and F. Lundquist, *Dansk. Tids. Farm.*, **17**, 173 (1943); *Chem. Abstr.*, **39**, 2506 (1945). K. A. Jensen, U. S. Patent **2,589,943** (March 18, 1952); *Chem. Abstr.*, **46**, 11249 (1952). A. Ziering, L. Berger, S. D. Heineman, and J. Lee, *J. Org. Chem.*, **12**, 894 (1947).

of esters of hydroxy ketones from epoxy ethers,[5] the synthesis of 2-methoxy-6-methyl-2-phenyl-1-ox-6-azaspiro[2.5]octane (I)[6] provided a method for preparing a series of esters (II) of 1-methyl-4-benzoyl-4-piperidinol, which are related structurally to the above esters.

The conversion of the epoxyether (I) to esters of simple organic acids was accomplished with ease by mixing a solution of I with the organic acid in ether and collecting the organic acid salt of the amino ester which precipitated. The amine was freed from this salt and converted to the desired mineral acid salt by conventional methods. Attempts to prepare the corresponding esters from amino acids by this method failed; such reactions gave the parent hydroxy ketone (XV). The esters of the amino acids did form, however, when pyridine was used as the solvent.



The promising results of the early pharmacological screening led to the expansion of the series of esters to include a number of esters of 1-benzyl-4-benzoyl-4-piperidinol (V) and 1-methyl-4-*p*-toluyl-4-piperidinol (X). These compounds were prepared by the same general procedures as used in the synthesis of the esters of 1-methyl-4-benzoyl-4-piperidinol (II).[6]



The only step which was questionable in these syntheses was the Friedel-Crafts acylation of toluene with 1-methylisonipecotyl chloride hydrochloride. That *para* substitution occurred, as would be predicted, was confirmed by the infrared absorption spectra of the derived epoxyether (IV) and the esters produced from IV. The absorption due to out-of-plane bending of the aromatic C—H bonds was at 823 cm.$^{-1}$, which is characteristic of *para* disubstituted benzenes and not the *ortho* isomers.[7]

Preliminary results of pharmacological tests. The esters VI–XVII (see Table I) were screened for local anesthetic action by the corneal irrigation and the infiltration methods. On the basis of the activity in both tests the more potent esters were the benzoates, IX and XVII. The *p*-aminobenzoate analog (XII) of XVII was much less active than XVII, which is surprising in view of the local anesthetic action of other esters of this amino acid.[3]

The data in Table I do not indicate any overall structure-activity relationships; however, in general, replacement of the 4-benzoyl by 4-*p*-toluyl gave esters of higher potency (compare XIV and XI, XV and X, and XVII and IX). Except for the benzoate (VIII), the esters of 1-benzyl-4-benzoyl-4-piperidinol (V) were more active than the corresponding derivatives of the 1-methyl-4-piperidinols, XV and X. The esters of V, however, formed salts of low solubility in water and thus could not be evaluated completely as to activity. This decreased solubility perhaps accounts for the lack of anesthetic action of VIII in the corneal irrigation procedure, for this lack of activity was unexpected in view of the high potency of the benzoates, IX and XVII, relative to this series.

All of the esters produced signs of irritation and thus the local anesthetic action is of no practical use. The esters of 1-benzyl-4-benzoyl-4-piperidinol (V) were significantly more irritating than those of the other two piperidinols.

The possibility that these compounds might have pharmacological activity of some other type was also investigated. 1-Methyl-4-benzoyl-4-piperidinol methobromide and 1-methyl-4-benzoyl-4-piperidyl benzoate hydrochloride (XVII) were screened for analgesic effects, and 1-methyl-4-benzoyl-4-piperidinol hydrochloride (XV) was tested for antispasmodic action and hypothermia. All of the tests indicated no activity in these areas.

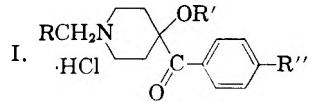
XV and XVII caused a rapid decrease in the blood pressure of test animals, and the animals recovered quickly from the effects of XV. XVII gave little change in heart rate. Neither of these compounds was successful in relieving hypertension.

The antispasmodic action of diphenylacetic

(5) C. L. Stevens and Bruce V. Ettling, *J. Am. Chem. Soc.*, **77**, 5412 (1955) and preceding papers.

(6) R. E. Lyle, S. A. Leone, H. J. Troscianiec, and G. H. Warner, *J. Org. Chem.*, **24**, 330 (1959).

(7) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley and Sons, Inc., New York, 1954.

TABLE I. 

R		R′	R″	Yield, %	M.P., °C.	Formula	Analyses: Calcd. Element, %	Analyses: Found Element, %	Corneal Irrigation (Rabbit): Conc., %	Corneal Irrigation (Rabbit): Anesthesia, min.	Infiltration (Guinea Pig): Conc., %	Infiltration (Guinea Pig): Anesthesia, min.
VI	Ph	CH_3CH_2CO	H	20[a]	246–249	$C_{22}H_{26}ClNO_3$	Cl, 9.22	Cl, 9.71	1	26[c]	0.05	29[d]
VII	Ph	CH_3CO	H	39[a]	265–267	$C_{21}H_{24}ClNO_3$	Cl, 9.49	Cl, 9.53	1	17[c]	0.05	30[d]
VIII	Ph	PhCO	H	41[a]	220–222	$C_{26}H_{26}ClNO_3$	Cl, 7.95	Cl, 8.13	2	0[e]	0.05 (0.1)	9 (87)[d]
IX	H	PhCO	CH_3	69[a]	255–256	$C_{21}H_{24}ClNO_3$	Cl, 9.48	Cl, 9.47	0.4	25[c]	0.05	20[e]
X	H	H	CH_3	See Experimental					1	23[f]	0.5 (0.25)	26 (9)[d]
XI	H	CH_3CH_2CO	CH_3	68[a]	231–233	$C_{17}H_{24}ClNO_3$	Cl, 10.86	Cl, 10.73	1	8[c]	0.25	21[d]
XII	H	p-$NH_2C_6H_4CO$	H	86[b]	179–180	$C_{20}H_{22}N_2O_3$[g]	C, 70.98; H, 6.71	C, 70.67; H, 6.61	1	15[c]	0.5 (0.25)	16 (12)[d]
XIII	H	4-C_5H_4N-CO	H	85[b]	126–128	$C_{19}H_{20}N_2O_3$[g]	C, 70.38; H, 6.22	C, 70.21; H, 6.07	2	0[c]	0.25	37[d]
XIV	H	CH_3CH_2CO	H	85[a]	254–255 dec.	$C_{16}H_{22}ClNO_3$	C, 61.64; H, 7.11; Cl, 11.37	C, 61.44; H, 7.34; Cl, 11.45	1	2[g]	1	14
XV	H	H	H	Ref. 6					1	0[g]	0.25	25[h]
XVI	H	$PhCONHCH_2CO$	H	39[a]	170 dec.	$C_{22}H_{25}ClN_2O_4$	Cl, 8.51	Cl, 8.41	1	60[g]	0.25 (0.1)	56 (12)[h]
XVII	H	PhCO	H	85[a]	256–258 dec.	$C_{20}H_{22}ClNO_3$	Cl, 9.86	Cl, 10.00	1	33[g]	0.1 (0.05)	72 (14)[i]

[a] These compounds were prepared by Procedure *A*. [b] These compounds were prepared by Procedure *B*. [c] Mild irritation was noted at these concentrations. [d] No irritation was noted at these concentrations. [e] As in [b], however, greater concentration produced necrosis at the site of injection. [f] No irritation was observed at this concentration, but greater concentration produced mild irritation. [g] These corneal irrigation tests were determined using guinea pig's eye. [h] Irritation was slight when determined using rabbit skin. [i] Irritation was negligible when determined using rabbit skin.

acid esters of amino alcohols[8] suggested the synthesis and screening of 1-methyl-4-benzoyl-4-piperidyl diphenylacetate methobromide (XVIII). This compound as well as the hydrochloride showed no spasmolytic action, however.

EXPERIMENTAL

1-Methyl-4-benzoyl-4-piperidyl benzoate. A solution of 0.3 g. of 2-methoxy-6-methyl-2-phenyl-1-ox-6-azaspiro[2.5]-octane (I) in 10 ml. of ether was added to 0.25 g. of benzoic acid in 10 ml. of ether. After standing 3 hr., the solution was concentrated, and the residue crystallized on standing. The solid was recrystallized from ether–petroleum ether to give 0.5 g. (88%) of the benzoic acid salt of 1-methyl-4-benzoyl-4-piperidyl benzoate, m.p. 128–130°.

Anal. Calcd. for $C_{27}H_{27}NO_6$: C, 72 79; H, 6 11. Found: C, 72.16, 72.07; H, 6.17, 6.16.

A solution of 0.1 g. of the benzoic acid salt in water-methanol was neutralized with sodium carbonate, precipitating an oil which crystallized on standing. The solid on recrystallization from petroleum ether gave 0.06 g. (68%) of the base of XVII, m.p. 112–114°.

Anal. Calcd. for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55. Found: C, 74.02, 74.23; H, 6.45, 6.49.

Preparation of 4-piperidinol esters. Procedure A. A solution of 1 mole of the epoxyether (I, III, or IV) and the organic acid, in excess of 2 moles (about 2.2 moles) in ether was allowed to stand for 12 hr. The solvent was removed by evaporation, and a solution of the residue in water was neutralized with base. The amine which precipitated was isolated by filtration, dried, and dissolved in anhydrous ether. Treatment of the ether solution with anhydrous hydrogen chloride caused the precipitation of the hydrochlorides listed in Table I.

Procedure B. A solution of 0.028 mole of the amino acid in 25 ml. of pyridine was added to 0.013 mole of the epoxy-ether (I) in 50 ml. of ether. After standing for 12 hr., the solution was concentrated, and the residue was dissolved in water. Addition of sodium carbonate to the water solution caused the precipitation of the amino acid esters listed in Table I.[9]

1-Methyl-4-benzoyl-4-piperidyl diphenylacetate. An ether solution of 4.0 g. of diphenylacetic acid and 2.2 g. of I was treated as in Procedure *A* to give 1.3 g. (34.9%) of the base of XVIII, m.p. 122–124°.

Anal. Calcd. for $C_{27}H_{27}NO_3$: C, 78.43; H, 6.58. Found: C, 78.54; H, 6.51.

The base of XVIII was converted to the hydrochloride in ether-acetone, and the salt was recrystallized from ethyl acetate–methanol giving *1-methyl-4-benzoyl-4-piperidyl diphenylacetate hydrochloride*, m.p. 246–248°.

Anal. Calcd. for $C_{27}H_{28}ClNO_3$: Cl, 7.88. Found: Cl, 8.02.

The base of XVIII was converted to the *methobromide* (XVIII) by methyl bromide in methanol. Recrystallization from ethyl acetate–methanol gave pure XVIII, m.p. 245–247°.

Anal. Calcd. for $C_{28}H_{30}BrNO_3$: Br, 15.72. Found: Br, 15.74.

1-Methyl-4-piperidyl p-tolyl ketone hydrobromide. The 1-methylisonipecotic acid hydrochloride (22.7 g., 0.14 mole) obtained from the hydrochloric acid hydrolysis of 20.0 g. of methyl 1-methylisonipecotate[6] was heated under reflux with 100 ml. of thionyl chloride for 2 hr., and the excess thionyl chloride was removed by distillation under reduced pressure. The residual solid was suspended in 150 ml. of anhydrous toluene, and 50 g. of anhydrous aluminum chloride was added in portions. The reaction mixture was heated for 10 hr., and, after cooling, was poured into 200 ml. of 10% hydrochloric acid and 100 g. of ice. The toluene was removed by steam distillation, and the remaining aqueous acidic solution was extracted with 300 ml. of ether which was discarded. The aqueous layer was made basic by the addition of solid sodium hydroxide, and the amine was removed by extraction with three portions of ether. The ether extracts were dried over anhydrous sodium carbonate, and gaseous hydrogen bromide was introduced. The solid which precipitated was collected by filtration and recrystallized from isopropyl alcohol giving an 82% yield of 1-methyl-4-piperidyl *p*-tolyl ketone hydrobromide, m.p. 217.5–219.5°.

Anal. Calcd. for $C_{14}H_{20}BrNO$: Br, 26.80. Found: Br, 26.86, 26.69.

1-Methyl-4-bromo-4-piperidyl p-tolyl ketone hydrobromide. A chloroform solution of 18.7 g. of 1-methyl-4-piperidyl *p*-tolyl ketone was treated with 9 ml. of bromine, and the mixture was allowed to stand overnight. The solvent and excess bromine were removed by distillation under reduced pressure. The residual solid was dissolved in methanol, and phenol was added to remove the perbromide-bromine.[6] On addition of ether 19.65 g. (96%) of 1-methyl-4-bromo-4-piperidyl *p*-tolyl ketone hydrobromide precipitated. The melting point was 157–158° after recrystallization from acetone.

Anal. Calcd. for $C_{14}H_{19}Br_2NO$: 1-Br, 21.19. Found: Br, 21.25, 21.13.

1-Methyl-4-p-toluyl-4-piperidinol hydrochloride (X). A solution of 19.6 g. of 1-methyl-4-bromo-4-piperidyl-*p*-tolyl ketone hydrobromide in methanol was added to a solution of sodium methoxide prepared from 8.5 g. of sodium in 100 ml. of methanol. The mixture was heated under reflux for 1 hr., and most of the methanol was removed by distillation under reduced pressure. Water was added, and the remaining methanol was removed by warming the solution under reduced pressure. The aqueous layer was extracted with ether, and the extracts were dried over sodium carbonate. Removal of the ether by distillation gave 9.0 g. (87%) of 2-methoxy-6-methyl-2-*p*-tolyl-1-ox-6-azaspiro[2.5]octane (IV), b.p. 135–140° at 3 mm.

Anal. Calcd. for $C_{15}H_{21}NO_2$: C, 72.87; H, 8.56. Found: C, 73.07; H, 8.72.

The infrared absorption spectrum of IV had no bands between 3100 and 4000 cm.$^{-1}$ or between 1650 and 1800 cm.$^{-1}$ indicating the absence of an hydroxyl and a carbonyl group, respectively. Strong bands at 1280 and 1220 cm.$^{-1}$ due to the epoxide ring and at 1075 cm.$^{-1}$ indicative of an aliphatic ether confirmed the epoxyether function. The strong band at 823 cm.$^{-1}$ and lack of absorption at 750 cm.$^{-1}$ showed that the aromatic ring was *para*-disubstituted.[7]

The addition of 3.2 g. of IV to dilute hydrochloric acid gave the crude base of X on neutralization with sodium carbonate. 1-Methyl-4-*p*-toluyl-4-piperidinol, after recrystallization from ethyl acetate, was dissolved in ether, and dry hydrogen chloride was added. Recrystallization of the precipitated solid from acetone gave 2.5 g. of pure X, m.p. 223–225°.

Anal. Calcd. for $C_{14}H_{20}ClNO_2$: Cl, 13.14; N, 5.19. Found: Cl, 13.23, 13.28; N, 5.07, 5.12.

1-Benzyl-4-benzoylpyridinium chloride. A solution of 18.3 g. of 4-benzoylpyridine and 12.6 g. of benzyl chloride in 200 ml. of methanol was heated under reflux for 12 hr. Concentration of the solution gave 24.6 g. (82%) of the pyridinium salt, m.p. 186–188°.

Anal. Calcd. for $C_{19}H_{16}ClNO$: Cl, 11.45. Found: Cl, 11.37.

1-Benzyl-4-piperidylphenylcarbinol hydrochloride. A solution of 15 g. of 1-benzyl-4-benzoylpyridinium chloride in methanol was reduced by hydrogenation at 3 atm. over platinum catalyst to give, after removal of the solvent, 14.8 g. (90%) of 1-benzyl-4-piperidylphenylcarbinol hydrochloride, m.p. 184–185°.

(8) J. H. Biel, H. L. Friedman, H. A. Leiser, and E. P. Sprengler, *J. Am. Chem. Soc.*, 74, 1485 (1952). R. R. Burtner and J. W. Cusic, *J. Am. Chem. Soc.*, 65, 262 (1943).

(9) The esters of amino acids were isolated and characterized as the base rather than the hydrochloride since the analyses of the salts indicated incomplete conversion to the dihydrochloride.

Anal. Calcd. for $C_{19}H_{24}ClNO$: Cl, 11.20. Found: Cl, 11.75, 11.77.

1-Benzyl-4-piperidyl phenyl ketone hydrobromide. A solution of 17 g. of 1-benzyl-4-piperidylphenylcarbinol hydrochloride and 4.1 g. of chromic acid in 200 ml. of acetic acid was heated on the steam bath for 1 hr. The solvent was removed by distillation under reduced pressure, and the residue was dissolved in chloroform. The solution was saturated with anhydrous hydrogen bromide, and the chloroform was removed by evaporation. The residue was recrystallized from isopropyl alcohol to give 12 g. (77%) of 1-benzyl-4-piperidyl phenyl ketone hydrobromide, m.p. 235–238°.

Anal. Calcd. for $C_{19}H_{23}BrNO$: Br, 22.18. Found: Br, 22.05.

1-Benzyl-4-bromo-4-piperidyl phenyl ketone hydrobromide. A suspension of 12 g. of 1-benzyl-4-piperidyl phenyl ketone hydrobromide in chloroform was treated with 2.5 ml. of bromine, and the mixture was allowed to stand overnight. The solvent was removed by distillation, and the residue was dissolved in methanol. Phenol was added to remove the perbromide-bromine,[6] and 13 g. (88%) of 1-benzyl-4-bromo-4-piperidyl phenyl ketone hydrobromide, m.p. 162–164°, precipitated as a white solid on addition of ether.

Anal. Calcd. for $C_{19}H_{23}Br_2NO$: 1 Br, 18.20. Found: Br, 18.29.

6-Benzyl-2-methoxy-2-phenyl-1-ox-6-azaspiro[2.5]octane (III). To a solution of 13.5 g. of sodium methoxide in 150 ml. of methanol was added 11 g. of 1-benzyl-4-bromo-4-piperidyl phenyl ketone hydrobromide. The solution was heated under reflux for 4 hr., and the solvent was removed by distillation under reduced pressure. The residue was distilled under reduced pressure to give 6.5 g. of 6-benzyl-2-methoxy-2-phenyl-1-ox-6-azaspiro[2.5]octane (III), b.p. 170–175° at 2 mm., which on treatment with organic acids in ether gave the esters in Table I.

Anal. Calcd. for $C_{20}H_{23}NO_2$: C, 77.63; H, 7.49. Found: C, 77.60, 77.78; H, 7.39, 7.52.

Acknowledgment. The authors wish to express appreciation to the National Heart Institute of the National Institutes of Health for partial support of this research under grant Number H-1713. The authors further thank the pharmaceutical companies which assisted in the screening program and in particular the assistance of Dr. K. K. Chen of Eli Lilly and Co.

DURHAM, N. H.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NEW HAMPSHIRE]

Hydrates of 1-Methyl-3- and -4-piperidone Hydrochlorides[1]

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The salts of 1-methyl-4-piperidone and 1-methyl-3-piperidone have been shown to crystallize with one molecule of water from solvents which contain water. The infrared absorption spectra of these hydrates clearly prove that the water is present as the hydrate of the carbonyl group. The preparation of 1-methyl-3-piperidone by a novel synthesis is reported.

The addition of water to the carbonyl group of aldehydes or ketones leads to stable hydrates in only a few cases. Those examples of stable hydrates that are known have in common one or more strongly electron-attracting groups attached to the carbonyl, and this structural feature is considered necessary for a stable hydrate. The formal positive charge of an amine salt, therefore, would be expected to stabilize the hydrate of a carbonyl located in the same molecule. Although stable hydrates of salts of amino-ketones have not been demonstrated, ketals have been reported to be formed by the reaction of 4-piperidone hydrochloride,[3b] 1-alkyl-4-piperidone quaternary salts,[4] and 1-alkyl-4-piperidone hydrochlorides[5] with alcohol. This reaction is promoted by the positive charge in the salt; however, the strain inherent in a tercovalent carbon within a six-membered ring[6] alone appears to provide the driving force for the formation of the ketal. Thus, unlike other ketones which undergo partial reaction with alcohols by addition,[7] cyclohexanone is converted to the ketal.[8] Since 1-methyl-4-piperidone hydrochloride

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(2) Abstracted in part from the Thesis of REA submitted to the Graduate School of the University of New Hampshire in partial fulfillment of the requirements of the degree of Master of Science.

(3) (a) S. M. McElvain and K. Rorig, *J. Am. Chem. Soc.*, **70**, 1820, 1826 (1948). (b) S. M. McElvain and R. McMahon, *J. Am. Chem. Soc.*, **71**, 901 (1949).

(4) H. M. E. Cardwell, *J. Chem. Soc.*, 1059 (1950).

(5) P. Brookes and J. Walker, *J. Chem. Soc.*, 3173 (1957).

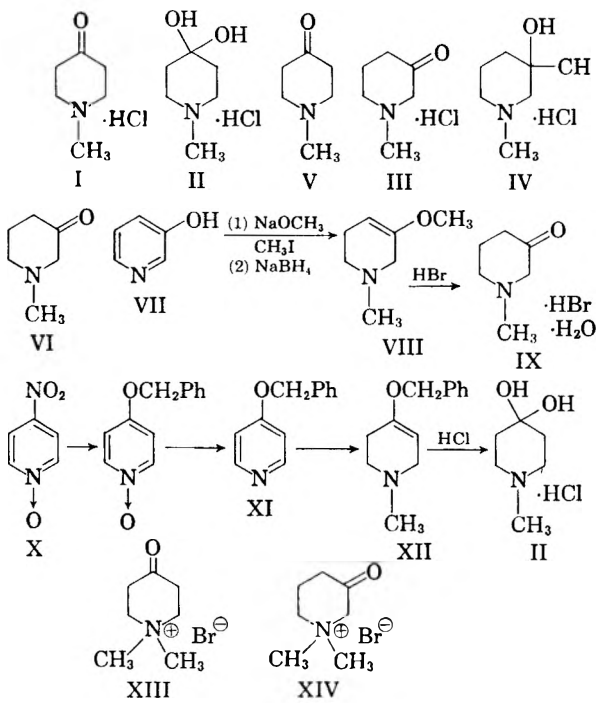
(6) H. C. Brown, R. S. Fletcher, and R. B. Johannesen, *J. Am. Chem. Soc.*, **73**, 212 (1951).

(7) O. H. Wheeler, *J. Am. Chem. Soc.*, **79**, 4191 (1957).

(8) R. E. McCoy, A. W. Baker, and R. S. Gohlke, *J. Org. Chem.*, **22**, 1175 (1957).

(I) has both structural features which would be expected to promote the stability of a ketone hydrate, the report by Craig and Tarbell[9] that I crystallized from aqueous solvents with a molecule of water suggested that the ketone hydrate (II) of I was stable and could be isolated. Since hydrates of these amino ketones would be of value in investigating the conformation of piperidines, the structures of the salts of 1-methyl-4- and -3-piperidones were elucidated.

The 1-methyl-4-piperidone hydrochloride (I) used in this investigation[10] was prepared by the method of McElvain and co-workers[3]; however, the previous methods of synthesis of 1-methyl-3-piperidone hydrochloride (III)[11] are complex due to the necessity of preparing an unsymmetrical amino diester for the Dieckmann cyclization, the conventional procedure for preparing piperidones. The selective reduction of pyridinium salts to tetrahydropyridines by sodium borohydride[12] suggested a shorter route to 1-methyl-3-piperidone (VI). 3-Hydroxypyridine (VII), available commercially,[13] was alkylated simultaneously on nitrogen and oxygen with methyl iodide, and, without isolation, the pyridinium salt was reduced with sodium borohydride to 1-methyl-1,2,5,6-tetrahydro-3-pyridyl methyl ether (VIII). On hydrolysis with hydrobromic acid, VIII gave 1-methyl-3-piperidone hydrobromide (IX).



This procedure also was evaluated as a method of synthesis of 1-methyl-4-piperidone (V). The conversion of 4-nitropyridine-1-oxide (X) to 4-benzyloxypyridine (XI) was accomplished by known procedures,[14] and the methiodide of XI was reduced to 1-methyl-1,2,3,6-tetrahydro-4-pyridyl benzyl ether (XII), which on hydrolysis with hydrochloric acid gave 1-methyl-4-piperidone hydrochloride hydrate (II). This method, however, was not superior to that of McElvain.[3]

The piperidone hydrochlorides (II and IV) each gave two melting points when determined on a Fisher hot stage apparatus. The lower temperature corresponded to that observed in a capillary. These results in conjunction with the halogen analyses showed that 1-methyl-3-piperidone hydrochloride (IV), as well as II, was a hydrate.

The structure determination of the hydrates II and IV was accomplished by a study of the infrared absorption spectra of these compounds in the solid state as mulls in Halocarbon[15] (1300–4000 cm.$^{-1}$) and Nujol (650–1300 cm.$^{-1}$). While the spectra of the amines V and VI, as liquid films, showed strong absorption at 1715–1716 cm.$^{-1}$ characteristic of carbon to oxygen double bond stretching, and no absorption above 3100 cm.$^{-1}$, the spectra of the hydrochlorides II and IV showed no absorption between 1500 and 2000 cm.$^{-1}$ The spectra of II and IV had large, broad bands at about 3300 cm.$^{-1}$ in addition to the broad N—H band of the salt at about 2700 cm.$^{-1}$ The spectrum of IV contained a small band at 2827 cm.$^{-1}$ not found in the spectrum of II.

The analyses and the infrared spectra require that II and IV, molecular formula $C_6H_{14}ClNO_2$, have no free carbonyl group but contain hydroxyl functions. These requirements are compatible with the hydrate structures II and IV, but do not eliminate the possibility of an hydrated enol of I and III or a hydrated product of transannular interaction between the nitrogen and the carbonyl. The possibility of an enol was removed by failure of II and IV to give a reaction with ferric chloride and the absence of absorption in the infrared spectrum characteristic of carbon to carbon double bond. The second possibility was unlikely in view of Leonard's results with related compounds,[16] and such interaction would be impossible with the quaternary salts of 1-methyl-3- and -4-piperidone

(9) L. E. Craig and D. S. Tarbell, *J. Am. Chem. Soc.*, **71**, 465 (1949).

(10) The authors wish to express appreciation to Eli Lilly and Co. for a generous sample of 1-methyl-4-piperidone hydrochloride and to Dr. Edwin R. Shepard of that company through whose assistance the compound was obtained.

(11) E. A. Prill and S. M. McElvain, *J. Am. Chem. Soc.*, **55**, 1233 (1933); S. M. McElvain and J. F. Vozza, *J. Am. Chem. Soc.*, **71**, 896 (1949); and N. J. Leonard and E. Barthel, *J. Am. Chem. Soc.*, **72**, 3632 (1950).

(12) A. E. Kerlin, B.S. thesis, University of New Hampshire (1956); R. Lyle, E. Perlowski, H. Troscianiec, and G. Lyle, *J. Org. Chem.*, **20**, 1761 (1955).

(13) The authors wish to express appreciation to Nepera Chemical Company, Yonkers 2, N. Y., for a sample of 3-hydroxypyridine used in this study.

(14) E. Ochiai, *J. Org. Chem.*, **18**, 534 (1953).

(15) Halocarbon Products Corp., 2012 88th St., North Bergen N. J. See D. S. Crocket and H. M. Haendler, *Anal. Chem.*, in press.

(16) N. J. Leonard, R. C. Fox, and M. Oki, *J. Am. Chem. Soc.*, **76**, 5708 (1954).

(V and VI). The methiodides XIII and XIV, however, were similar in properties to II and IV. Thus, the hydrates of 1-methyl-3- and -4-piperidone hydrochlorides must be represented by the *gem*-diols II and IV. The protection of the carbonyl group of 1-methyl-3-piperidone hydrochloride (III) by the formation of the hydrate (IV) would explain the greater stability to air of the hydrochloride as compared to the base (VI).

The double melting points of II and IV determined on a hot stage led to the attempted preparation of the anhydrous hydrochlorides I and III by sublimation of the hydrates. This technique gave I having a melting point corresponding to that reported by Craig and Tarbell.[9] The infrared absorption spectrum of I as a solid mull gave a very small band at 3300 cm.$^{-1}$ but a strong broad band at 1733 cm.$^{-1}$ This shift of 18 cm.$^{-1}$ of the carbonyl stretching frequency on formation of the salt is a result of the repression of delocalization of the *pi* electrons of the carbonyl group due to the proximity of the formal charge on the nitrogen. The absorption of the N—H bond of the salt was altered also. The structure of the band was very complex and was shifted to lower frequencies (*ca.* 2500 cm.$^{-1}$). This change also reflects the interaction of the carbonyl function and the positive nitrogen.

The anhydrous hydrochloride (III) of 1-methyl-3-piperidone did not appear as the sublimate but could be formed by heating the hydrate IV under reduced pressure. The halogen analysis of III corresponded to the anhydrous hydrochloride, and the infrared absorption spectrum also supported this structure. The spectrum showed strong absorption at 1725 cm.$^{-1}$, indicating a free carbonyl, and the N—H absorption band was complex and shifted to about 2470 cm.$^{-1}$. These changes are closely related to those observed with I and II.

The methobromides of 1-methyl-3- and -4-piperidones behaved similarly to the hydrochlorides. The salts, XIII and XIV, were prepared in anhydrous ether, and the analyses and infrared absorption spectra indicated only traces of the hydrates. The carbonyl stretching frequencies were 1723 (XIII) and 1729 (XIV) cm.$^{-1}$. Recrystallization of the methobromides from water-acetone gave the corresponding hydrates. The infrared spectrum of 1 - methyl - 4 - piperidone methobromide hydrate (XIIIa) gave an hydroxyl band at 3360 cm.$^{-1}$ and a weak band at 1723 cm.$^{-1}$. The spectrum of 1-methyl-3-piperidone methobromide hydrate (XIVa) indicated the presence of the hydroxyl groups by absorption at 3080 and 3300 cm.$^{-1}$. The melting points of the hydrates XIIIa and XIVa were identical with anhydrous salts XIII and XIV unless the hydrates were introduced into a bath at 150° in which case they both melted completely.

This study proved that the salts of 1-methyl-3- and -4-piperidones form stable hydrates of the carbonyl, and that the isolation of the anhydrous forms of the hydrochlorides is difficult. Thus it is evident that there is the possibility that the salt of any amino ketone may add readily the elements of water necessitating a careful examination of any amino ketone salt.

EXPERIMENTAL

Infrared absorption spectra. The infrared absorption spectra were determined using a Perkin-Elmer, Model 21, infrared spectrophotometer, with sodium chloride optics. The spectra of solids were determined as mulls in series 11–14 Halocarbon oil[15] from 1300 to 4000 cm.$^{-1}$ and in Nujol from 650 to 1300 cm.$^{-1}$

1-Methyl-4-piperidone hydrochloride hydrate (II). The material used in this investigation was prepared by the method of McElvain and co-workers.[3]

4-Benzyloxypyridine (XI). A solution of 1 g. of 4-benzyloxypyridine-1-oxide[14] in 15 ml. of cold chloroform was treated with 1.9 ml. of phosphorus trichloride. The solution was heated at 70–80° for 1 hr., cooled, and diluted with 15 ml. of water. The mixture was neutralized with sodium hydroxide, and the layers were separated. The aqueous layer was extracted three times with chloroform, and the combined chloroform layers were dried over anhydrous potassium carbonate. Fractional distillation of the solution gave 0.45 g. (49%) of 4-benzyloxypyridine (XI), b.p. 193–196°/20 mm., m.p. 49–52°; lit.[17] b.p. 155–160°/4 mm., m.p. 55–56°. The methiodide of 4-benzyloxypyridine (XI) was prepared in acetone and melted at 148–151°.

1-Methyl-1,2,3,6-tetrahydro-4-pyridylbenzyl ether (XII). A solution of 5.29 g. of 4-benzyloxypyridine methiodide in 50 ml. of methanol was treated with 1.5 g. of sodium borohydride. The solvent (31 ml.) was removed by distillation, and water was added to the residue. Anhydrous potassium carbonate was added, and the aqueous solution was extracted with four portions of ether. After drying over potassium carbonate, the ether solution was concentrated, and the residue was distilled under reduced pressure to give 2.81 g. (86.4%) of 1-methyl-1,2,3,6-tetrahydro-4-pyridylbenzyl ether (XII), b.p. 170–175/17 mm., n_D^{22} 1.5399.

Anal. Calcd. for $C_{13}H_{17}NO$: C, 76.80; H, 8.43. Found: C, 76.49; H, 8.53.

1-Methyl-4-piperidone (V). A solution of 2.31 g. of XII in 10 ml. of concentrated hydrochloric acid and 4 ml. of water was heated under reflux for 4 hr. On cooling, the solution was extracted with ether to remove the benzyl alcohol, and the remaining acidic solution was neutralized with potassium carbonate and extracted with ether. The ether extract was dried and fractionally distilled to give 0.92 g. (71.5%) of 1-methyl-4-piperidone (V), b.p. 68–71°/17 mm., n_D^{23} 1.4556; lit.[3] b.p. 63–65°/18 mm. n_D^{25} 1.4581.

1-Methyl-4-piperidone hydrochloride hydrate (II). A solution of 1-methyl-4-piperidone in dilute hydrochloric acid was evaporated under reduced pressure. The residue crystallized on washing with acetone to give II, m.p. 88–91° in a capillary. On a hot stage the solid melted at 88–91°, resolidified, and melted at 157–163°.

Anal. Calcd. for $C_6H_{14}ClNO_2$: Cl, 21.15. Found: 21.10, 21.02.

Anhydrous 1-methyl-4-piperidone hydrochloride (I). A sample of II was sublimed under a pressure of 2 mm. at 120°. The sublimate melted at 165–168°, lit.[9] m.p. 164–167°.

Anal. Calcd. for $C_6H_{12}ClNO$: Cl, 23.70. Found: Cl, 23.70, 23.77.

Anhydrous 1-methyl-4-piperidone methobromide (XIII). A solution of 2.0 g. of 1-methyl-4-piperidone (V) in ether was saturated with methyl bromide. The precipitate which formed was removed by filtration to give 1.7 g. of 1-methyl-4-piperidone methobromide (XIII), m.p. 187–190°.

(17) E. Shaw, *J. Am. Chem. Soc.*, 71, 68 (1949).

Anal. Calcd. for $C_7H_{14}BrNO$: Br, 38.41. Found: 38.17, 38.11.

1-Methyl-4-piperidone methobromide hydrate (XIIIa). The methobromide (XIII) was dissolved in water and precipitated by addition of acetone. The resulting solid melted when introduced into a bath at 150°.

Anal. Calcd. for $C_7H_{16}BrNO_2$: Br, 35.34. Found: Br, 35.29, 35.30.

1-Methyl-1,2,5,6-tetrahydro-3-pyridyl methyl ether (VIII). A solution of 32 g. of 3-hydroxypyridine (VII) and 21 g. of sodium methoxide in 150 ml. of methanol was treated with 100 g. of methyl iodide. The mixture was heated under reflux for 7 hr., cooled, and 26 g. of sodium borohydride was added portionwise. The solvent was removed by distillation, and water was added to the residue. Potassium carbonate was added to the aqueous solution, and ether was used for extraction. After drying over potassium carbonate, the ether solution was concentrated, and the residual oil was distilled under reduced pressure to give 12.93 g. (40%) of 1-methyl-1,2,5,6-tetrahydro-3-pyridyl methyl ether (VIII), b.p. 60–63°/11 mm., n_D^{24} 1.4663.

Anal. Calcd. for $C_7H_{13}NO$: C, 66.09; H, 10.30. Found: C, 66.13; H, 10.63.

The *picrate* was prepared in ethanol, m.p. 119–120°. The molecular weight determined by the ultraviolet absorption method[18] was 354; the calculated value is 356.

Anal. Calcd. for $C_{13}H_{16}N_4O_8$: C, 43.82; H, 4.53, Found: C, 44.19; H, 4.48.

1-Methyl-3-piperidone (VI). A solution of 12.9 g. of VIII in 40 ml. of 48% hydrobromic acid was heated under reflux for 6 hr. The solution was neutralized and extracted with ether. The ether solution was concentrated, and the residue was distilled under reduced pressure to give 10.7 g. of 1-methyl-3-piperidone (VI), b.p. 65–70°/15 mm., n_D^{26} 1.4535; lit.[11] b.p. 63–64°/13 mm., n_D^{25} 1.4559. Addition of anhydrous hydrogen chloride to a solution of the 1-methyl-3-piperidone in ether gave 12.00 g. of 1-methyl-3-piperidone hydrochloride hydrate, m.p. 105–108°; lit.[11] m.p. 110–111°.

Anal. Calcd. for $C_6H_{14}ClNO_2$: Cl, 21.15; Found: Cl, 21.19, 21.02.

1-Methyl-3-piperidone hydrobromide (IX). A solution of 10.8 g. of VIII in 33 ml. of hydrobromic acid was heated under reflux for 8 hr. and evaporated to dryness under reduced pressure to give an oily residue which crystallized on treatment with acetone. The solid was isolated by filtration to give 15.9 g. of IX, m.p. 103–106°.

Anal. Calcd. for $C_6H_{12}BrNO$: Br, 41.18. Calcd. for $C_6H_{14}BrNO_2$: Br, 37.68. Found: Br, 38.02, 37.99.

Anhydrous 1-methyl-3-piperidone hydrochloride (III). A sample of the hydrate IV was heated under reduced pressure. The residue, III, melted at 138–141°.

Anal. Calcd. for $C_6H_{12}ClNO$: Cl, 23.70. Found: 23.39.

Anhydrous 1-methyl-3-piperidone methobromide (XIV). A solution of 1-methyl-3-piperidone (VI) and methyl bromide in ether deposited the methobromide (XIV) m.p. 175–179°, on standing.

Anal. Calcd. for $C_7H_{14}BrNO$: Br, 38.41. Found: Br, 37.97, 38.14.

1-methyl-3-piperidone methobromide hydrate (XIVa). A solution of the salt XIV was treated with acetone to precipitate 1-methyl-3-piperidone methobromide hydrate (XIVa) which melted on introduction into a bath at 150°.

Anal. Calcd. for $C_7H_{16}BrNO_2$: Br, 35.34. Found: Br, 35.29.

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(18) K. C. Cunningham, W. Dawson, and F. S. Spring, *J. Chem. Soc.*, 2305 (1951).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, BROOKLYN COLLEGE]

Synthesis of 2,6-Disubstituted Pyrazines and Related Derivatives

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A number of 2,6-disubstituted pyrazines and related derivatives have been prepared. A new procedure for the preparation of 7-methyllumazine is described. 7-Methyllumazine has been cleaved to furnish both 6-methyl-2-pyrazinol and 2-amino-6-pyrazinol was coupled to furnish a new series of azopyrazine dyes. These azopyrazine dyes were reduced in acid solution to furnish 5-amino-6-methyl 2-pyrazinols.

7-Methyllumazine (2,4-dihydroxypyrimido-4,5-6-pyrazine) (I) is readily cleaved by alkali.[1] The products are 2-amino-6-methyl-3-pyrazinoic acid (II) and 2-hydroxy-6-methyl-3-pyrazinoic acid (III). These carboxylic acids are readily decarboxylated to the 2-amino- (IV) and the 2-hydroxypyrazines (XII). The conventional approach to lumazine synthesis involving the condensation of a 4,5-diaminopyrimidine with an α,β-dicarbonyl compound[2,3] gives brown gelatinous products. A fine, yellow, crystalline 7-methyllumazine is obtained here by condensation in acid solution of 5,6-diaminouracil with stabilized methylglyoxal (30% solution).[4] This procedure furnished practically quantitative yields of micro crystalline 7-methyllumazine and also permitted quantitative detection of α-dicarbonyl compounds in quantities as low as 5 γ per ml. equivalent to 2 γ of methyl glyoxal.[5]

Owing to the paucity of 2,6-disubstituted pyrozines, it was of interest to investigate further the preparation of compounds of this class. In approaching this problem, the method of Weijlard and coworkers for the conversion of 7-methyllumazine into 2-amino-6-methylpyrazine (IV) was used. Efforts to prepare 2,6-diaminopyrazine through a

(1) J. Weijlard, M. Tishler, and A. E. Erickson, *J. Am. Chem. Soc.*, **67**, 802 (1945).

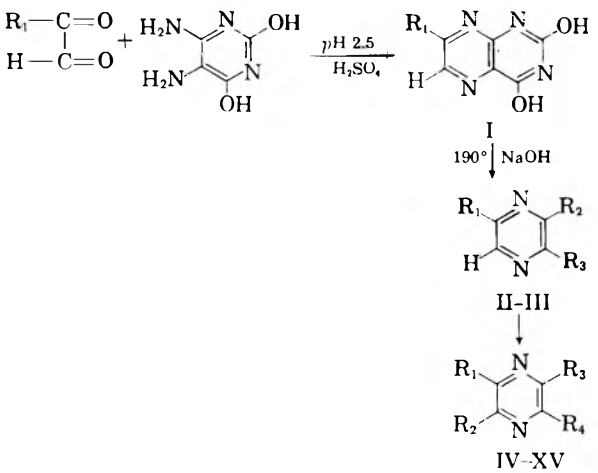
(2) (a) R. Kuhn and W. Cook, *Ber.*, **70**, 761 (1937); (b) J. Ganapti, *J. Indian Chem. Soc.*, **14**, 627 (1937).

(3) E. C. Taylor, R. B. Garland, and C. F. Howell, *J. Am. Chem. Soc.*, **78**, 210 (1956).

(4) Methyl glyoxal 930% stabilized solution was obtained from Carbide and Carbon Chemicals Co. 30 2. 42nd St., New York, N. Y.

(5) L. Sattler and F. W. Zerban, *Ind. Eng. Chem.*, **41**, 1401 (1949).

Curtius-Schmidt reaction on 2-acetamido-6-pyrazinoic acid (IV) proved unsuccessful.[6] No attempt was made here to try a Hofmann reaction on 2-carboxamido-6-acetamidopyrazine (IX) in view of the known resistance of carboxamidopyrazines to such degradations.[7] Although tetralin served as an excellent high boiling decarboxylating medium for converting 2-amino-6-methyl-3-pyrazinoic acid (II) to 2-amino-6-methylpyrazine (IV), it did not serve to decarboxylate 2-amino-3-bromo-6-pyrazinoic acid (XI) to the desired 2-amino-3-bromopyrazine even under more strenuous conditions. If decarboxylation had been successful it would have been possible to prepare it by ammonolysis to the known 2,3-diaminopyrazine for authenticity.[7b]



	R_1	R_2	R_3	R_4
I.	CH_3			
II.	CH_3	NH_2	COOH	H
III.	CH_3	OH	COOH	H
IV.	CH_3	NH_2	H	H
V.	CH_3	NHAc	H	H
VI.	COOH	NHAc	H	H
VII.	COOH	NH_2	H	H
VIII.	$COOCH_3$	NHAc	H	H
IX.	$CONH_2$	NHAc	H	H
X.	COOH	NHAc	Br	H
XI.	COOH	NH_2	Br	H
XII.	CH_3	OH	H	H
XIIIa.	CH_3	ONa	H	p-$NaSO_3SC_6H_5N{=}N-$
XIIIb.	CH_3	ONa	H	p-$NO_2C_6H_4N{=}N-$
XIV.	CH_3	OH	H	NH_2
XV.	CH_3	$=N-NHC_6H_3(NO_2)_2$	H	NH_2

Although Weijlard *et al.*[1] have stated that 7-methyllumazine (I) by alkaline cleavage conditions would furnish 2-amino-6-methyl-3-pyrazinoic acid exclusively by heating at 170° for 20 hr., it was found possible by doubling the heating time and raising the temperature to 190° to also produce 2-hydroxy-6-methyl-3-pyrazinoic acid (III).[8] From it in turn 6-methyl-2-pyrazinol (XII) could be obtained by decarboxylation in either 80% sulfuric acid at 180° or in boiling tetralin solution at 205°. No attempt was made to produce 6-methyl-2-pyrazinol (XII) exclusively under these conditions since a separation of the two products after decarboxylation was successful.

Derivatives of 6-methyl-2-pyrazinol (XII) could not be made by acetylation or benzoylation in pyridine solution due to keto-enolization of the 2-hydroxy group with the adjacent ring nitrogen. This has been noted also by others in the failure of 2-pyrazinol to acetylate.[9]

A new series of azo coupled pyrazine dyes (XIII a,b) was formed by coupling 6-methyl-2-pyrazinol with diazotized aromatic amines. Aqueous solutions of these dyes are yellow to orange in acid solution and orange to red in alkali solution.

Vigorous reduction of one of these pyrazinol dyes (XIIIa) with stannous chloride split the azo linkage to yield the original aromatic amine and the aminated pyrazinol, 5-amino-6-methyl-2-pyrazinol (XIV). The 5-amino-6-methyl-2-pyrazinol was isolated as its sodio salt and derivatized by means of 2,4-dinitrophenylhydrazine as the insoluble orange hydrazone (XV).

Ultraviolet absorption maxima and minima were determined and were considered as representative for 2,6-disubstituted pyrazines. The absorption curves of the 5-azo coupled pyrazolinate dyes were continued into the near infrared region to obtain values for absorption due to the azobenzene linkage as well as that of the substituted pyrazine ring.

EXPERIMENTAL

Preparation of 7-methyllumazine (I). Fifty grams of uracil 5,6-diamino sulfate (5,6-diamino-2,4-dihydroxypyrimidine)[10] were suspended in 1400 ml. of water. Then 130 ml. of methyl glyoxal, 30% aqueous solution, were added and followed by 60 ml. of 10% sulfuric acid to pH 2.5. The mixture was boiled for 2 hr. or until the volume was reduced to 950 ml. The mixture was made alkaline with sodium hydroxide to pH 9.5 and then cooled to 2°. After 2 hr. in the ice bath, the fine crystals were filtered, washed once with ice water, and air dried. The light yellow crystals were very soluble in water. An aqueous solution of 7-methyllumazine

(6) D. M. Sharefkin and P. E. Spoerri, *J. Am. Chem. Soc.*, **73**, 1637 (1951).

(7) (a) P. E. Spoerri and A. E. Erickson, *J. Am. Chem. Soc.*, **60**, 400 (1938); (b) R. C. Ellingson and R. L. Henry, *J. Am. Chem. Soc.*, **71**, 2798 (1949).

(8) R. G. Jones, *J. Am. Chem. Soc.*, **71**, 78 (1949).

(9) I. Krems and P. E. Spoerri, *Chem. Revs.*, **40**, 2, April, 1947.

(10) M. T. Bogert and D. Davidson, *J. Am. Chem. Soc.*, **55**, 1668 (1933).

was strongly fluorescent in sunlight. The average yield was 38 g. or 98%.

Since the members of the lumazines cannot be distinguished because of a lack of melting points within the series, ultraviolet absorption spectrograms were made in the range of 220 mμ to 400 mμ for both acid and alkaline solutions of 7-methyllumazine.

Preparation of 2-amino-6-methylpyrazine (IV). 7-Methyllumazine was cleaved in strong alkaline solution at 170° for 20 hr. to furnish 2-amino-6-methyl-3-pyrazinoic acid.[1] Fifteen g. of the crude acid (II) were suspended in 250 ml. of dry tetralin and refluxed at 205° for 30 min. during which time the solid dissolved. The solution was cooled and extracted with small portions of 10% hydrochloric acid until the acid extract was no longer yellow colored. The combined acid extracts were washed with petroleum ether to remove traces of tetralin and then made alkaline with 20% sodium hydroxide. Several extractions with ether were necessary to remove the amine. The combined ether extracts were dried, reduced in volume to produce 8 g. of yellow crystalline solid, m.p. 124–125°, or 78%.

Preparation of 2-acetamido-6-methylpyrazine (V). 2-Amino-6-methylpyrazine (IV) (10.9 g.) was added to a solution of 14 ml. of acetic anhydride in 60 ml. of glacial acetic acid. The mixture was stirred on the steam bath for 3 hr. When cooled, ether was added to precipitate the acetylated compound. After filtration, the filtrate was treated with a small volume of acetyl chloride to obtain a second crop of the white solid. The total weight after crystallization from absolute methanol was 11 g. or 64%, m.p. 168–169°.

Anal. Calcd. for $C_7H_9ON_3$: N, 27.871. Found: N, 27.94.

Preparation of 2-acetamido-6-pyrazinoic acid (VI). Eight grams of 2-acetamido-6-methylpyrazine (V) were dissolved in a solution of 12 g. of magnesium sulfate in 600 ml. of warm water. The solution was heated to 75° and 16.5 g. of potassium permanganate was added in small portions. The temperature was kept at 85° until discharge of the color. The mixture was filtered hot and the residue washed twice with boiling water. The combined filtrates were reduced in volume to 200 ml. and *p*H adjusted to 2.5 with dilute sulfuric acid. After cooling in the ice bath 5.4 g. of white solid was obtained. The solid was recrystallized from boiling water also adjusted to *p*H 2.5 with dilute sulfuric acid, to yield 5 g. of the 2-acetamido-6-pyrazinoic acid, m.p. 173°.

Anal. Calcd. for $C_7H_7O_3N_3$; C, 46.42; N, 23.22. Found: C, 46; 51; N, 27.04, 27.71.

The discrepancy in the nitrogen analysis was believed due to irregularity in the behavior of the substance during combustion. Two different samples prepared at different times gave the same analytical anomalies. Its precursor, 2-acetamido-6-methyl pyrazine (V) and its derivatives, the 6-methyl ester (VIII) and the 3-bromo pyrazines (X) and (XI) gave analytical results which were in agreement with the calculated values.

Preparation of 2-amino-6-pyrazinoic acid (VII). One-half gram of 2-acetamido-6-pyrazinoic acid (VI) were suspended in 10 ml. of 3*N* hydrochloric acid and boiled for 20 min. The solution was decolorized with Norit and then made *p*H 6.5 by addition of solid sodium bicarbonate. The solution was extracted with 100 ml. of ether in 5 portions. The combined extracts were dried and concentrated to produce 0.25 g. of bright yellow crystals of the amino acid, m.p. 120–121°. Acetylation of the yellow crystals produced a white solid which gave a mixed melt at 173°, identical with that of the 2-acetamido-6-pyrazinoic acid (VI).

Attempted Curtius-Schmidt reaction on 2-acetamido-6-pyrazinoic (VI). In an attempt to prepare 2,6-diaminopyrazine by a modified Curtius reaction, 0.26 g. of sodium azide was added over a 3-hr. period to a solution of 0.197 g. of 2-acetamido-6-pyrazinoic acid in 4 ml. of concentrated sulfuric acid containing 1.5 g. of trichloroacetic acid. The reaction was maintained at 60° with continuous stirring, cooled, and poured onto 10 g. of crushed ice. After making alkaline with sodium hydroxide, the mixture was extracted with three 25-ml. portions of ether. The combined ether extracts were dried over anhydrous sodium sulfate and the ether solution concentrated. The yellow solid which formed on cooling of the other concentrate melted at 120° and was the 2-amino-6-pyrazinoic acid as shown by its indicator test as a B_wP_w, and by the formation of an acetylated derivative, the 2-acetamido-6-pyrazinoic acid (VI), which melted at 173°.

Preparation of 2-acetamido-6-carbomethoxy pyrazine (VIII). To 3 g. of 2-acetamido-6-pyrazinoic acid (VI) suspended in 30 ml. of absolute methanol there were added 1 g. of anhydrous sodium sulfate and 0.2 ml. of concentrated sulfuric acid. After 3 hr. of refluxing, Norit was added and the mixture filtered hot. The solution was reduced in volume to 15 ml. and the acidity adjusted to *p*H 2.5 with a few drops of 10% sodium hydroxide. After cooling, 2.4 g. of fine crystals were collected and dried, m.p. 159°.

Anal. Calcd. for $C_8H_9O_3N_3$: N, 21.50. Found: N, 21.56.

Preparation of 2-acetamido-6-carboxamido pyrazine (IX). A hot solution of 0.3 g. of 6-carbomethoxy pyrazine (VIII) in 10 ml. of absolute methanol was poured into 15 ml. of 28% ammonia and heated until the total volume was reduced to 10 ml. The solution was then cooled to obtain a white solid which after washing with methanol and drying did not melt over 300°.

Anal. Calcd. for $C_7H_8O_2N_4$: N, 31.00. Found: N, 31.06.

Preparation of 2-acetamido-3-bromo-6-pyrazinoic acid (X). To a solution of 1.6 g. of 2-acetamido-6-pyrazinoic acid (VI) in 20 ml. of warm acetic acid, 0.6 ml. of bromine were added dropwise over a 30-min. period. The clear red solution was poured over 20 g. of crushed ice to produce a heavy precipitate. A sample recrystallized from 10 ml. of absolute methanol yielded white needles, m.p. 173°.

Anal. Calcd.: for $C_7H_6O_3Br$: N, 16.16. Found: N, 15.84.

Preparation of 2-amino-3-bromo-6-pyrazinoic acid (XI). To a solution of 3 g. of 2-acetamido-3-bromo-6-pyrazinoic acid (X) in 600 ml. of hot water there was added 10 ml. of concentrated hydrochloric acid. The solution was boiled for 15 min., filtered, and then evaporated slowly to 30 ml. The solid obtained on cooling was filtered and dried to yield, 2.1 g. of a white solid m.p. 152–153°. After recrystallization from ethanol, the solid melted 153–154°.

Anal. Calcd.: for $C_5H_4O_2N_3Br$: N, 19.20. Found: N, 19.05.

Attempted decarboxylation of 2-amino-3-bromo-6-pyrazinoic acid (XI). One gram of 2-amino-3-bromo-6-pyrazinoic acid (XI) was added to 10 ml. of dry tetralin and the mixture refluxed at 205° for 30 min. Norit was added to the hot solution, and filtered. Crystals formed on chilling the filtrate in the ice bath. The filtered crystals were washed with petroleum ether and dried, m.p. 153–154°. The material recovered was the unchanged 2-amino-3-bromo-6-pyrazinoic acid.

Preparation of 6-methyl-2-pyrazinol (XII). A suspension of 37.4 g. of 7-methyllumazine (I) in a solution of 37 g. of sodium hydroxide in 190 ml. of water was prepared. This mixture was sealed into a steel bomb tube and heated at 180–190° for 50 hr. After cooling, the solution was filtered to remove a slight sediment. There was a very strong odor of ammonia from the tube. The solution was reduced in volume of 100 ml. and then made *p*H 2.5 with hydrochloric acid to precipitate a mixture of 2-amino-6-methyl-3-pyrazinoic acid (II) and 2-hydroxy-6-methyl-3-pyrazinoic acid.

There was no attempt made to separate the mixture of the crude acids at this point. Separation was considered more effective after decarboxylation of the two acids by heating 12.5-g. portion of the crude acids in 40 ml. of 80% sulfuric acid at 180° for 10 min. The acid solution was poured onto 250 g. of crushed ice and then made alkaline with 50% sodium hydroxide. Ether extraction removed a small amount (3.5 g.) of 2-amino-6-methylpyrazine (IV).

The solution was adjusted to *p*H 6.8 and then extracted with 2.4 l. of ethyl acetate in 6 portions. The combined extracts were dried over anhydrous sodium sulfate and reduced in volume to 200 ml. Cooling produced shining platelets

of the yellow 6-methyl-2-pyrazinol (XII). Recrystallization from anhyd. ethyl acetate furnished 4.4 g. of the yellow platelets, m.p. 240°.

Anal. Calcd. for $C_5H_6N_2O$: N, 25.44. Found: N, 25.80.

Preparation of azo coupled compounds of 6-methyl-2-pyrazinol (XIII). *A. Disodio salt of 6-methyl-5-azobenzenesulfonate-2-pyrazinolate* (XIIIA). Two ml. of 6*N* sodium hydroxide solution were added to a suspension of 1.8 g. (0.01*M*) of sulfanilic acid in 15 ml. of water. Solution was obtained on warming. Then 0.7 g. of sodium nitrite was added and the solution cooled to room temperature. Then this solution was poured into a mixture of 1.3 ml. of concentrated sulfuric acid, 26 g. of ice, and 20 ml. of water, and allowed to stand for 30 min. After which, a solution of 1.6 g. (0.01*M*) of 6-methyl-2-pyrazinol (XII) in 20 ml. of water and 10 drops of 20% sodium hydroxide was added to the diazotized sulfanilic acid. The reaction mixture was stirred for 5 min., after which 10% sodium hydroxide was added to make *p*H 6. After an orange precipitate had formed, 30 ml. of saturated sodium chloride solution was added and the mixture cooled for 10 min. Filtration produced 2.1 g. of orange yellow solid. The solid was recrystallized from 125 ml. of distilled water at 95°, to give 2 g. of bright yellow solid. Aqueous solutions are colored red in acid and orange red in alkaline solution. The solid did not melt up to 300°.

Anal. Calcd. for $C_{11}H_8O_4N_6SNa_2$: N, 16.38. Found: N, 15.01, 15.31.

B. Sodio salt of 6-methyl-5-p-nitrobenzeneazo-2-pyrazinol (XIIIB). A suspension of 1.4 g. of *p*-nitroaniline in 5 ml. of concentrated hydrochloric acid was prepared. Solution was obtained by heating to 80°. On cooling to room temperature, 10 g. of ice and a solution of 0.8 g. of sodium nitrite were added. To the diazotized *p*-nitroaniline, a solution of 1.3 g. of 6-methyl-2-pyrazinol (XII) in 20 ml. of water and 10 drops of 20% sodium hydroxide was added with stirring. The reaction mixture stood for 10 min. and then a solution of 0.6 g. of anhydrous sodium acetate in 2 ml. of water was added. After 15 min., the solid was filtered, washed with ice water, and dried. The dried solid was digested with a small amount of benzene to remove unchanged *p*-nitroaniline. For analysis, a sample was recrystallized from 95% ethanol; no m.p. up to 300°.

Anal. Calcd. for $C_{11}H_8O_3N_6Na$: N, 24.90. Found: N, 24.73.

Preparation of 5-amino-6-methyl-2-pyrazinol (XIV). To a solution of the disodio salt of 5-azobenzenesulfonate 6-methyl-2-pyrazinolate (XIIIA) in 60 ml. of water at 85°, there was added a solution of 8 g. stannous chloride in 20 ml. of concentrated hydrochloric acid. The mixture was warmed until the dye color was lost. Then the mixture was cooled in an ice salt bath until there was no further precipitation of sulfanilic acid. After filtration of the sulfanilic acid, sodium hydroxide solution (20%) was added to precipitate stannic oxide. The filtrate was evaporated to dryness on the steam bath and then extracted with absolute methanol, 300 ml. in 3 portions. The alcoholic extracts were combined and reduced in volume to 25 ml. Cooling to 0°, produced a light tan solid. The solid was recrystallized from absolute methanol to yield 0.5 g. of pale yellow solid (62%), which did not melt up to 300°.

Anal. Calcd. for $C_5H_6ON_3Na$: C, 40.81; H, 4.11. Found: C, 41.11; H, 4.22.

Preparation of 5-amino-6-methyl-2-(2,4-dinitrophenylhydrazone) pyrazinone (XV). A saturated solution of 2,4-dinitrophenylhydrazine in 2*M* hydrochloric acid–methanol was added dropwise to a solution of 1.5 g. of 5-amino-6-methyl-2-pyrazinol (XIV) until precipitation was complete. The yellow orange micro crystals were recrystallized from hot methanol-water to yield 2 g. of product. The hydrazone gave a dark red color on addition of 2*M* alcoholic potassium hydroxide solution indicating the aromatic nature of the pyrazine ring. The hydrazone was dried, m.p. 125°.

Anal. Calcd. for $C_{11}H_{11}O_4N_7$: C, 45.32; H, 3,63. Found: C, 45.56; H, 3.44.

ULTRAVIOLET ABSORPTION MAXIMA AND MINIMA

	Max., Mμ	Min., Mμ
7-Methyllumazine (I) acid solution	325	270
7-Methyllumazine (I) sodio salt	275,342	255,292
2-Acetamido-5-methylpyrazine (V)	300	260,400
6-Methyl-2-pyrazinol (XII)	250	324,410
2-Amino-3-bromo 6-pyrazinoic acid (XI)	243,340	285,400
5-Amino-6-methyl 2-pyrazinol (XIV)	253	236,360
5-Benezenesulfonate-6-methyl-2-pyrazinolate disodio salt (XIIA)	362	260
5-Benzenesulfonate-6-methyl-2-pyrazinolate disodio salt (XIIIA) at *p*H 11	410	700

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Chromatographic Separation of Nitration Products of Ester-Blocked 2-Hydroxybiphenyl[1]

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Nitration of the benzenesulfonate of *o*-hydroxybiphenyl yields 2'- and 4'-mononitro derivatives. Hydrolysis of these esters and nitration of the resulting mononitrohydroxybiphenyls lead to mononitro and dinitro substitution in the phenolic ring. A satisfactory separation of the nitrohydroxybiphenyls has been accomplished by chromatographic methods.

The direction of entering nitro groups to positions in the nonphenolic ring of the hydroxybiphenyls by the "ester block" method has been reported by Bell and Kenyon,[2] Hazlet *et al.*[3,4] and others. In addition to the 4'-mononitro derivative,

(1) Abstracted from a thesis submitted by D. Paul Denny to the faculty of the University of Oklahoma in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June 1957.

(2) F. Bell and J. Kenyon, *J. Chem. Soc.*, 129, 3044 (1926).

(3) S. E. Hazlet, G. Alliger, and R. Tiede, *J. Am. Chem. Soc.*, 61, 1447 (1939).

(4) S. E. Hazlet, L. C. Hensley, and H. Hass, *J. Am. Chem. Soc.*, 64, 2449 (1942).

Campbell and Morrill,[5] working with 4-biphenylyl benzoate, reported the 2′-derivative.

This directional effect has been explained on the basis of steric hindrance. While there is some agreement that the extent of this type of substitution increases with increase in size of the blocking group, Campbell and Morrill's[5] experiments indicate that the steric factor may be of only moderate influence. Evidence for a change in the directional influence of the phenolic hydroxy group comes from work with ester-blocked 3- and 4-hydroxybiphenyl.[3,6] In 3-hydroxybiphenyl, a blocking group might affect both ortho positions and substitution at the para position might be hindered by the phenyl group. In 4-hydroxybiphenyl, substitution at the ortho positions might be hindered by a blocking group and since the para position is substituted by the phenyl group no test of spatial crowding *vs.* electronic effects beyond the ortho position can be obtained. In 2-hydroxybiphenyl the para position is unhindered by spatial crowding. Nitration of the benzenesulfonate of 2-hydroxybiphenyl should provide useful information since dominant entry of the nitro group into the unsubstituted ring rather than the position para to the phenolic hydroxyl group would indicate the significance of electronic rather than steric effects.

In the present research nitration occurred almost exclusively in the non-phenolic ring of ester-blocked 2-hydroxybiphenyl. The compounds obtained were the benzene sulfonates of 4′-nitro-2-hydroxybiphenyl and to a lesser extent 2′-nitro-2-hydroxybiphenyl. When the reaction mixture of these esters was hydrolyzed and placed on the chromatographic column 4′-nitro-2-hydroxybiphenyl was accompanied by trace amounts of a second phenol whose melting point was the same as that of 5-nitro-2-hydroxybiphenyl. The blocking group causes deactivation of all positions on the phenolic ring even though one of these positions is far removed from the blocked phenolic group.

Failure to isolate a phenolic ring mononitration product in significant amounts and production of the 4′ and 2′-mononitro derivatives lends strength to the assumption that electronic effects are of major significance in the reaction. While steric hindrance may be of importance to ortho positions the degree of activation or deactivation of each ring by its substituents determines nitration products of 2-hydroxybiphenyl. Since only the 2′- and 4′-mononitro derivatives were found, it is apparent that the ester-blocked phenolic ring is ortho, para directing.

The use of chromatographic techniques provided the tool for the separation of the nitrohydroxybiphenyls. Differences in solubilities and acidities cause the nitro derivatives of the hydroxybiphenyls to be spaced on an adsorbent column as colored bands. This technique was not used by early workers in the field.

General nitration procedure involved dropwise addition of fuming nitric acid to the ester contained in an equal volume of reaction solvent. The reaction was allowed to proceed during a period of heating and finally stopped with ice water. The benzene sulfonate of 4′-nitro-2 hydroxybiphenyl was crystallized from an ethanol solution of the gummy nitration products. After removal of the ethanol, the residue was a light-yellow, oily sirup. Hydrolysis of the 4′-mononitro ester derivative with alcoholic KOH produced 4′-nitro-2-hydroxybiphenyl in 57 to 81% yields. This was the only nitro derivative isolated directly from the crude nitrated ester products. In later runs the entire crude product was hydrolyzed and the hydrolyzate chromatographed. Since 2′-nitro-2-hydroxybiphenyl was recovered from the column it was evident that the ester of 2′-nitro-2-hydroxybiphenyl was contained in the residual oil mentioned above.

Satisfactory nitration of the ester when nitromethane was used as solvent was governed by the amount of nitric acid used. Below an acid-ester mole ratio of 3:1, only unchanged starting materials were recovered. A ratio of 6:1 caused oxidation of the ring system and reduced yields. Best results were obtained using a 4:1 ratio.

When glacial acetic acid was used as the solvent, there was little oxidation even with an acid-ester mole ratio of 12:1. Although there was little nitration with a 6:1 acid-ester ratio, satisfactory yields were obtained with higher ratios. Glacial acetic acid was the solvent of choice.

TABLE I

RESULTS OF NITRATION OF ESTER-BLOCKED *o*-HYDROXYBIPHENYL UNDER VARYING CONDITIONS OF ACID STRENGTH, SOLVENT AND REACTION TEMPERATURES[a]

Acid-Ester Mole Ratio	Solvent	Total Solvent, ml.	Reaction Temp.	Percentage Yield of Mononitro Ester
3:1	Nm[b]	4	Room	14.41
4:1				41.92
6:1				28.21
6:1	G.a.a.			26.02
8:1				35.89
8:1			Reflux	Oxidation
8:1		6	Room	11.40
9:1		4	90°[c]	53.10
9:1			80°[c]	26.20
9:1		3	Room	47.58
10:1		4		52.05
10:1		3		49.22
10:1		2		33.24
12:1		4		49.04

[a] All reaction mixtures refluxed on water bath for 1.5 hr. after addition of nitrating mixture unless otherwise indicated. [b] Abbreviations: Nm—Nitromethane; G.a.a.—Glacial acetic acid. Total solvent indicates ml. per g. of ester. [c] Nitrated at temperature shown and held at this temperature for 1.25 hr. without any reflux period.

(5) I. G. M. Campbell and D. J. Morrill, *Chem. and Ind. (London)*, 1229 (1953).

(6) J. C. Colbert and C. F. Robinson, to be reported.

Reactions carried out at either room temperature or at temperature ranges between 80° and 90° gave about the same results. The temperature at which the nitrating agent is added does not appear to be a factor as long as a period of heating on the water bath follows the addition.

The volume of the solvent plays a role. Higher yields resulted when the total acetic acid was 3–4 ml. per gram of ester.

Since nitration of the hydroxybiphenyls has been shown to produce a variety of mono-, di-, and trinitro derivatives,[7] a column adsorbent was required which would permit separation of the principal products. An adsorbent of strong retaining power was necessary to slow the speed of mononitration products (low acidity and high solubility) down the column to the point where retention was of sufficient duration for bands to be separated. On the other hand the adsorbent had to be of sufficiently low retaining power so that the di- and trinitro derivatives (low solubility and high acidity) would move far enough down the column for individual bands to form and thus facilitate separation by extrusion. Magnesol[8] was found to hold highly soluble–low acidity type nitrophenols firmly enough to slow down the speed of elution and at the same time permit band formation from low solubility–high acidity type nitrophenols. Benzene solutions of the hydrolyzed, nitrated products from one-gram samples of the sulfonate ester were placed on the column and eluted with benzene under a working pressure of five pounds gage. Both the 4′- and 2′-nitro derivatives were recovered from the column by elution. Typical yields of the 4′-nitro and 2′-nitro derivatives were 30% and 20%, respectively.

The two principal products were separable in one run using a Magnesol column 4.5 cm. × 50 cm. when less than 2.5-gram samples of the sulfonate ester of 2-hydroxybiphenyl were nitrated and the column was packed with a benzene slurry under 10 pounds pressure followed by elution with benzene under five pounds pressure.

4′-Mononitro and 2′-mononitro-2-hydroxybiphenyl were further nitrated under milder reaction conditions[7] since the phenolic ring was now unencumbered with a blocking group. The 3,5,4′-trinitro derivative[9] was easily prepared and isolated. With a 4:1 mole ratio, fuming or concentrated nitric acid, to 4′-mononitro-2-hydroxybiphenyl using glacial acetic acid as the solvent, the trinitro derivative dropped out at room temperature. When 4-nitro-2-hydroxybiphenyl was further nitrated in glacial acetic acid with fuming nitric acid, (1:1 mole ratio, acid to sample), the reaction proceeded smoothly at room temperature. Reaction products formed two principal and two insignificant bands on the column. The two principal bands were more highly colored (orange to red) than those developed from the initial ester nitration. Nitrogen analysis of these two bands indicated dinitro compounds. The material from each band was further nitrated to the same 3,5,4′-trinitro derivative. It was assumed that one of these two products was the 3,4′- and the other the 5,4′-dinitro derivative. Since 3-nitro-2-hydroxybiphenyl melts at 63–64° and 5-nitro-2-hydroxybiphenyl at 124–126°, it is probable that further work will show that of the two dinitro phenols obtained by further nitration of 4′nitro-2-hydroxybiphenyl, the higher melting (226–228°) is 5,4′-dinitro-2-hydroxybiphenyl and the lower melting (194–195°) is 3,4′-dinitro-2-hydroxybiphenyl.

Samples of the 2′- derivative were nitrated using a 4:1 mole ratio, acid to sample, in glacial acetic acid, and a 1:1 mole ratio in nitromethane. Evidently the 2′- derivative is more difficult to nitrate than the 4′-nitro derivative since a light orange, fast-moving principal band associated with the 1:1 mole ratio in nitromethane yielded starting material. Only one product was isolated from the column other than this starting material. Considering the low acid-sample mole ratio and results obtained with the 4′-derivative, this product was assumed to be either the 3,2′-dinitro or the 5,2′-dinitro-2-hydroxybiphenyl.

In the reaction employing a 4:1 mole ratio, acid to sample, and glacial acetic acid as the solvent, only one principal band was observed. Since analysis indicated three nitro groups, the material may have been 3,5,2′-trinitro-2-hydroxybiphenyl.

Separation of the nitro derivatives of the hydroxybiphenyls by chromatographic methods proved satisfactory. Not only was the technique effective for fast-moving mononitro products but was applicable to the dinitro derivatives by extrusion and extraction methods. Proofs of structure for the three dinitrophenols obtained will be offered when further work has been carried out.

EXPERIMENTAL

The benzenesulfonate of 2-hydroxybiphenyl. Twenty-five grams (0.147 mole) of 2-hydroxybiphenyl was dissolved in 75 ml. of pyridine and 20 ml. of benzenesulfonyl chloride (6.6% excess) was added to the pyridine solution with the temperature held below 10°. After standing for 1 hr., the reaction mixture was heated on the water bath for an additional hour. Overnight, long needle crystals of the benzenesulfonate separated and were collected on the filter. The mother liquor was poured over 200 g. of crushed ice and a further yield of the ester removed by filtration. Recrystallization from 95% ethanol gave 40.5 g., 88.9% m.p. 66–67°.

Nitration of the benzenesulfonate of 2-hydroxybiphenyl. One gram, (0.003 mole) of the ester was dissolved in 2 ml. of warm glacial acetic acid. A nitration mixture made up of 1.25 ml. of fuming nitric acid (0.029 mole) and an equal volume of

(7) J. C. Colbert, D. W. Fox, and C. Matuszak, *J. Am. Chem. Soc.*, **77**, 2447 (1955).

(8) Magnesol, a synthetic magnesium silicate, was obtained from Westvaco Chlor-Alkali Division of the Food Machinery and Chemical Corporation.

(9) H. B. Hill and W. J. Hale, *Am. Chem. J.*, **33**, 1–21 (1905).

glacial acetic acid was added dropwise with shaking to the solution at room temperature. The reaction mixture was heated on the water bath for 1.5 hr. during which the color became a reddish brown. The mixture was poured into 50 ml. of ice water after standing for 20 hr. There was an immediate precipitation of a gummy, white, mass which took on a pinkish cast upon standing. This crude product was washed free of acid on the filter with distilled water and dissolved in 15 ml. of hot 95% ethanol. Within 1 to 2 hr., following addition of water, whitish yellow crystals were precipitated. These crystals were washed with cold dilute ethanol and dried in the desiccator. The yield was 0.544 g., 47.6% on a mononitro basis, m.p. 136–137°.

Two samples of the sulfonate ester (1 g. each) were dissolved in separate 3-ml. portions of glacial acetic acid and each sample nitrated with 1.25 ml. (0.029 mole) of fuming nitric acid mixed with 1 ml. of glacial acetic acid. One sample was heated at 90° during the period of dropwise nitration and held at this temperature for 75 min. The second sample was similarly treated at 80°. Employing the general procedure outlined above, the first sample produced 0.608 g., 53.7% of the nitrated ester m.p. 136–137°. The yield from the second sample was 0.30 g. (26.2%).

Hydrolysis of the nitrated ester of m.p. 136–137°. One gram of the nitrated ester was dissolved in 15 ml. of 95% ethanol and 1.0 g. of KOH in 3 ml. of distilled water was added to the alcoholic solution. There was immediate reaction and appearance of a dark red color characteristic of alkali salts of nitrated phenols. The hydrolysis mixture was refluxed for 3 hr. and was then poured into 50 ml. of distilled water. The wine red solution was acidified with hydrochloric acid and extracted with 15-ml. portions of chloroform until only a faint yellow color was shown by a chloroform portion. The chloroform solution was extracted with 15-ml. portions of 5% KOH solution until no further color was shown by the alkali extract. The alkali solution was acidified with hydrochloric acid and the slightly acidic solution exhaustively extracted with 15-ml. portions of benzene. The benzene extract was reduced in volume to 25 ml. and washed twice with 5-ml. portions of cold water to which 2 drops of dilute hydrochloric acid had been added. Two washings with cold water followed. The benzene solution was dried over anhydrous sodium sulfate, 10 ml. of *n*-heptane were added after which the solution was evaporated to dryness on the hot plate. The weight of nitrated phenols was 0.494 g., 81.6% yield on a mononitro basis.

Hydrolysis of the nitrated ester and recovery on the column. The crude, gummy nitration products (4.772 g.) from two 5-g. samples of the sulfonate ester were dissolved in 75 ml. of 95% ethanol and hydrolyzed, using the procedure described earlier. The final benzene extract was dried over anhydrous sodium sulfate, made up to 50 ml., the solution divided, and the 2 equal portions placed on like columns of Magnesol. The chromatograph was then developed with benzene. The materials from bands 3 and 4 (the only significant bands) were crystallized from their concentrated benzene solutions with *n*-heptane. Total yield from the 4.772 g. of nitrated sulfonate esters was 1.8516 g. of nitrated phenols. This is a 64.07% yield on a mononitro basis.

4′-Nitro-2-hydroxybiphenyl. Two and one half grams (0.008 mole) of the sulfonate ester dissolved in 7.5 ml. of glacial acetic acid was nitrated at room temperature with a nitrating mixture composed of 3.4 ml. of fuming nitric acid (sp. gr. 1.49–1.5) (0.078 mole) and an equal volume of glacial acetic acid. The gummy nitration products were hydrolyzed and, following the usual procedure, the nitrohydroxybiphenyls were dissolved in 25 ml. of benzene and placed on a Magnesol column. Yields of the first and second colored bands, which moved rapidly down the column, were insignificant. The third and fourth colored bands contained the principal products—the 4′- and 2′-mononitro derivatives.

The material from band number three, which was of a pronounced yellow color, was crystallized from benzene-*n*-heptane as a mixture of yellow prisms and pale, yellow needle clusters. The 0.52 g. obtained represented a 30% yield on a mononitro basis. Both crystal forms melted at 122–123°. A mixed melting point of the 2 forms showed no depression. When both crystal forms were heated to 115° a slight amount of material sublimed to form long, pointed needles melting at 125–126°. This is the melting point of 2-hydroxy-5-nitrobiphenyl.

Anal. Calcd. for $C_{12}H_9O_3N$: N, 6.51. Found: N, 6.36.

Oxidation of 4′-nitro-2-hydroxybiphenyl. A solution of chromic acid (2.1 g., 0.02 mole) in 10 ml. of 65% acetic acid was added dropwise with stirring to 0.27 g. of the yellow prisms (described in the preceding section) dissolved in 4 ml. of glacial acetic acid. When addition was completed, the mixture was heated at a gentle reflux for 90 min. and a 40% formaldehyde solution added dropwise to the reaction mixture until reaction ceased. A further 0.5 ml. of formaldehyde was added to ensure reduction of the excess chromic acid. The mixture was cooled to room temperature and an equal volume of concentrated hydrochloric acid added. The mixture was extracted with four 10-ml. portions of ether and the ether extract washed twice with 10 ml. of ice water. Evaporation of the ether gave 0.11 g. of a product which melted at 236°. This melting point is 4 degrees lower than that recorded for *p*-nitrobenzoic acid.

2′-Nitro-2-hydroxybiphenyl. The material in the fourth band, which followed the third colored band just described, required roughly twice the volume of eluent used for the third band. Recrystallization from benzene-*n*-heptane as well as from chloroform-*n*-heptane, gave moderately large, dark yellow prisms m.p. 139–141°. Recrystallization from boiling water, in which solubility was slight, gave crystals lighter in color, m.p. 142–144°. The dark yellow crystals sublimed at 120° to small, well formed, light yellow prisms. The 0.36 g. recovered represents a 20.9% yield based on *o*-hydroxybiphenyl. Chromic acid oxidation produced *o*-nitrobenzoic acid, m.p. 147–148°.

Anal. Calcd. for $C_{12}H_9O_3N$: N, 6.51. Found: N, 6.68.

3,5,4′-Trinitro-2-hydroxybiphenyl. One and eight tenths ml. (0.042 mole) of fuming nitric acid in 2 ml. of glacial acetic acid were added to a sample of 4′-nitro-2-hydroxybiphenyl (2.15 g., 0.01 mole) dissolved in 15 ml. of glacial acetic acid. Precipitation was observed during addition of the nitrating mixture. The temperature was held at 25° by cooling with tap water. The reaction mixture stood for 2 hr. after addition of the nitrating agent. The precipitate was washed with a 5% solution of sodium bicarbonate followed by water. The crystal mass was dissolved in a mixture composed of 15 ml. of benzene and 10 ml. of *n*-heptane. The solvent was evaporated to a volume of 3 ml. on the hot plate. This treatment was repeated and the crystal mass dissolved in 15 ml. of benzene followed by drying over anhydrous sodium sulfate. Crystallization was obtained by addition of 10 ml. of *n*-heptane. The crystals were thin, brownish yellow needles, yield 2.285 g., 71.9%, m.p. 162–163°. Crystals were also obtained from hot, dilute alcohol. Chromic acid oxidation produced *p*-nitrobenzoic acid.

Anal. Calcd. for $C_{12}H_7O_7N_3$: N, 13.76. Found: N, 13.76.

Nitration of 4′-nitro-2-hydroxybiphenyl to 3,4′- and 5,4′-dinitro-2-hydroxybiphenyl. A (0.5 g., 0.0023 mole) sample of 4′-nitro-2-hydroxybiphenyl was dissolved in 7 ml. of glacial acetic acid and nitrated at room temperature using 1 ml. of a nitration mixture composed of 1 ml. of fuming nitric acid (0.023 mole) and 9 ml. of glacial acetic acid. The dark-colored reaction mixture was set aside for 2 hr. and poured into 50 ml. of ice water. The yellow precipitate was washed on the filter with cold dilute acetic acid and with water. The precipitate was dissolved in 15 ml. of *n*-heptane and the solution evaporated to near-dryness on the hot plate. The precipitate was again dissolved in benzene and the treatment with *n*-heptane repeated. The crystals were dissolved in 25 ml. of benzene, the solution was dried over anhydrous sodium sulfate and placed on the column. Four bands appeared, however, material was recovered from only

the first two. The first band was treated by elution and the second by extrusion and extraction with ethanol. The material from the first band crystallized readily from benzene, *n*-heptane as yellow needles with a slight greenish cast, m.p. 194–195°. The yield was 0.19 g., 31.59% on a dinitro basis.

Anal. Calcd. for $C_{12}H_8O_5N_2$: N, 10.77. Found: N, 10.73.

After extrusion and extraction with 95% ethanol, the material from the second band was crystallized from chloroform–*n*-heptane as shiny plates of pale yellow color, m.p. 226–228°. The yield was 0.073 g., 12% on a dinitro basis. When the compounds from the first and second bands were oxidized using chromic acid, and the products separately mixed with *p*-nitrobenzoic acid and heated, no lowering of the m.p. was observed. This shows that the second nitro group enters the phenolic ring.

Anal. Calcd. for $C_{12}H_8O_5N_2$: N, 10.77. Found: N, 10.56.

Further nitration of 3,4'- and 5,4'-dinitro-2-hydroxybiphenyl to 3,5,4'-tri-nitro-2-hydroxybiphenyl. A sample (0.208 g.) of the compound from the first band was dissolved in 10 ml. of glacial acetic acid and nitrated at room temperature with 1.0 ml. (0.0023 mole) nitric acid. A stock of this nitrating mixture was made up by mixing 1.3 ml. of fuming nitric acid and 8.7 ml. of glacial acetic acid. The mixture was set aside for 2 hr. and poured into 25 ml. of ice water. The yellow precipitate was collected on the filter, washed free of acid with water, and taken up in benzene. The benzene solution was twice taken to dryness with added *n*-heptane and the residue redissolved in 15 ml. of benzene. Addition of an equal volume of *n*-heptane caused a precipitate of brown-yellow needles m.p. 162–163° following recrystallization. A mixed melting point with 3,5,4'-trinitro-2-hydroxybiphenyl, previously prepared, showed no depression. A sample of the compound from the second band (0.186 g.) was dissolved in 10 ml. of glacial acetic acid and nitrated at room temperature with 1 ml. of the nitrating mixture previously described. The reaction mixture was refluxed on the water bath for 30 min. The product was worked up in the same manner as that described for the material from band 1. The purified product melted 161–163°. The melting point was not lowered by admixture with previously prepared 3,5,4'-trinitro-2-hydroxybiphenyl.

Further nitration of 2'-nitro-2-hydroxybiphenyl. A sample of 2'-nitro-2-hydroxybiphenyl (0.25 g., 0.0012 mole) was dissolved in 5 ml. of nitromethane and 1 ml. of nitration mixture (0.0012 mole nitric acid) added dropwise at room temperature. The nitrating mixture was made up with 0.5 ml. of fuming nitric acid and 9.5 ml. of nitromethane. There was immediate darkening of the reaction mixture and a moderate increase in temperature. The reaction mixture was set aside for 2 hr. and poured into 25 ml. of ice water. The precipitated material was prepared for the column in the usual manner. The first band, when eluted, gave 0.06 g. of starting material. The second band was extruded and extracted with 95% ethanol. Crystallization from hot benzene,*n*-heptane gave pale yellow fernlike leaflets which, when heated, showed a change of state above 200° forming rectangular plates, m.p. 228–229°, yield 0.09 g., 40.95%. This product was assumed to be either the 3,2'- or the 5,2'-dinitro derivative.

Further nitration of 2'-nitro-2-hydroxybiphenyl in glacial acetic acid. A sample of 2'-nitro-2-hydroxybiphenyl (0.25 g., 0.0012 mole) was dissolved in 5 ml. of glacial acetic acid and nitrated with 4 ml. of a nitrating mixture made up of 0.5 ml. fuming nitric acid dissolved in 9.5 ml. glacial acetic acid (0.0047 mole nitric acid). The reaction mixture darkened at once and a precipitate came down during the latter part of the addition period. The product was worked up as usual and placed on the column. Three bands developed of which the first was narrow, dim yellow in color and moved, under moderate elution with benzene, with sufficient speed to enable extrusion of a second band which was the principal one. This was the only band from which material could be isolated. The material from this band crystallized readily from benzene,*n*-heptane as yellow needles, m.p. 152–153°. The weight was 0.17 g., 48.02%. These yellow, needlelike crystals were assumed to be 3,5,2'-trinitro-2-hydroxybiphenyl. A sample of these crystals when oxidized with chromic acid formed a product whose m.p. of 146–147° approximated that of *o*-nitrobenzoic acid.

Anal. Calcd. for $C_{12}H_7O_7N_3$: N, 13.77. Found: N, 13.60.

NORMAN, OKLA.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

Cleavage Studies of Some Organogermanium Compounds

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n-Butyltriethylgermane, benzyltriethylgermane, and 2-biphenylyltriethylgermane were prepared and characterized. *n*-Octadecyldiphenyl-2-phenylethylgermane was prepared *via* two independent routes from diphenyl-2-phenylethylgermyllithium and *n*-octadecyl bromide or from *n*-octadecyldiphenylgermyllithium and 2-phenylethyl bromide.

The cleavage of tetraethylgermane was investigated under a variety of experimental conditions. When lithium wire or lithium dispersion was employed, there was little evidence of reaction; but when sodium-potassium alloy was used, it appeared that triethylgermylpotassium was formed but immediately reacted in some unknown manner with the solvent. Attempts were also made to cleave other R_4Ge and $R_3R'Ge$ compounds.

The only trialkylgermylmetallic compound which has been successfully synthesized and characterized is triethylgermylpotassium,[1] prepared from hexaethyldigermane and potassium in ethylamine.

Triphenylgermylmetallic reagents have been more completely investigated. Kraus and Foster[2] cleaved hexaphenyldigermane with sodium in ammonia, forming triphenylgermylsodium. Triphenylgermyllithium was prepared initially by the cleavage of triethylsilyltriphenylgermane in ethylamine.[3] The preparation of triphenylgermyl-

(1) C. A. Kraus and E. A. Flood, *J. Am. Chem. Soc.*, **54**, 1635 (1932).

(2) C. A. Kraus and L. S. Foster, *J. Am. Chem. Soc.*, **49**, 457 (1927).

(3) C. A. Kraus and W. K. Nelson, *J. Am. Chem. Soc.*, **56**, 195 (1934).

potassium and -lithium, *via* the cleavage of hexaphenyldigermane in ethylene glycol dimethyl ether or in diethyl ether in the presence of catalytic amounts of tetrahydrofuran or bromobenzene, have been reported more recently.[4] These investigators also found they could cleave tetraphenylgermane under essentially the same conditions.[5]

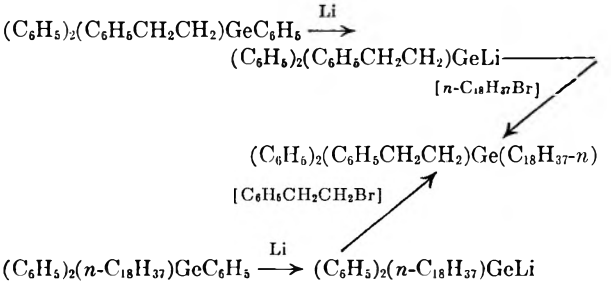
A review of the preparation of the corresponding silylmetallic compounds has appeared,[6] as well as a summary of the authors' attempts to prepare trialkylsilylmetallic compounds by the metallic cleavage of hexaalkyldisilanes and trialkyltriaryldisilanes. Inasmuch as the germanium-carbon bond energy is less than the silicon-carbon bond energy, 63 kcal/mole[7a] *vs.* 68 kcal/mole,[7b] it was felt that a trialkylgermylmetallic compound might be prepared where efforts to synthesize the corresponding silylmetallic compounds had been only partially successful.

Tetraethylgermane was prepared from germanium tetrabromide and ethylmagnesium bromide according to published procedures[1] in yields varying from 35 to 80% of the theoretical. Hexaethyldigermane was isolated as a by-product during the preparation of the tetrasubstituted compound.[8] Maximum yield of the digermane was 8%. Substitution of germanium tetrachloride for the tetrabromide did not alter the yield of products significantly. However, the use of ethyllithium rather than the Grignard reagent did affect the course of the reaction radically, giving rise to only a 12% yield of tetraethylgermane and 8.6% of hexaethyldigermane in addition to a large amount of unidentified polymeric material.

Attempts to cleave tetraethylgermane using lithium wire or lithium dispersion proved unsuccessful, a high recovery of starting material being realized. A variety of solvents as well as a number of initiators was investigated. When sodium-potassium alloy was employed as cleaving agent, there was no recovery of starting material. Cleavage may have occurred followed by immediate reaction of the germylpotassium reagent with the solvent, but none of these possible products were isolated. The results of these attempted cleavages are summarized in Tables I and II.

The cleavage of tetra-*n*-butyl-, tetra-*n*-octyl-, tetrabenzyl-, and tetrakis(2-phenylethyl)germane was also investigated.

Another approach to the preparation of trialkylgermylmetallic reagents involved the step-wise cleavage of phenyl groups from a tetrasubstituted germane with lithium in ethylene glycol dimethyl ether and derivatization of the germyllithium intermediates so formed with alkyl halides. *n*-Octadecyltriphenylgermane and triphenyl-2-phenylethylgermane were prepared and cleaved, followed by addition of 2-phenylethyl bromide and *n*-octadecyl bromide, respectively, to give *n*-octadecyldiphenyl-2-phenylethylgermane. However, the yields were too low to make the process synthetically attractive. An attempt to cleave tri-*n*-hexylphenylsilane was unsuccessful.



n-Butyltriethylgermane, benzyltriethylgermane, and 2-biphenylyltriethylgermane were prepared from chlorotriethylgermane and the appropriate organometallic reagent and their physical properties determined so the compounds could serve as reference materials.

EXPERIMENTAL[9]

Tetraethylgermane. The technique of Kraus and Flood[1] was used, employing ethylmagnesium bromide and germanium tetrabromide in diethyl ether. In nine preparations, the yield varied from 35 to 80% of the theoretical with an average yield of 50%. In the later runs, hexaethyldigermane,[1] b.p. 61–62° (0.007 mm.), n_D^{20} 1.4960, was isolated in about 8% yield.

The use of ethyllithium, in hopes of increasing the yield of the digermane, resulted in low yields of both tetraethylgermane (12%) and hexaethyldigermane (8.6%) in addition to a large amount of polymeric material.[10]

n-Butyltriethylgermane. To a stirred solution of 5.6 g. (0.029 mole) of chlorotriethylgermane in ether was added 0.032 mole of *n*-butyllithium.[11] A white solid appeared suspended in the liquid shortly after addition was begun and heat was evolved. After addition was complete, the mixture was stirred overnight.

Hydrolysis was effected with ice water, and the aqueous layer was separated and extracted three times with ether before being discarded. Distillation of the organic material, after drying over sodium sulfate, afforded 3.93 g. of crude product, b.p. 175–182°. Redistillation gave 3.21 g. (51.1%) of pure *n*-butyltriethylgermane, b.p. 181–181.5°, n_D^{20} 1.4475.

(4) H. Gilman and C. W. Gerow, *J. Am. Chem. Soc.*, **77**, 5509 (1955); *J. Am. Chem. Soc.*, **77**, 5740 (1955).

(5) H. Gilman and C. W. Gerow, *J. Am. Chem. Soc.*, **77**, 4675 (1955).

(6) H. Gilman, R. K. Ingham, and A. G. Smith, *J. Org. Chem.*, **18**, 1743 (1953). See also A. G. Brook, *Chem. in Can.*, 43 (1955).

(7) (a) M. L. Huggins, *J. Am. Chem. Soc.*, **75**, 4123 (1953). (b) M. L. Huggins, *J. Am. Chem. Soc.*, **75**, 4126 (1953).

(8) See some recent related studies by Seyferth, *J. Am. Chem. Soc.*, **79**, 2738 (1957).

(9) All reactions were carried out under an atmosphere of dry, oxygen-free nitrogen in sodium-dried solvents. Melting and boiling points reported herein are uncorrected.

(10) O. H. Johnson and D. M. Harris, *J. Am. Chem. Soc.*, **72**, 5564 (1950), report 60% yields of hexaphenyldigermane from germanium tetrachloride and phenylmagnesium bromide.

(11) 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).

Anal. Calcd. for $C_{10}H_{24}Ge$: Ge, 33.51. Found: Ge, 33.28.

Benzyltriethylgermane. To a stirred solution of 5.8 g. (0.03 mole) of chlorotriethylgermane in ether was added 0.033 mole of benzylmagnesium chloride. A solid formed and a small amount of heat was generated during the addition. Work-up as described above resulted in the isolation of 5.94 g. (79%) of benzyltriethylgermane, b.p. 78–81° (1.0 mm.), n_D^{20} 1.5178.

Anal. Calcd. for $C_{13}H_{22}Ge$: Ge, 28.97. Found: Ge, 29.15.

2-Biphenylyltriethylgermane. An ethereal solution of 0.067 mole of 2-biphenylyllithium was added to 11.5 g. (0.059 mole) of chlorotriethylgermane at such a rate as to maintain gentle reflux. After addition was complete, the mixture was stirred at reflux for 12 hr. before being hydrolyzed and worked up. Two distillations of the organic material afforded 11.5 g. (62.4%) of 2-biphenylyltriethylgermane, b.p. 150–152° (3.3 mm.), n_D^{20} 1.5697.

Anal. Calcd. for $C_{18}H_{24}Ge$: Ge, 23.20. Found: Ge, 23.06, 23.00.

Attempted cleavage of tetraethylgermane. (*a*) *With lithium wire.* Seven attempts were made to cleave tetraethylgermane using lithium wire under a variety of conditions.

Color Test I[12] was taken at regular intervals and was usually negative. Sometimes toward the end of the extended cleavage reactions, the Color Test was weakly positive, possibly indicative of the formation of triethylgermyllithium and ethyllithium which would be expected to exhibit a positive Color Test; but in light of the high recovery of starting material, this could also have been due to the presence of very finely subdivided lithium metal which is known to give a weak Color Test I.

The results are summarized in Table I.

TABLE I

ATTEMPTED CLEAVAGE OF TETRAETHYLGERMANE WITH LITHIUM WIRE IN ETHYLENE GLYCOL DIMETHYL ETHER

Run	Initiator	Reaction Time, Hr.	Temp., °C.	Derivatizing Agent	Recovery of Et_4Ge, %
1	...	8	25	H_2O	72
2	...	12	80	H_2O	72
3	...	48	80	H_2O	35
4	...	60	80	$(C_6H_5)_3SiCl$	0
5	Tetrahydrofuran	8	80	H_2O	70
6	Bromobenzene	30	80	H_2O	72
7	Ethyl bromide	30	80	H_2O	50

(*b*) *With lithium dispersion.* A mixture of 5 ml. (4.9 g., 0.026 mole) of tetraethylgermane and 0.38 g. (0.055 g.-atom) of lithium contained in 1.27 g of a lithium dispersion in xylene (courtesy of Lithium Corporation of America) and 40 ml. of xylene was stirred for 4 days at room temperature. A brown color developed in the solution during this time.

Addition of excess *n*-butyl bromide caused gentle refluxing. Following hydrolysis with water and the usual work-up, fractional distillation failed to yield any identifiable material.

(*c*) *With sodium-potassium alloy.* Nineteen attempts were made to cleave tetraethylgermane with sodium-potassium alloy using a variety of solvents, reaction times and temperatures, and initiators. In most cases colors were observed during the reaction and work-up, but no material isolated was identified. It is possible that triethylgermylpotassium formed and immediately reacted in some unknown manner with the solvent or initiator, where one was used.

The sodium-potassium alloy contained sodium and potassium in the ratio of 1 to 5 by weight. In some of the first reactions, the excess alloy was amalgamated with mercury before derivatization, but later runs were treated with a large excess of derivatizing agent in lieu of amalgamation.

In all reactions, 5 ml. (4.9 g., 0.026 mole) of tetraethylgermane, 5 ml. of solvent, and 4 ml. of Na-K alloy (0.08 g.-atom of potassium) were stirred together. During the first 30 min. an additional 25 ml. of solvent was added as well as 0.5 ml. of initiator, where one was used. Following the usual work-up, final distillation was achieved through a 4-in. Vigreux column.

The details of the reactions are summarized in Table II.

TABLE II

ATTEMPTED CLEAVAGE OF TETRAETHYLGERMANE WITH SODIUM-POTASSIUM ALLOY

Run	Solvent[a]	Initiator	Reaction Time, hr.	Temp., °C.	Derivatizing Agent
1	Et_2O	...	1	25	$(C_6H_5)_3SiCl$
2	Et_2O	...	24	25	$(C_6H_5)_3SiCl$
3	Et_2O	...	36	35	H_2O
4	Et_2O	...	72	25	$(C_6H_5)_3SiCl$
5	Et_2O	Bromobenzene	12	25	$(C_6H_5)_3SiCl$
6	GDME[b]	...	144	85	H_2O
7	GDME	Bromobenzene	108	25	*n*-C_4H_9Br
8	GDME	Bromobenzene	48	85	*n*-C_4H_9Br
9	GDME	Bromobenzene	96	85	H_2O
10	$(n\text{-}C_4H_9)_2O$	...	100	140	*n*-C_4H_9Br
11	Benzene	...	168	75	*n*-C_4H_9Br
12	Xylene	...	48	135	*n*-C_4H_9Br
13	Xylene	...	48	135	$C_6H_5CH_2Cl$
14	Dioxane	...	72	100	*n*-C_4H_9Br
15	Et_3N	...	2.5	25	*n*-C_4H_9Br
16	Et_3N	...	72	25	*n*-C_4H_9Br
17	Et_3N	...	2	25	$(C_6H_5)_3SiCl$
18	Et_3N	...	2	25	$(C_6H_5)_3GeCl$
19	THF[c]	...	2	25	*n*-C_4H_9Br

[a] Recent studies by Dr. M. V. George of this laboratory indicate tetrahydropyran may be a better solvent for the cleavage reactions inasmuch as it exhibits greater stability toward cleavage by silylmetallic intermediates. [b] Ethylene glycol dimethyl ether. [c] Tetrahydrofuran.

Cleavage of tetra-n-butylgermane. (*Attempted*). (*a*) *With lithium.* After a mixture of 6.02 g. (0.02 mole) of tetra-*n*-butylgermane, 1.2 g. (0.173 g.-atom) of lithium and 10 ml. of ethylene glycol dimethyl ether had been stirred for 96 hr. the mixture was black, but Color Test I was negative. Water was added to hydrolyze the mixture; the black color was dissipated and heat was evolved. Distillation of the residue which remained after the usual work-up and removal of solvents afforded 5.52 g. (92%) of starting material boiling 110–113° (0.7 mm.).

(*b*) *With sodium-potassium alloy.* After a mixture of 3.01 g. (0.01 mole) of tetra-*n*-butylgermane, 1.1 ml. (0.022 g.-atom of potassium) of sodium-potassium alloy and 20 ml. of ethylene glycol dimethyl ether had been stirred 115 hr., the alloy was still bright and the mixture slightly grey. The alloy was amalgamated and the suspension transferred to an addition funnel; thereafter, it was added rapidly to 5.9 g. (0.02 mole) of chlorotriphenylsilane dissolved in the same

(12) H. Gilman and F. Schulze, *J. Am. Chem. Soc.*, **47**, 2002 (1925).

solvent. There was no evidence of reaction. After stirring overnight, water was added and the mixture worked up as usual. The residue remaining after removal of the ether was washed with petroleum ether (b.p. 60–70°) to give 5.3 g. of insoluble solid melting over the range of 148–155°. This was recrystallized from the same solvent to give 3.6 g. (66%) of triphenylsilanol (mixture m.p.) melting 155–157°. The original petroleum ether filtrate was distilled to give 3.0 g. (100%) of starting material, boiling 148° (11 mm.).

Cleavage of Tetra-n-octylgermane. (Attempted). After stirring a mixture of 5.3 g. (0.01 mole) of tetra-*n*-octylgermane, 1.3 g. (0.186 g.-atom) of lithium and 10 ml. of ethylene glycol dimethyl ether for 18 hr., a reddish color had developed and Color Test I was positive; after 67 hr. the red solution was pipetted into a dropping funnel and added to 7.7 g. (0.02 mole) of bromotriphenylgermane dissolved in 25 ml. of GDME. The red color was dissipated immediately. After stirring for 4 hr., water was added and the mixture was extracted with ether and filtered to give 2.6 g. of solid melting at 186–189°. The ether solution was dried and the solvents distilled to leave a residue which was washed with petroleum ether (b.p. 60–70°) to give 2.5 g. of insoluble solid melting over the range 160–188°. The two solids were recrystallized from chloroform-petroleum ether (b.p. 60–70°) to yield 4.3 g. (68%) of hexaphenyldigermoxane, melting 184–185°. The original ether filtrate was distilled to give 3.57 g. (67%) of starting material, b.p. 223° (0.015 mm.).

Cleavage of tetrabenzylgermane. (Attempted). Five g. (0.0114 mole) of tetrabenzylgermane, 0.8 g. (0.12 g.-atom) of lithium and 10 ml. of ethylene glycol dimethyl ether were stirred for 3 min., a red-brown color developing, accompanied by evolution of heat. After stirring 5 hr. Color Test I was positive so the mixture was pipetted into a dropping funnel and added to 2.54 g. (0.023 mole) of ethyl bromide. Heat was generated and the dark color dissipated. After stirring overnight, water was added, and the mixture worked up as usual. Distillation of the material remaining after removal of solvents gave fractions having the following boiling ranges: 212–216° (0.08 mm.), 216–221° (0.08 mm.), below 186° (0.005 mm.), and 186–198° (0.005 mm). No tribenzylethylgermane[13] was isolated.

Cleavage of tetrakis(2-phenylethyl)germane. (Attempted). After stirring a mixture of 4.9 g. (0.01 mole) of tetrakis(2-phenylethyl)germane, 1.3 g. (0.19 g.-atom) of lithium and 25 ml. of ethylene glycol dimethyl ether for 68 hr., the color was dark brown and Color Test I was positive. The solution was pipetted into a dropping funnel and added rapidly to 5.9 g. (0.02 mole) of chlorotriphenylsilane dissolved in GDME. Heat was evolved and the dark color dissipated. After stirring overnight, water was added and the mixture extracted with ether. The ether was dried and the solvents distilled to leave a residue which gave 5.1 g. (97%) of triphenylsilanol, m.p. 142–149°. Recrystallization from petroleum ether (b.p. 60–70°) gave 4.5 g., m.p. 151–153°. The original petroleum ether filtrate was distilled to give 4.8 g. (100%) of crude starting material, m.p. 42–44°. Recrystallization from ethyl alcohol gave 3.8 g. of pure starting material, m.p. 48.5–50°.

Triphenyl-2-phenylethylgermane. To a stirred solution of 7.4 g. (0.04 mole) of 2-phenylethyl bromide in 35 ml. of ethylene glycol dimethyl ether was added a 60-ml. solution of triphenylgermyllithium, prepared from 12.14 g. (0.02 mole) of hexaphenyldigermane in GDME.[4] Ten min. after addition was complete, Color Test I was negative. The mixture was hydrolyzed with 100 ml. of a saturated ammonium chloride solution. A white solid which separated at the interface was filtered off before the aqueous layer was separated, extracted three times with ether and discarded. This white material weighed 16.19 g. and melted over the range 143–146°. Two recrystallizations from petroleum ether (b.p. 60–70°) gave 9.83 g. (60%) of triphenyl-2-phenylethylgermane, m.p. 147–149°. Reduction in volume of the mother liquor resulted in the isolation of another 1.7 g. (10.6%) of product.

Anal. Calcd. for $C_{26}H_{24}Ge$: C, 76.34; H, 5.91. Found: C, 76.38, 76.24; H, 6.08, 5.95.

Another run, exactly as above except that the triphenylgermyllithium from 0.03 mole of hexaphenyldigermane was interacted with 0.06 mole of 2-phenylethyl bromide, resulted in the isolation of 24 g. of crude product. One recrystallization from ethanol gave 18 g. (73%) of triphenyl-2-phenylethylgermane.

n-Octadecyltriphenylgermane. To a stirred solution of 20.0 g. (0.06 mole) of *n*-octadecyl bromide in 60 ml. of ethylene glycol dimethyl ether was added an 80-ml. solution of triphenylgermyllithium prepared from 0.03 mole of hexaphenyldigermane in GDME.[4] The reaction mixture warmed slightly during the addition and 5 min. after addition was complete, Color Test I was negative. The mixture was hydrolyzed with 100 ml. of saturated ammonium chloride solution and the solid which appeared at the interface was filtered off. This material weighed 28.78 g. and melted from 76 to 79°. Recrystallization of this solid from ethanol gave 23.29 g. (70%) of pure *n*-octadecyltriphenylgermane, m.p. 76.5–77.5°. Several grams of less pure material was isolated upon concentration of the mother liquor. A mixture m.p. with an authentic sample[14] was not depressed.

n-Octadecyldiphenyl-2-phenylethylgermane. (a) From n-octadecyldiphenylgermyllithium and 2-phenylethyl bromide. A mixture of 11.13 g. (0.02 mole) of *n*-octadecyltriphenylgermane, 50 cm. (1.5 g., 0.22 g.-atom) of finely cut lithium wire and 15 ml. of ethylene glycol dimethyl ether was stirred for 5 hr. Shortly after stirring was begun, a green color developed to be gradually replaced by a red-brown color as cleavage proceeded and an additional 35 ml. of GDME was added. At the end of the cleavage period, Color Test I was positive and the reagent was pipetted into an addition funnel.

The germyllithium reagent was added over a 10-min. period to a stirred solution of 3.7 g. (0.02 mole) of 2-phenylethyl bromide in 40 ml. of GDME. Color Test I was negative immediately upon completion of addition. The mixture was hydrolyzed with a saturated ammonium chloride solution and worked up in the usual manner. After removal of all the solvents, there remained an oil. Distillation resulted in the recovery of 2.37 g. (21%) of starting material and 1.19 g. of solid, m.p. 34–36°. Recrystallization of this waxy solid from methanol gave 1.03 g. (17.6% based on unrecovered starting material) of *n*-octadecyldiphenyl-2-phenylethylgermane, m.p. 34.5–36°.

Anal. Calcd. for $C_{38}H_{56}Ge$: Ge, 12.40. Found: Ge, 12.98, 12.47.

An infrared spectrum of the compound, as a carbon disulfide solution, had bands at 3.3, 3.5, and 9.2μ, characteristic of aromatic C—H, aliphatic C—H and the germanium—phenyl bonds, respectively.

(b) From diphenyl-2-phenylethylgermyllithium and n-octadecyl bromide. A mixture of 4.09 g. (0.01 mole) of triphenyl-2-phenylethylgermane, 75 cm. (2.25 g., 0.32 g.-atom) of finely cut lithium wire and 10 ml. of GDME was stirred for 3.5 hr. About 10 min. after stirring was begun, a yellow-green color developed and was gradually replaced by a red-brown color as cleavage progressed and an additional 40 ml. of GDME was added. At the end of the cleavage period, the germyllithium reagent was pipetted into an addition funnel and added slowly to a stirred solution of 3.33 g. (0.01 mole) of *n*-octadecyl bromide in GDME. Immediately after addition was complete, Color Test I was negative. Hydrolysis was effected with a saturated ammonium chloride solution and the usual method of work-up was employed. Distillation of the material remaining after the solvents had been stripped off resulted in the recovery of a

(13) H. Bauer and K. Burschkies, *Ber.*, **67**, 1041 (1934).

(14) H. Gilman and C. W. Gerow, *J. Am. Chem. Soc.*, 79, 342 (1957).

small amount of *n*-octadecyl bromide, 2.74 g. (67%) of unreacted triphenyl-2-phenylethylgermane and 0.63 g. of product boiling over the range 180–185° at 0.005 mm. Recrystallization of this latter fraction from methanol gave 0.5 g. (28.6%) based on unrecovered starting material) of *n*-octadecyldiphenyl-2-phenylethylgermane, m.p. and mixture m.p. 34.5–35.5°.

Cleavage of tri-n-hexylphenylgermane. (Attempted). A mixture of 2.03 g. (0.005 mole) of tri-*n*-hexylphenylgermane, 0.3 g. (0.043 g.-atom) of lithium and 7 ml. of ethylene glycol dimethyl ether was stirred for 24 hr. to yield a deep red solution giving a positive Color Test I. The solution was pipetted into a dropping funnel and added to 1.7 g (0.01 mole) of *n*-hexyl bromide dissolved in 20 ml. of GDME. After stirring 5 min., Color Test I was negative. Water was added and the mixture extracted with ether. The ether portions were dried and the solvents distilled to leave a residue which was distilled under reduced pressure to give 1.3 g. (65%) of starting material, b.p. 186–188° (0.7 mm.), n_D^{19} 1.4959.

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[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, STANDARD OIL COMPANY (INDIANA)]

Acid-Catalyzed Addition of Phosphine to Olefins

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Phosphine adds to olefins in the presence of non-oxidizing acid catalysts to give good yields of monoalkylphosphines and small amounts of dialkylphosphines. Reaction takes place readily at 30 to 60° under 20 to 40 atmospheres of phosphine. Because tertiary olefins react most easily, a carbonium ion mechanism seems likely. Nearly stoichiometric amounts of catalyst are needed because monoalkylphosphines react with the catalyst to form monoalkylphosphonium salts.

Phosphine adds to olefins in the presence of acid catalysts.[1] This addition is particularly interesting because phosphine is intermediate in basicity between two other hydrides: hydrogen sulfide and ammonia. Hydrogen sulfide reacts stepwise with olefins in the presence of acid catalysts to yield mercaptans and thioethers.[2] Because olefins are more basic than hydrogen sulfide or mercaptan, a carbonium ion intermediate can form easily and only a small amount of catalyst is needed. By contrast, no carbonium ion can form in the presence of ammonia. However, weakly basic derivatives of ammonia, such as urea, permit carbonium ions to form and can add to olefins with acid catalysts.[3]

The addition of phosphine to olefins has therefore been studied to determine qualitatively the relation of phosphine to hydrogen sulfide and ammonia in the presence of acid catalysts. Olefin reactivity was studied with primary, tertiary,[4] cyclic, and substituted olefins with methanesulfonic acid as catalyst. As catalysts, mineral acids, carboxylic acids, sulfonic acids, hydrogen halides, and Lewis acids were tested with a polypropene as the olefin. The effects of temperature and catalyst concentration were measured with methanesulfonic acid and a polypropene. Product distribution between mono- and dialkylphosphine was determined with typical olefins.

EXPERIMENTAL

Phosphine was prepared by adding water to a mixture of phosphorus and phosphorus tetraiodide[5] at 80° and scrubbing the evolved gases with aqueous sodium hydroxide. The scrubbed gases were dried in a coil cooled in Dry Ice and condensed in a pressure vessel cooled in liquid nitrogen. The mass spectrum showed the product to be pure phosphine.

Ten olefins were studied. Propene, dodecene-1, isobutene, and 2-ethylhexene-1 were commercial materials. C_{12}-polypropene was fractionated from a mixture of polypropenes obtained by polymerization with phosphoric acid. This fraction contained about 85% tertiary olefins. Polybutenes were obtained by polymerizing mixed butenes and butanes with aluminum chloride. Fractions containing an average of 26 and 65 carbon atoms were used. Two cyclic olefins, 1-methylcyclopentene-1 and 4-methylcyclohexene-1 were synthesized. A mixture of the two di-isobutene isomers was chlorinated and the product was fractionated to isolate the unsaturated monochloride.

Detailed studies were carried out with C_{12}-polypropene because of its stability toward acids. This stability was demonstrated by stirring a sample with an equimolar amount of methanesulfonic acid for 16 hr. at 85° and distilling the recovered olefins. A plot of the refractive index and boiling point at 5% increment of the distillation showed no significant variation from a similar distillation of untreated C_{12}-polypropylene. Also, no measurable polymeri-

(1) H. C. Brown, U. S. Patent 2,584,112 (1952).

(2) W. A. Proell and W. F. Wolff, U. S. Patent 2,615,786 (1952).

(3) H. C. Brown, U. S. Patent 2,548,585 (1951).

(4) Olefins in which one of the carbon atoms of the double bond is also bonded to two other carbon atoms; isobutene is the simplest example.

(5) W. C. Fernelius, "Inorganic Synthesis, Vol. II", McGraw-Hill Book Co., Inc., New York, New York, 1946, p. 41.

zation occurred. By contrast, 1-methylcyclopentene polymerizes rapidly at room temperature even with smaller amounts of acid.

Thirteen acids were studied as catalysts. Methanesulfonic acid was distilled twice to remove water and sulfuric acid, 85% phosphoric acid was reacted with sufficient phosphorus pentoxide to form 100% phosphoric acid, and dodecylphosphonous acid and phosphonium iodide were synthesized. The other catalysts were used as obtained commercially.

Phosphine was added to olefins in a 100-ml. stainless steel Magne-Dash reactor. The reactor was thoroughly flushed with nitrogen before each run. Usually, about 0.2 moles of olefin was charged, the phosphine was pressured in, the reactor was heated to the desired temperature, and then the catalyst was added. Solid catalysts had to be charged first; to minimize polymerization, the reactor was then cooled in Dry Ice before olefin was added. For the experiments with propene, isobutene, and C_{65}-polybutene, *n*-heptane was used as a solvent.

After a run was completed, the reactor was cooled, the excess phosphine was vented, and the product was diluted with heptane and washed with water to remove the catalyst. All product handling was done under nitrogen. The heptane solution was analyzed both by measuring total phosphorus content and by potentiometrically titrating the acids in an aliquot oxidized with hydrogen peroxide.[6] Good agreement was obtained between the values for total phosphorus and total acid. Total yield of alkyl phosphine was calculated from these values.

The dialkylphosphine was measured directly by potentiometric titration with hydrogen chloride in acetic acid; this titration showed no trialkylphosphines to be present. A Beckman Model 2-H *p*H meter with a calomel-glass electrode pair was used. Solvent was C.P. glacial acetic acid, titrant was *N*/10 anhydrous HCl in C.P. glacial acetic acid. In this system, dialkylphosphines titrated at about 560 millivolts and trialkylphosphines at 500 millivolts.

To substantiate that alkylphosphines were the product of the addition reaction, three derivatives were prepared from the adduct of phosphine to C_{12}-polypropene: the phosphonous acid, the phosphonic acid, and the dipotassium phosphonate.

t-Dodecylphosphonous acid was obtained by oxidizing a heptane solution of the C_{12}-polypropene product with 30% hydrogen peroxide at 50°. Titration of the oil phase from the oxidation indicated a 79% yield of *t*-dodecylphosphonous acid and a 6% yield of *t*-dodecylphosphonic acid. Most of the remaining 15% was recovered as phosphoric acid in the aqueous phase. The isolated product was a pale yellow syrup. Potentiometric titration gave a curve with two breaks that corresponds to a mixture of 93 mole % phosphonous acid and 7 mole % phosphonic acid. Neutral equivalent: Calcd., 235; Found, 238.

t-Dodecylphosphonic acid was obtained by oxidizing a heptane solution of the phosphonous acid with concentrated nitric acid at 90°. Titration of the oxidized solution indicated a 92% yield of mixed acids. The isolated product—again a pale yellow syrup—comprised 91 mole % of phosphonic acid and 9 mole % of phosphonous acid. Neutral equivalent: Calcd., 249; Found, 256. Phosphorus: Calcd., 12.4%; Found, 12.3%.

The dipotassium salt was prepared by treating a *n*-heptane solution of the phosphonic acid with the theoretical amount of potassium hydroxide in an aqueous solution, distilling off the water, filtering the remaining heptane solution, and removing the heptane. The salt was an amorphous brittle solid. Phosphorus: Calcd., 9.7%; Found, 9.5%. Potassium: Calcd., 22.3%; Found, 21.4%.

(6) Addition of 1 ml. of a non-ionic detergent greatly facilitated the titration in the two-phase system.

DISCUSSION OF RESULTS

The yields of monoalkylphosphines obtained from the different olefins with methanesulfonic acid as catalyst are summarized in Table I. Best yields were obtained with tertiary olefins. A simple carbonium ion mechanism therefore seems likely. A normal Markownikoff addition presumably takes place to yield a product with the phosphorus atom bonded to the tertiary carbon atom:

$$R_2C{=}CH_2 + H^+ \rightleftharpoons R_2\overset{+}{C}{-}CH_3 \quad (1)$$

$$R_2\overset{+}{C}{-}CH_3 + PH_3 \rightleftharpoons [H_3P{-}C(R_2)CH_3]^+ \quad (2)$$

$$[H_3P{-}C(R_2)CH_3]^+ \rightleftharpoons H_2P{-}C(R_2)CH_3 + H^+ \quad (3)$$

Among the tertiary olefins, the lower yields for isobutene, 2-ethylhexene-1, and 1-methylcyclopentene-1 are probably due to the relative ease of polymerization of these compounds, compared to the C_{12}-polypropene. The high yields obtained from the polybutenes reflect a surprising degree of reactivity.

Mineral acids, sulfonic acids, carboxylic acids, hydrogen fluoride, and Lewis acids all catalyze phosphine addition. Table II compares the activity of these catalysts using C_{12}-polypropene as the olefin. The catalysts all show the same magnitude of activity with the exception of the phosphoric acid-phosphorus pentoxide. This mxiture was extremely viscous; hence the low yield may reflect inadequate stirring rather than low activity. Dodecylphosphonous acid, hydrogen iodide (as phosphonium iodide), aluminum bromide, phosphoric acid on Kieselguhr, oxalic acid, and Filtrol clay were also tested; none gave yields above 5 per cent. Sulfuric acid was reduced to an unidentified solid.

Nearly stoichiometric amounts of catalyst are required for complete reaction. In Fig. 1 are com-

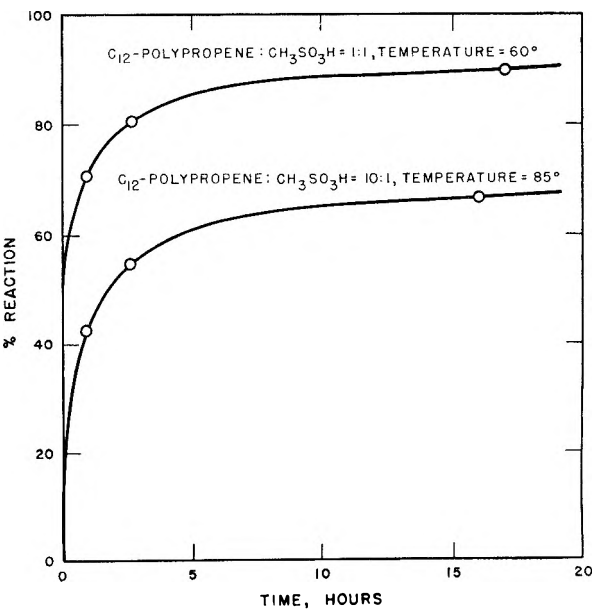

Fig. 1. Effect of catalyst concentration

pared reaction rate curves in which the C_{12}-polypropene: CH_3SO_3H mole ratio was 1:1 and 10:1. PH_3 pressure was 38–43 atmospheres. In both cases the reaction is nearly complete in 3 to 4 hours. With the 1:1 ratio the amount of reaction at this time corresponds closely to the tertiary olefin content of the feed. Subsequent slow reaction probably results from reaction of non-tertiary olefins. With the 10:1 ratio, reaction is slower and stops at 60 to 70% even though a higher temperature is used. The reaction is not limited by polymerization because the C_{12}-polypropene used as olefin was shown not to polymerize at 85°C even with greater amounts of catalyst. Hence, reactive tertiary olefin is undoubtedly present at the end of the reaction.

Several other factors could limit the conversion when the lesser amount of catalyst is used. The higher temperature also used would decrease the phosphine concentration and make the equilibrium shown in Equation 2 less favorable. However, a run carried out at 90° with an olefin catalyst ratio of 1:1 showed a conversion of 86% at 4 hours, somewhat higher than that obtained at 60°, and indicated that temperature does not significantly affect phosphine concentration. Another explanation for the limited conversion with the small amount of catalyst is that the monoalkylphosphine formed is a much stronger base than phosphine or the olefin and ties up the catalyst as a phosphonium ion. If so, higher temperatures should favor an increased conversion because, similarly to ammonium and phosphonium halide, the dissociation of alkylphosphonium ions (Equation 3) would also be favored by increased temperature. The released protons would then catalyze further reaction. This theory is supported by the results summarized in Fig. 2. These are yields from runs carried out at 30, 60, and 85° and a PH_3:C_{12}-polypropene:CH_3SO_3H mole ratio of 2.8:1:0.1.

All runs lasted 16 hours and the yields are believed to reflect equilibrium yields and not reaction rate. The difference in total conversion is interpreted as representing the change in equilibrium,

$$RPH_2 + H^+ \rightleftarrows [RPH_3]^+,$$

as a function of temperature. Thus at 30° about 2 equivalents of RPH_2 are sufficient to deactivate the catalyst; at 60° nearly 6 equivalents are required.

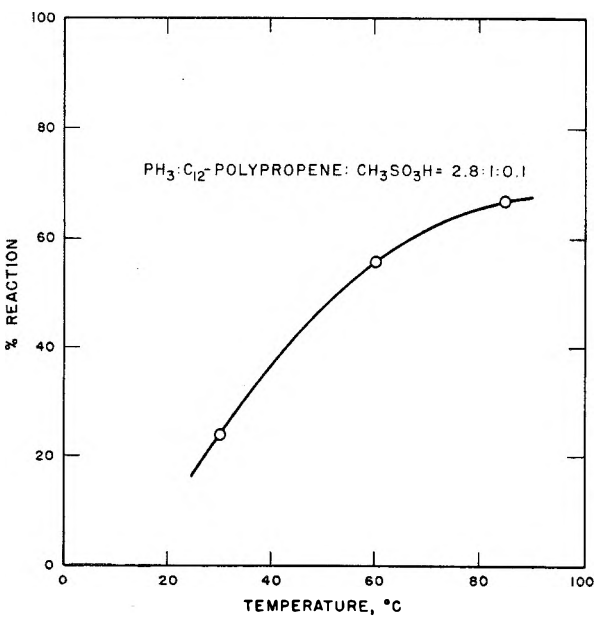

Fig. 2. Effect of temperature

TABLE I

REACTIVITY OF OLEFINS

	Moles per Mole Olefin					
	PH_3	CH_3SO_3H	Time, Hrs.	Temp., °C.	Pressure, Atm.	Mole % RPH_2 + R_2PH
Propene	3.3	1.0	16	80	38	20
Dodecene-1	2.8	1.0	16	60	43	14
Isobutene	2.9	1.0	3	60	33	61
2-Ethylhexene-1	4.2	1.0	16	60	43	76
C_{12}-Polypropene	4.3	1.0	16	60	47	90
C_{26}-Polybutene	3.8	1.0	17	90	39	72
C_{65}-Polybutene	20.0	10.0	16	95	..	81
1-Methylcyclopentene-1	1.8	0.5	16	60	30	41
4-Methylcyclohexene-1	1.8	0.5	16	60	32	33
Monochlorodiisobutene	2.4	1.0	16	60	35	21

TABLE II

EFFECTIVENESS OF CATALYSTS

	C_{12}-Polyprolene Moles per Mole					
	PH_3	Catalyst	Time, Hrs.	Temp., °C.	Pressure, Atm.	Mole % RPH_2 + R_2PH
Methanesulfonic acid	4.2	1.0	3	60	38	81
Benzenesulfonic acid	2.4	0.5	3	60	36	72
Trifluoroacetic acid	3.7	1.0	3	60	37	60
85% H_3PO_4 + P_2O_5	3.8	1.0	3	60	44	17
Methanesulfonic acid	2.8	1.0	1.5	30	24	40
Boron trifluoride etherate	3.6	0.3	3	30	26	30
Hydrogen fluoride	3.7	1.0	3	30	29	53

Small amounts of dialkylphosphines are formed. Data summarizing the product distribution from phosphine addition to a primary, a tertiary, and two cyclic olefins are shown in Table III. The amounts of dialkylphosphine formed are small and reflect the tendency of the more basic monoalkylphosphine to exist as RPH_3^+. Because monoalkylphosphines are more basic than phosphine and capture most of the protons present, the concentration of both olefin cation and free monoalkylphosphine is low. Hence, formation of dialkylphosphine is slow. Olefin type appears to have little effect on the product distribution.

The increased basicity of monoalkylphosphines over that of phosphine decreases carbonium ion formation in acid-catalyzed systems so that addition of RPH_2 to olefins is a slow reaction. Therefore, high yields of monoalkylphosphines can be obtained. Acid-catalyzed addition of phosphine to tertiary olefins provides a synthesis of alkylphosphines having phosphorus bonded to a tertiary carbon atom.

TABLE III

COMPOSITION OF PRODUCTS

Time = 16 hours Catalyst = CH_3SO_3H

	Olefin Reacted, Mole %	°C.	PH_3, Atm.	Product Composition, Mole % RPH_2	R_2PH
Dodecene-1	28	90	41	98	2
4-Methylcyclohexene-1[a]	34	60	32	97	3
1-Methylcyclopentene-1	41	60	30	90	10
C_{12}-Polypropene	91	90	50	96	4

[a] Rapid isomerization to 1-methylcyclohexene-1 is caused by the acid catalyst.

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Unsymmetrical Tetraalkylmethanes. III.[1] Syntheses from 3-Ethyl-3-methylglutaric Acid

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Two unsymmetrical tetraalkylmethanes, 11-ethyl-11-methyltricosane (X) and 11-ethyl-11-methylpentacosane (XIV), have been synthesized from 3-ethyl-3-methylglutaric acid by the reactions summarized in Chart I.

In the course of an investigation of methods for the synthesis of unsymmetrical tetraalkylmethanes, a number of procedures have been considered for building up the desired quaternary carbon atom structure. The possibility of an approach of some generality appeared to be through β,β-disubstituted glutaric acids. These compounds may be obtained from the condensation of simple or cyclic ketones with alkyl cyanoacetates according to the method of Guareschi,[4] which has been extended by Vogel.[5]

The present report describes the methods by which two relatively high molecular weight unsymmetrical tetraalkylmethanes were synthesized from 3-ethyl-3-methylglutaric acid. The reactions employed are summarized by the equations shown in Chart I.

The direct conversion of 3-ethyl-3-methylglutaric anhydride to a 3-ethyl-3-methyl-5-keto acid, such as compound XII, was suggested by the work of Newman and Smith[6] who have studied the addition of Grignard reagents to anhydrides at low temperatures. However, negative results were obtained when an ether-pyridine solution of 3-ethyl-3-methylglutaric anhydride was treated with ethylmagnesium bromide.

It was decided then to synthesize the keto acid, XII, through the ester–acid chloride, II. This compound was obtained readily from 3-ethyl-3-methylglutaric anhydride via the intermediate ester acid, I.

Percival, Wagner, and Cook[7] have prepared highly-branched ketones in quite satisfactory yields by the reaction of acid chlorides with Grignard reagents at −65° in the presence of ferric chloride. It was felt, however, that this method would have no special advantages, for the present purposes,

(1) Paper II. N. Rabjohn and H. H. Farmer, *J. Org. Chem.*, **23**, 522 (1958).

(2) Abstracted in part from the Ph.D. thesis of H. H. Farmer, 1955.

(3) Supported in part by the Petroleum Research Fund of the American Chemical Society.

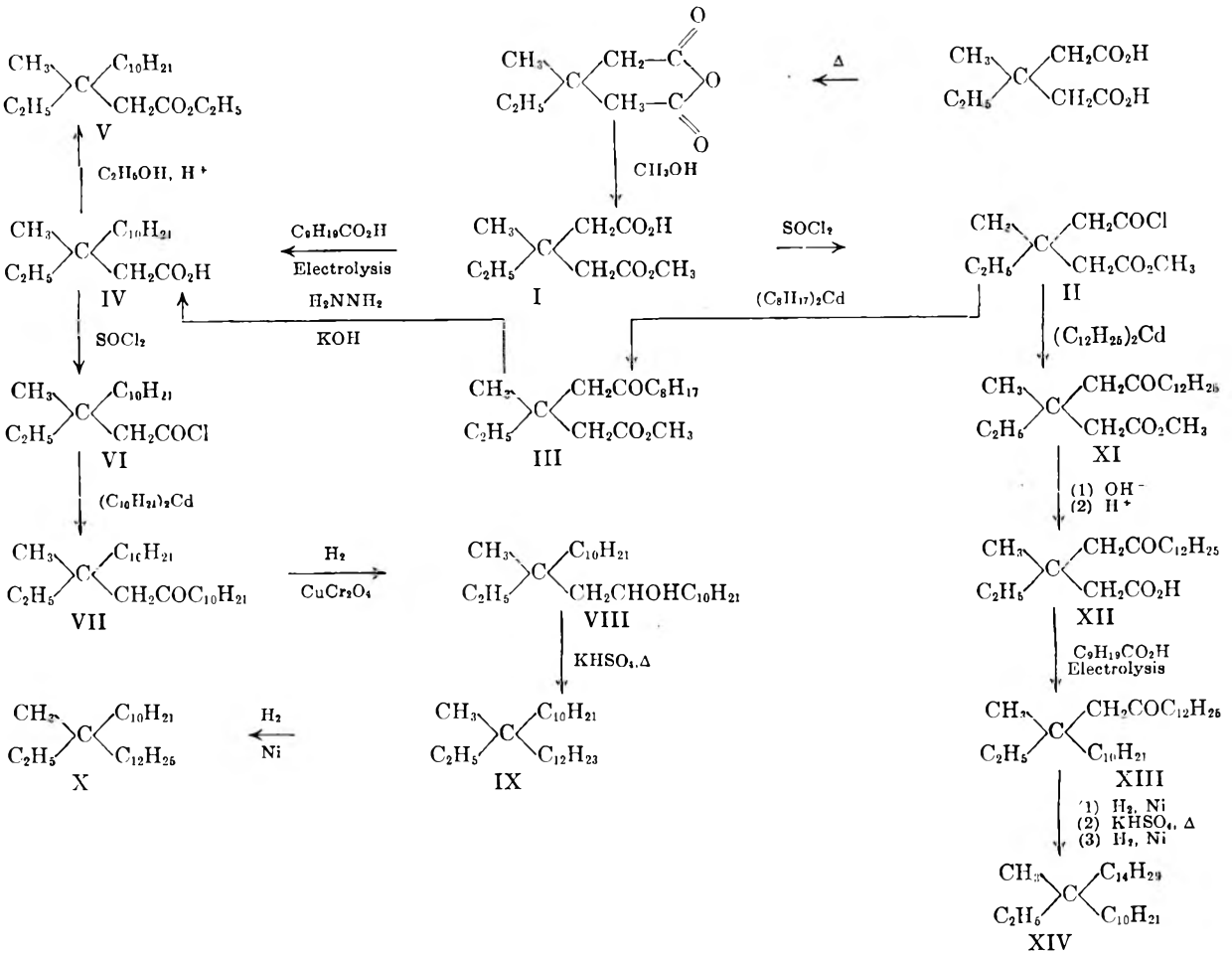
(4) I. Guareschi, *Atti. accad. sci. Torino*, **36**, 443 (1900).

(5) A. I. Vogel, *J. Chem. Soc.*, 1758 (1934).

(6) M. S. Newman and A. S. Smith, *J. Org. Chem.*, **13**, 592 (1948).

(7) W. C. Percival, R. B. Wagner, and N. C. Cook, *J. Am. Chem. Soc.*, **75**, 3731 (1953).

CHART I



over the well known use of alkylcadmium reagents since it was contemplated that only cadmium reagents from primary halides would be employed.[8]

Accordingly, the ester–acid chloride II was caused to react with dioctyl- and didodecylcadmium to give the keto esters III and XI, respectively, in good yields. An organocadmium reagent, didodecylcadmium, was used also to transform the dialkyl substituted tridecanoic acid (IV) to the branched ketone VII. The acid IV was obtained without difficulty from the keto ester III by the conventional Huang-Minlon modification of the Wolff-Kishner reaction.[9]

The Kolbe electrolysis reaction,[10] which provides one of the nicest means of extending a carbon chain, was employed to convert the acid-ester I to the acid IV, and the dialkyl substituted ketoheptadecanoic acid XII to the highly substituted ketone XIII. An electrolytic cell was employed with smooth platinum electrodes of about 150 cm.^{2} area. With this apparatus, the reactions could be carried out at a current of approximately 10 amp. at about 100 volts. The successful reactions were accomplished in yields of 30–50% in methanol with a concentration of sodium ion of about 0.05 molar. Water and isopropyl alcohol were tried as solvents, but none of the expected acid could be isolated from these runs.

The ketones VII and XIII were taken to the tetraalkylmethanes X and XIV by way of intermediate alcohols and olefins, such as VIII and IX. In the case of the transformation XIII→XIV, the intermediates were not isolated. The ketones were reduced catalytically over copper–chromium oxide and Raney nickel catalysts, with the latter appearing to be the more effective. The results of the high pressure reductions of the ketones were disappointing in that the yields were nowhere near quantitative.

The secondary alcohols were dehydrated easily at reduced pressure over potassium acid sulfate to give mixtures of olefins. The latter were reduced in the presence of Raney nickel catalyst at 150°. This relatively higher temperature appeared to be necessary to complete the reductions. The products were washed repeatedly with cold, concentrated sulfuric acid to remove any traces of olefins.

(8) J. Cason, *Chem. Revs.*, 40, 15 (1947).
(9) Huang-Minlon, *J. Am. Chem. Soc.*, 68, 2487 (1946).
(10) For leading references see B. W. Baker, R. P. Linstead, and B. C. L. Weedon, *J. Chem. Soc.*, 2218 (1955) and S. Stallberg-Stenhagen, *Arkiv Kemi*, 6, 537 (1954).

Infrared absorption spectra of the quaternary hydrocarbons X and XIV indicated that they were free of olefins and oxygen containing compounds which had been employed as intermediates in the syntheses.

The twenty-six carbon hydrocarbon, 11-ethyl-11-methyltricosane (X), was found to melt at −6 to −7° while the twenty-eight carbon compound, 11-ethyl-11-methylpentacosane (XIV), had a melting point of 6 to 8°. Their straight chain analogs are reported[11] to melt at 56–57° and 61–72°, respectively.

EXPERIMENTAL[12]

Methyl hydrogen 3-ethyl-3-methylglutarate (I). 3-Ethyl-3-methylglutaric acid[13] (334 g.) was converted to its anhydride by heating at 125–130°/25 mm. The material (275 g.) which distilled at 160–170°/25 mm. was collected and a small sample was converted to 3-ethyl-3-methylglutaric acid mono-α-naphthamide for identification purposes, m.p., 126–127°; lit.[14] anhydride, b.p. 185°/20 mm., mono-α-naphthamide, m.p. 126°. This anhydride (274 g.) was heated under reflux for 2 hr. with 100 ml. of methanol and the reaction mixture was distilled. There was obtained 250 g. (75%) of the acid ester (I); b.p. 128–130°/2 mm., n_D^{25} 1.4470.

Anal. Calcd. for $C_9H_{16}O_4$: C, 57.43; H, 8.57; neut. equiv. 188. Found: C, 57.62; H, 8.51; neut. equiv. 189.

Reaction of ethylmagnesium bromide with 3-ethyl-3-methylglutaric anhydride. A solution of 23.5 g. (0.16 mole) of 3-ethyl-3-methylglutaric anhydride in 100 ml. of dry ether and 100 ml. of dry pyridine was cooled in a Dry Ice–acetone bath. It was stirred vigorously while 0.16 mole of ethylmagnesium bromide in 100 ml. of ether was added dropwise over a period of 1 hr. An insoluble, yellow complex formed as the Grignard reagent was added. The reaction mixture was stirred for an additional hour and was decomposed by pouring onto an ice and saturated ammonium chloride solution. A vigorous evolution of gas took place. The ether layer was separated and the water solution was extracted several times with ether. The combined ether solutions were extracted with 4 portions of 5% sodium bicarbonate solution and these extracts were acidified then with hydrochloric acid. Extraction of this mixture with ether afforded 2 g. of an oil which boiled at 165–170°/18 mm. It gave a positive test with 2,4-dinitrophenylhydrazine reagent, but failed to form an hydantoin derivative. It was caused to react with thionyl chloride, and the reaction product was treated with aniline; no anilide could be isolated.

4-Carbomethoxy-3-ethyl-3-methylbutanoyl chloride (II). A mixture of 23 g. (0.12 mole) of methyl hydrogen 3-ethyl-3-methylglutarate (I) and 44 g. (0.37 mole) of thionyl chloride was allowed to stand at room temperature for 36 hr. Distillation afforded 23.9 g. (95%) of the acid chloride; b.p. 120–122°/20 mm. A sample of this material was converted to an α-naphthamide derivative for identification purposes; m.p., 71–73°.

Anal. Calcd. for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40. Found: C, 72.86; H, 7.56.

Methyl 3-ethyl-3-methyl-5-ketotridecanoate (III). A Grignard reagent was prepared from 3.15 g. (0.13 g.-atom) of magnesium, 25 g. (0.13 mole) of *n*-octyl bromide, and 150 ml. of dry ether. It was treated with 14 g. (0.07 mole) of cadmium chloride, and the ether was replaced with benzene in the usual manner. A solution of 23.9 g. (0.12 mole) of 4-carbomethoxy-3-ethyl-3-methylbutanoyl chloride (II) in 50 ml. of dry benzene was added then dropwise so that the heat of the reaction just kept the solvent refluxing. After all of the acid chloride had been added, the reaction mixture was heated under reflux for 1.5 hr., allowed to cool, and poured onto a mixture of ice and water. The benzene layer was separated and the aqueous portion was extracted with benzene. The combined benzene extracts were washed with water, 5% sodium bicarbonate solution, again with water, and dried over anhydrous calcium sulfate. After removing the drying agent and solvent, the residue was distilled to give 23 g. (70%) of product; b.p., 144–146°/1 mm., n_D^{25} 1.4460.

Anal. Calcd. for $C_{17}H_{32}O_3$: C, 71.78; H, 11.34. Found: C, 71.74; H, 11.29.

3-Ethyl-3-methyltridecanoic acid (IV). *A.* A mixture of 20 g. (0.07 mole) of methyl 3-ethyl-3-methyl-5-ketotridecanoate (III), 14 g. of potassium hydroxide (85%), 13 ml. of 85% hydrazine hydrate, and 100 ml. of diethylene glycol was heated under reflux for 2 hr. The condenser was removed and the heating was continued until the temperature in the flask had risen to 215°. The condenser was replaced and the reaction mixture was heated at reflux temperature for 5 hr. The solution was allowed to cool, was diluted with 500 ml. of water, and was made acidic to Congo Red with hydrochloric acid. The oil which separated was taken up in ether and separated from the aqueous portion. The ether extract was dried over anhydrous calcium sulfate, the ether was removed, and the residue distilled. There was obtained 9.3 g. (51%) of product which boiled at 165–170°/1 mm., n_D^{25} 1.4521.

B. The Kolbe electrolysis reactions were carried out in a 2-l. resin pot with four openings on the top flange. These were fitted with a condenser, a single-blade mechanical stirrer, a two-hole rubber through which passed a copper cooling coil, and an electrode assembly. The latter consisted of an outer smooth platinum cylinder 10 cm. long and 3 cm. in diameter, an inner smooth platinum cylinder 6 cm. long and 2.5 cm. in diameter, and a coil of 20-gage platinum wire 5 cm. long and 1 cm. in diameter placed inside the inner cylinder. The outer cylinder and the central coil were attached to a common lead, and served as the anode. The metal parts were supported on a glass frame which was inserted in a rubber stopper.

The resin pot was placed in a metal bath and water at about 20° was circulated through the cooling coil and bath.

In the resin pot were placed 188 g. (1 mole) of 4-carbomethoxy-3-ethyl-3-methylbutyric acid (I), 515 g. (3 moles) of capric acid, 4 g. of sodium dissolved in methanol, and enough additional methanol to bring the total volume to about 2 l. The stirrer was located near the bottom of the outer electrode, and the solution was stirred rapidly while a current of 7 amp. was passed through the mixture for 14 hr.

The reaction mixture was transferred to a 5-l. flask and diluted with 500 ml. of water to which had been added 80 g. of potassium hydroxide. Most of the methanol was removed by distillation, and the aqueous and organic layers were separated. The aqueous layer was washed well with ether, heated, and acidified with concentrated hydrochloric acid. The material which separated was taken up in ether, and the solution was washed with water and dried over anhydrous calcium sulfate. After evaporating the ether, the residue was distilled to give 91 g. (48%) of material which boiled at 168–171°/1 mm.; n_D^{25} 1.4515.

Anal. Calcd. for $C_{16}H_{32}O_2$: C, 74.94; H, 12.58. Found: C, 74.83; H, 12.79.

Ethyl 3-ethyl-3-methyltridecanoate (V). A solution of 100 g. (0.4 mole) of 3-ethyl-3-methyltridecanoic acid (IV) in 500 ml. of absolute ethanol and 5 ml. of concentrated sulfuric

(11) G. Egloff, *Physical Constants of Hydrocarbons*, Vol. V, Reinhold Publishing Co., N. Y., 1953, pp. 248, 258.

(12) All melting points are uncorrected. The authors are indebted to R. L. Elliott and R. E. Bolin for the semimicro carbon and hydrogen analyses. They would like also to thank Dr. E. E. Pickett for the infrared data.

(13) H. H. Farmer and N. Rabjohn, *Org. Syntheses*, **36**, 28 (1956).

(14) F. B. Thole and J. F. Thorpe, *J. Chem. Soc.*, **99**, 422 (1911).

acid was refluxed for 20 hr. under a Soxhlet extractor which contained calcium carbide to remove the water formed during the course of the reaction. The reaction mixture was poured slowly into about 1 l. of 5% sodium bicarbonate solution and the organic layer was taken up in ether. The ether solution was washed well with water, dried over anhydrous calcium sulfate, filtered, and concentrated. The residue was distilled to give 93 g. (84%) of ester; b.p., 132–133°/1 mm., n_D^{25} 1.4411.

Anal. Calcd. for $C_{18}H_{36}O_2$: C, 75.99; H, 12.76. Found: C, 75.67; H, 12.69.

3-Ethyl-3-methyltridecanoyl chloride (VI). From 103 g. (0.4 mole) of 3-ethyl-3-methyltridecanoic acid (IV) and 142 g. (1.2 moles) of thionyl chloride there was obtained 99 g. (90%) of acid chloride; b.p., 138–142°/1 mm.

Anal. Calcd. for $C_{16}H_{31}OCl$: C, 69.91; H, 11.37. Found: C, 69.86; H, 11.66.

11-Ethyl-11-methyl-13-ketotricosane (VII). A Grignard reagent was prepared from 9.4 g. (0.4 g.-atom) of magnesium, 88 g. (0.4 mole) of *n*-decyl bromide, and 250 ml. of dry ether. To this was added 36.6 g. (0.2 mole) of cadmium chloride, and the ether was replaced with dry benzene in the usual fashion. A solution of 99 g. (0.36 mole) of 3-ethyl-3-methyltridecanoyl chloride (VI) in 100 ml. of dry benzene then was added over a period of about 30 min. and the reaction mixture was heated under reflux for 2 hr. It was allowed to cool and was decomposed by pouring onto a mixture of ice and dilute sulfuric acid. The organic layer was separated, washed with water, and concentrated by distillation. The residue was distilled to give 45 g. (33%) of product; b.p., 178–183°/1 mm., n_D^{25} 1.4529.

Anal. Calcd. for $C_{26}H_{52}O$: C, 82.03; H, 13.77. Found: C, 82.20; H, 13.90.

11-Ethyl-11-methyl-13-tricosanol (VIII). A mixture of 38 g. (0.1 mole) of 11-ethyl-11-methyl-13-tricosanone (VII), 15 g. of copper–chromium oxide catalyst, and 50 ml. of methylcyclohexane was hydrogenated at 200° and 2500 p.s.i. for 9 hr. After removal of the catalyst and solvent, the residue was distilled to give 21.1 g. (55%) of material which boiled at 195–197°/0.5 mm.; n_D^{25} 1.4570.

Anal. Calcd. for $C_{26}H_{54}O$: C, 81.60; H, 14.22. Found: C, 81.91; H, 14.47.

11-Ethyl-11-methyl-12(13)tricosene (IX). A mixture of 20 g. (0.05 mole) of 11-ethyl-11-methyl-13-tricosanol (VIII) and 10 g. of potassium acid sulfate was heated at 150–170°/1 mm. for 10 hr. It was filtered and the filtrate was distilled to give 13.5 g. (71%) of a mixture of olefins which boiled at 176–179°/1 mm., n_D^{25} 1.4541.

Anal. Calcd. for $C_{26}H_{52}$: C, 85.63; H, 14.37. Found: C, 85.77; H, 14.52.

11-Ethyl-11-methyltricosane (X). A mixture of 14 g. (0.04 mole) of 11-ethyl-11-methyl-12(13)-tricosene (IX), 6 g. of Raney nickel catalyst, and 50 ml. of methylcyclohexane was hydrogenated at 150° and 2500 p.s.i. for 6 hr. After removal of the catalyst and solvent, the residue was distilled to afford 9.6 g. (69%) of a fraction which boiled at 180–188°/1 mm. This was washed 3 times with concentrated sulfuric acid, then with water, 5% sodium bicarbonate solution, and again with water. Upon redistillation the hydrocarbon boiled at 185–188°/1 mm., n_D^{25} 1.4496.

Anal. Calcd. for $C_{26}H_{54}$: C, 85.15; H, 14.84. Found: C, 85.20; H, 15.13.

Methyl 3-ethyl-3-methyl-5-ketoheptadecanoate (XI). A Grignard reagent was prepared from 150 g. (0.6 mole) of dodecyl bromide and 15.7 g. (0.65 g.-atom) of magnesium in 200 ml. of anhydrous ether. It was treated with 64 g. (0.35 mole) of anhydrous cadmium chloride, and the ether was replaced with 150 ml. of dry benzene in the usual fashion. A solution of (103 g. 0.5 mole) of 4-carbomethoxy-3-ethyl-3-methylbutanoyl chloride (II) in 200 ml. of benzene was added dropwise then to the organocadmium reagent. After all had been added, the mixture was heated to reflux for 2 hr., allowed to cool and poured onto ice and sulfuric acid. The benzene layer was separated, washed with water, 5% sodium bicarbonate solution, water, saturated sodium chloride solution, and finally dried over anhydrous calcium sulfate. The solvent was removed by distillation and the residue was distilled. The material which boiled at 165–195°/1 mm. was collected, and it solidified partially upon standing. It was dissolved in methanol, and on cooling there was obtained 7 g. of a white solid; m.p., 47–50°. It was presumed to be tetracosane; lit.,[15] m.p. 50–52°. The methanol was removed by distillation and the residual keto ester was distilled. There was obtained 96.5 g. (57%) of material which boiled at 178–180°/1 mm., n_D^{25} 1.4520.

Anal. Calcd. for $C_{21}H_{40}O_3$: C, 74.06; H, 11.84. Found: C, 74.04; H, 11.98.

3-Ethyl-3-methyl-5-ketoheptadecanoic acid (XII). A mixture of 94 g. (0.28 mole) of methyl 3-ethyl-3-methyl-5-ketoheptadecanoate (XI), 40 g. (1 mole) of sodium hydroxide and 1.25 l. of water was heated under reflux for 4 hr., allowed to cool, acidified with concentrated hydrochloric acid, and extracted with ether. The ether solution was concentrated and distilled to give 90 g. (99%) of acid; b.p., 201–202°/1 mm., n_D^{25} 1.4600.

Anal. Calcd. for $C_{20}H_{38}O_3$: C, 73.57; H, 11.73. Found: C, 73.46; H, 11.63.

11-Ethyl-11-methyl-13-pentacosanone (XIII). The previously described apparatus for the Kolbe electrolysis was employed. In the resin flask were placed 90 g. (0.28 mole) of 3-ethyl-3-methyl-5-ketoheptadecanoic acid (XII), 258 g. (1.5 moles) of capric acid, 2 g. of sodium dissolved in methanol, and enough methanol to bring the volume of the solution to approximately 2 l. A current of 7–8 amp. was passed through the reaction mixture for 8 hr. It was transferred to a 3-l. flask, 56 g. (0.85 mole) of 85% potassium hydroxide was added, and the mixture was distilled slowly until 500 ml. of methanol had been collected. To the residue was added 1 l. of water and the distillation was continued until the temperature of the distillate reached 100°. The mixture was allowed to cool, the layers were separated, and the aqueous layer was extracted twice with petroleum ether (b.p. 60–68°). The aqueous solution was acidified, extracted with ether, and worked up to give 21 g. of crude 3-ethyl-3-methyl-5-ketoheptadecanoic acid; b.p. 130–185°/1 mm.

The combined organic layers were washed with water, the petroleum ether removed by distillation, and the residue was distilled to afford 27.4 g. (25%) of ketone which boiled at 215–217°/0.5 mm., n_D^{25} 1.4521.

Anal. Calcd. for $C_{23}H_{66}O$: C, 82.27; H, 13.81. Found: C, 82.04; H, 13.97.

11-Ethyl-11-methylpentacosane (XIV). A mixture of 27.4 g. (0.07 mole) of 11-ethyl-1-methyl-13-pentacosanone (XIII), 10 g. of Raney nickel catalyst, and 50 ml. of methylcyclohexane was hydrogenated at 150° and 2700 p.s.i. for 10 hr. The catalyst was removed by filtration, and the filtrate was concentrated to remove the solvent. The residue was heated then with 10 g. of potassium acid sulfate at 150–160°/1 mm. for 8 hr. The reaction mixture was filtered to remove the dehydrating agent. The filtrate was distilled to give 16.1 g. of a mixture of olefins which boiled at 190–197°/0.5 mm.; n_D^{25} 1.4531. This material was dissolved in 50 ml. of methylcyclohexane, 6 g. of Raney nickel catalyst was added, and the mixture was hydrogenated at 150° and 2000 p.s.i. for 7 hr. The catalyst was removed by filtration and the solvent was evaporated. The residue was treated with three 25-ml. portions of concentrated sulfuric acid. The hydrocarbon was dissolved in petroleum ether (b.p. 60–68°) and the solution was washed with water, 5% sodium bicarbonate solution, again with water, and dried. After removing the solvent, there was obtained 10.1 g. (43% based on original ketone) of hydrocarbon which boiled at 181–183°/1 mm., n_D^{25} 1.4496.

Anal. Calcd. for $C_{28}H_{58}$: C, 85.19; H, 14.81. Found: C, 85.40; H, 14.98.

COLUMBIA, MO.

(15) Ref. (11), p. 244.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, LUTHER COLLEGE]

A Rearrangement of *p*-Benzoquinonedioxime to *p*-Nitroaniline[1]

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When *p*-benzoquinonedioxime is heated in polyphosphoric acid at 130–140° it rearranges to *p*-nitroaniline. Two bis(benzenesulfonyl) derivatives of *p*-benzoquinonedioxime have been prepared.

The possibility that a Beckmann rearrangement of *p*-benzoquinonemonoxime would lead to a seven-membered, heterocyclic compound related to tropolone stimulated a reexamination[2–4] of the yellow product formed by heating the benzenesulfonyl derivative of *p*-benzoquinonemonoxime in pyridine.[5] This yellow product, however, proved to be *p*-azoxyphenol, not a Beckmann rearrangement product.

Horning and co-workers discovered that polyphosphoric acid is an efficient and specific agent which effects the Beckmann rearrangement of oximes that had not previously been observed to rearrange with conventional catalysts.[6] We thought it desirable, therefore, to investigate the action of polyphosphoric acid on both the monoxime and the dioxime of *p*-benzoquinone.

When *p*-benzoquinonemonoxime was heated in polyphosphoric acid, extensive decomposition occurred with evolution of gaseous products. Only tars were found in the diluted reaction mixture. The benzenesulfonate of the monoxime in polyphosphoric acid either at elevated temperatures or at room temperature, underwent no reaction other than tar formation.[7] A portion of the starting material was recovered in most cases either as the monoxime or as the benzenesulfonate.

The dioxime of *p*-benzoquinone proved to be much more stable in polyphosphoric acid. This substance could be recovered nearly quantitatively from a reaction mixture which had been heated briefly to 130°. Heating the dioxime with polyphosphoric acid for 90 minutes produced *p*-nitroaniline in 40–45% yield. A small amount of the dioxime was also recovered. The *p*-nitroaniline was identified by conversion to *p*-nitroacetanilide and *p*-nitrobenzenesulfonanilide. Mixed melting points with authentic samples were used in each case. The recovered dioxime was identified by melting point and formation of dinitrosobenzene by potassium ferricyanide oxidation.[8]

Several unsuccessful attempts were made to promote the rearrangement to *p*-nitroaniline by the use of sulfuric acid. In concentrated acid or in non-aqueous dilute solutions decomposition was the only reaction observed.

The bis(benzenesulfonate) of the dioxime was next investigated in view of the increased ease with which certain oxime sulfonates undergo the Beckmann rearrangement.[9] The synthesis of the bis(benzenesulfonyl) derivative (m.p. 175–178°) by the action of benzenesulfonylchloride in pyridine solution was reported by Beckmann and Liesche.[5] By the same procedure we obtained a product from which two white substances were separated by fractional crystallization. These appear to be derivatives of the syn and anti forms of the dioxime. One form melts with decomposition at 157–158°, the other with decomposition at 196–197° (203–204° in a preheated bath).

These two substances are considered to be geometrical isomers on the basis of the carbon, hydrogen, and nitrogen analyses, and on the basis of a comparison of the ultraviolet absorption spectra with those of *p*-benzoquinonedioxime and its diacetate. The ultraviolet spectrum of each of these substances has a single, broad absorption maximum: *p*-benzoquinonedioxime, 318 mμ; the diacetate, 303 mμ; the higher melting bis(benzenesulfonate), 307 mμ, ϵ = 48,300 in CH_2Cl_2; the lower melting, 305 mμ, ϵ = 39,800 in CH_2Cl_2.

In the study of the effect of polyphosphoric acid on the bis(benzenesulfonate) of the dioxime a mixture of the two forms was used. This disulfonate required a higher temperature for the reaction than the dioxime itself, and from the reaction mixture *p*-nitroaniline was obtained in low yield with a small amount of the dioxime.

EXPERIMENTAL[10]

p-Benzoquinonemonoxime. The monoxime was prepared by acidification of a solution of *p*-nitrosophenol sodium salt (EKC 2354). The dried, impure *p*-nitrosophenol was dissolved in ether and treated with decolorizing carbon until a pure green solution was obtained. This solution was diluted with an equal volume of petroleum ether, b.p. 35–60°, and

(1) This work was supported by a Frederick Gardner Cottrell Grant from the Research Corporation.

(2) R. A. Raphael and E. Vogel, *J. Chem. Soc.*, 1958 (1952).

(3) N. J. Leonard and J. W. Curry, *J. Org. Chem.*, **17**, 1071 (1952).

(4) Unpublished work done in this laboratory.

(5) E. Beckmann and O. Liesche, *Ber.*, **56**, 1 (1923).

(6) E. C. Horning, V. L. Stromberg, and H. A. Lloyd, *J. Am. Chem. Soc.* **74**, 5153 (1952).

(7) J. L. Tveten performed a part of the investigation of this reaction.

(8) R. Nietski and F. Kehrmann, *Ber.*, **28**, 342 (1895).

(9) B. Jones, *Chem. Revs.*, **35**, 335 (1944).

(10) All melting points are uncorrected.

cooled to −20°. The crystalline material obtained was pale tan in color and melted at 137° with decomposition.

p-Benzoquinonedioxime was prepared by the method of J. H. Trepagnier.[11] Decomposition of our samples began in the range 230° to 240°.

p-Benzoquinonedioxime to p-Nitroaniline. Three g. (0.0217 mole) of the dioxime and 170 g. of polyphosphoric acid (Victor Chemical Works, 115% ortho equivalent) in a 200 ml., 3-necked flask were heated by an oil bath to 133–137° for 90 min. with rapid stirring. The reaction mixture was poured over a 400–500 ml. volume of crushed ice. The purple, aqueous solution was filtered by suction to remove a small amount of black, gummy material and then extracted 12–14 times with 50 ml. portions of ether.

The combined ether extracts were washed with two portions of 10% sodium hydroxide, dried over anhydrous magnesium sulfate, and distilled. The residue, after removing the last trace of solvent i.v., weighed 1.26 g. (42%) and melted only one degree lower than pure *p*-nitroaniline. Identification was made by conversion to the acetyl and benzenesulfonyl derivatives and determination of mixed melting points with authentic samples.

The sodium hydroxide wash solution was neutralized to *p*H 7.5–8 and extracted four times with ether, yielding 0.1 g. of the dioxime.

p-Benzoquinonemonoxime benzenesulfonate. A modification of previously published procedures was used.[3,5,12] To 6.0 g. (0.049 mole) of nitrosophenol dissolved in 70 ml. of pyridine was added slowly 8.6 g. (0.049 mole) of benzenesulfonyl chloride, keeping the temperature of the reaction mixture under 25°. After the reaction mixture had been allowed to stand for 5 min., water was added slowly, with cooling, to precipitate the benzenesulfonate. The product was filtered, washed with 3*N* HCl and water until the odor of pyridine had been removed, and dried in a vacuum desiccator. The yield was 11.2 g. (94%) of fine, yellow needles, m.p. 130–131°, sufficiently pure for the subsequent steps. Pure material can be obtained by recrystallization from ether, m.p. 132.5–133°.[3]

p-Benzoquinonedioxime bis(benzenesulfonate)s. To 4 g. (0.029 mole) of *p*-benzoquinonedioxime dissolved in 45 ml. of pyridine was slowly added 14.8 g. (0.87 mole) of benzenesulfonyl chloride keeping the temperature of the reaction mixture under 55°. After 5 minutes of shaking, the reaction mixture was diluted with 150 ml. of water. The resulting precipitate was filtered, washed with 3*N* HCl and water, and dried in a vacuum desiccator. The yield was 11.95 g. (95%) of tan product which decomposed and sintered over the range 160–170°.

This product was recrystallized, with decolorization, from acetone to effect the primary separation of the high and low melting forms. The granules which formed, consisting mainly of the higher melting form, were filtered and dried, and purified by repeated crystallization from dry acetone. Sparkling, chunky crystals, m.p. 196–197° (dec.), or 203–204° (dec.) in a preheated bath.

Anal. Calcd. for $C_{18}H_{14}O_6N_2S_2$: C, 51.66; H, 3.37; N, 6.70; S, 15.33. Found: C, 52.15; H, 3.65; N, 6.85; S, 16.01.

To the filtrate from the primary separation was added enough water to precipitate the remainder of the derivative. By recrystallization of this product from carbon tetrachloride, the pure low melting form was obtained. Small white needles, m.p. 157–158° (dec.).

Anal. Calcd. for $C_{18}H_{14}O_6N_2S_2$: C, 51.66; H, 3.37; N, 6.70; S, 15.33. Found: C, 51.38; H, 3.43; N, 6.21; S, 15.43.

DECORAH, IOWA

(11) U. S. Patent 2,446,165, *Chem. Abstr.*, 42, 8213d (1948).

(12) E. Bornstein, *Ber.*, 29, 1484 (1896).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY STATE UNIVERSITY OF IOWA]

Abnormal Beckmann Rearrangement of 9,10-Dihydro-9,10-(11-ketoethano)anthracene Oxime[1]

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9,10-Dihydro-9,10-(11-ketoethano)anthracene oxime undergoes an abnormal Beckmann rearrangement when treated with either phosphorus pentachloride, benzenesulfonyl chloride and alkali, polyphosphoric acid, boron trifluoride, or hydrogen chloride. The first two reagents formed 9-anthranylacetonitrile while the last three gave 9-anthranylacetamide. The structures of these two products were demonstrated by synthesis.

In previous work on the determination of the importance of three dimensional structures in the analgetic behavior of compounds, 9,10-dihydro-9,10-(11-aminoethano)anthracenes were synthesized and found to be inactive as analgetics.[3]

Attempts to modify this three dimensional structural feature by including the nitrogen in the bridge is described in the present work. A Beckmann rearrangement of 9,10-dihydro-9,10-(11-ketoethano)-anthracene oxime (I) was tried with phosphorus pentachloride and found to yield 9-anthranylacetonitrile (II). This reaction is analogous to the second order Beckmann rearrangement observed with the oximes of aldehydes, pivalophenone[4] and other tertiary ketones[5] under similar conditions.

Since benzenesulfonyl chloride and alkali and hydrogen chloride in acetic acid often give a normal rearrangement with some of these examples,[4] these reagents were also tried on the oxime I. The first of these gave the nitrile II while the

(1) Abstracted in part from the Ph.D. thesis of J. V. Hallum, August 1952.

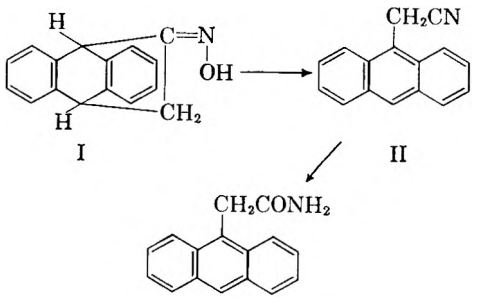
(2) Public Health Research Fellow of the National Institutes of Health, 1951–52.

(3) S. Wawzonek and J. V. Hallum, *J. Org. Chem.*, 18, 288 (1953).

(4) R. F. Brown, N. M. van Gulick, and G. H. Schmid, *J. Am. Chem. Soc.*, 77, 1094 (1955).

(5) R. E. Lyle and G. G. Lyle, *J. Org. Chem.*, 18, 1058 (1953).

second one produced a mixture of the amide III and the nitrile II in which the former predominated. The newer Beckmann reagents, polyphosphoric acid[6] and boron trifluoride,[7] behaved similarly and



I II III

caused a rearrangement to 9-anthranylacetamide (III). Abnormal Beckmann rearrangements have already been reported for polyphosphoric acid.[8] The present example is the first observed using boron trifluoride.

The structure of the nitrile was demonstrated by synthesis from 9-chloromethylanthracene using sodium cyanide and by the catalytic reduction of α-benzoxy-9-anthranylacetonitrile. The other compound possible from the Beckmann reaction, 9-methyl-10-cyanoanthracene, was also synthesized from 10-methyl-9-anthraldehyde oxime and was found to be different from the Beckmann rearrangement product (II).

The identity of 9-anthranylacetamide (III) was demonstrated by its formation in the hydrolysis of the acetonitrile (II) with boron trifluoride in acetic acid and water. The use of sulfuric acid in this reaction gave mainly a mixture of 9-anthranylacetic acid and its decarboxylated product, 9-methylanthracene.

The observed abnormal Beckmann rearrangement is unique in that no tertiary groups are attached to the ketone moiety in the molecule. The tendency to form an aromatic system by the loss of a proton in the group involved, seems to be the driving force in this example.

EXPERIMENTAL[9]

9-Anthranylacetonitrile (II). (*a*) 9,10-Dihydro-9,10-(11-ketoethano)anthracene oxime[3] (25 g.) was dissolved in 300 g. of phosphorus oxychloride at 0° and phosphorus pentachloride (30 g.) was added slowly keeping the temperature below 10°. The resulting solution was heated to reflux and poured onto ice. The pale green solid (21.8 g.) was filtered and after crystallization twice from petroleum ether (b.p. 86–100°) and once from acetic acid, melted at 161–3°.

Anal. Calcd. for $C_{16}H_{10}N$: C, 88.48; H, 5.07; N, 6.45. Found: C, 88.03; H, 4.89; N, 6.96.

(*b*) The oxime (II) (1.17 g.) was mixed with benzenesulfonyl chloride (0.9 g.), and sodium hydroxide (0.5 g.) in 20 ml. of acetone containing 5 ml. of water and refluxed for 2 hr. The resulting dark red solution upon pouring into water gave 0.85 g. of the nitrile melting at 159–162° after one recrystallization from acetic acid.

(*c*) 9-Chloromethylanthracene[10] (0.4 g.) in 20 ml. of 95% ethanol was refluxed with sodium cyanide (0.1 g.) in 1 ml. of water for 1 hr. Concentration of the solution gave the nitrile (II) (0.1 g.) melting at 159–163° after one crystallization from acetic acid.

(*d*) α-Benzoxy-9-anthranylacetonitrile (1 g.) was refluxed in 10 ml. of tetralin with palladium black (0.2 g.) for 19 hr. Removal of the tetralin and naphthalene by steam distillation gave the nitrile (II) (0.25 g.) melting at 162–164° after crystallization from petroleum ether (86–100°) and acetic acid respectively.

9-Anthranylacetamide (III). (*a*) 9,10-Dihydro-9,10-(ketoethano) anthracene oxime (2.35 g.) was heated with stirring with polyphosphoric acid (64 g.) at 100–130° for 5 min. and at 130° for an additional 5 min. The resultant dark green solution was cooled and poured into water. The gray solid (2.05 g.) obtained after successive crystallizations from ethyl acetate and ethanol gave yellow needles melting at 253–6° (dec.).

Anal. Calcd. for $C_{16}H_{13}ON$: C, 81.70; H, 5.53. Found: C, 81.31; H, 5.31.

(*b*) 9,10-Dihydro-9,10-(11-ketoethano)anthracene oxime (I) (2.0 g.) in 20 ml. of acetic acid was treated with gaseous boron trifluoride until the solid went into solution. Addition of water and dilute sodium hydroxide precipitated 1.8 g. of 9-anthranylacetamide (III).

(*c*) The oxime I (5.0 g.) in acetic acid (110 ml.) was treated with gaseous hydrogen chloride for 30 min. and the resulting solution was allowed to stand for 24 days. The solution was resaturated with hydrogen chloride several times during this period. The solid (2.3 g.) was filtered off and melted at 250–255° (dec.). The filtrate was poured into water and extracted with methylene chloride. The extract after washing with sodium carbonate solution was concentrated and gave an additional 0.92 g. of the amide (III). Further concentration gave a mixture (0.25 g.) of the amide (III) and the oxime (I). Evaporation to dryness gave a mixture (1.5 g.) consisting of the nitrile (II), amide (III), and the oxime (I).

(*d*) 9-Anthranylacetonitrile (II) (0.5 g.) in a mixture of acetic acid (20 ml.) and water (2 ml.) was treated with gaseous BF_3 until the temperature reached 140°. The resulting solution was cooled and treated with 6*N* sodium hydroxide (130 ml.). The solid formed was filtered; yield, 0.51 g. Crystallization from ethyl acetate gave 9-anthranylacetamide melting at 253–255° (dec.).

9-Anthranylacetic Acid. 9-Anthranylacetonitrile (III) (3.0 g.) was refluxed in acetic acid (75 ml.) with 50% sulfuric acid (25 ml.) for 3 hr. The resulting solution was poured into water and extracted with ether. Extraction of the ether with sodium carbonate followed by acidification gave 9-anthranylacetic acid (1.61 g.) melting at 212–220° (dec.). Two recrystallizations from benzene gave a sample melting at 215–226° (dec.). The actual melting point varied with the rate of heating.

Anal. Calcd. for $C_{16}H_{12}O_2$: C, 81.36; H, 5.09. Found: C, 81.42; H, 5.04.

The ether layer on concentration gave impure 9-anthranylacetamide (0.25 g.) melting at 240° and 9-methylanthracene which after one crystallization from methanol melted at 75–78°; yield 0.5 g. A second crystallization gave

(6) E. C. Horning and V. L. Stromberg, *J. Am. Chem. Soc.*, **74**, 2680 (1952).

(7) C. R. Hauser and D. S. Hoffenberg, *J. Org. Chem.*, **20**, 1482 (1955).

(8) R. K. Hill and R. T. Conley, *Chem. & Ind. (London)*, 1314 (1956).

(9) Melting points are not corrected.

(10) W. T. Hunter, J. S. Buck, F. W. Gubitz, and C. H. Bolen, *J. Org. Chem.*, **21**, 1512 (1956).

a sample melting at 79–81°. Comparison of this material with an authentic sample[11] confirmed this structure.

α-Benzoxy-9-anthranylacetonitrile. To a mixture of 9-anthraldehyde[12] (4.6 g.) and benzoyl chloride (3.5 g.) in 30 ml. of dioxane at 0–5°, sodium cyanide (2.5 g.) in water (40 ml.) was added dropwise with stirring during the course of 1 hr. The resulting solution after stirring for an additional 2 hr. and standing at room temperature overnight was poured into water. The resulting oil solidified on standing and was taken up in ether. Partial removal of the solvent gave crystals melting at 146–150°; yield 1.8 g. Two successive crystallizations from benzene and from ethyl acetate, respectively, gave a sample melting at 148.5–150°.

Anal. Calcd. for $C_{23}H_{15}O_2N$: C, 81.90; H, 4.45. Found: C, 81.63; H, 4.44.

Further concentration of the ether gave 2.0 g. of anthraldehyde.

9-Methyl-10-cyanoanthracene. 9-Methyl-10-anthraldehyde oxime[13] (0.94 g.) was refluxed with 20 ml. of acetic anhydride for 15 min. The solution after cooling was poured into water and gave 0.80 g. of 9-methyl-10-cyanoanthracene melting at 208–210°. One recrystallization from a mixture of benzene and 60–68° petroleum ether melted at 208–210°. A mixture with the above oxime melted at 170–178°.

Anal. Calcd. for $C_{16}H_{11}N$: C, 88.48; H, 5.07. Found: C, 87.76; H, 5.02.

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(11) L. Fieser and J. L. Hartwell, *J. Am. Chem. Soc.*, 60, 2555 (1938).

(12) L. F. Fieser, J. L. Hartwell, and J. E. Jones, *Org. Syntheses*, Coll. Vol. III, 98 (1955).

(13) L. F. Fieser and J. E. Jones, *J. Am. Chem. Soc.*, 64, 1666 (1942).

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

Acenaphthene Chemistry. V.[1] 1,2-Diketopyracene[2]

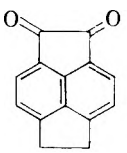
HENRY J. RICHTER AND FREDERICK B. STOCKER

Received September 4, 1958

1,2-Diketopyracene was prepared by the reaction of oxalyl bromide and acenaphthene with aluminum bromide as the catalyst. Reduction of the diketone formed pyracene. The reaction of 1,2-diketopyracene with phenylmagnesium bromide formed 1,2-diphenyl-1, 2-dihydroxypyracene which was oxidized to 5,6-dibenzoylacenaphthene.

The older literature describing attempts to synthesize compounds containing two five-membered rings fused to the opposite *peri* positions of naphthalene has been reviewed by Kloetzel and Chubb.[3] These authors prepared 1,2-benzopyracene. Anderson and Wade[4] synthesized the unsubstituted hydrocarbon, pyracene.

In one of the early attempts to prepare a compound with the pyracene ring system, Fleischer and Wolff[5] treated acenaphthene with oxalyl bromide in the presence of aluminum chloride and obtained an impure compound which was described as pyracene hemiquinone (1,2-diketopyracene, I). The analysis did not confirm this suggested structure. We repeated their experiment and obtained in low yield the yellow product which they described as pyracene hemiquinone. It was purified chromatographically and shown to correspond to di-5-acenaphthyl ketone (II) described by Dziewonski and co-workers.[6] This product was not totally unexpected since it is known that oxalyl halides decompose to carbon monoxide and carbonyl halide.[7] Liebermann[8] obtained 5-acenaphthoic acid from acenaphthene and oxalyl chloride with aluminum chloride catalyst and in our experiment, also, some of the acid was obtained.



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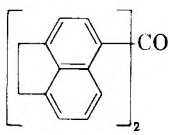

II

With aluminum bromide as the catalyst we obtained yellow needles, m.p. 305–306°. This new substance formed a bisulfite addition compound and a quinoxaline derivative indicating 1,2-diketopyracene (I). A Clemmensen reduction of the 1,2-diketone formed pyracene which was confirmed by a mixed melting point determination with an authentic sample.[9]

In previous work[1] it was shown that the dibenzoylation of acenaphthene with aluminum chloride as catalyst formed 3,6-dibenzoylacenaphthene m.p. 149–150°. The 5,6-dibenzoyl derivative, m.p. 207–208°, was obtained from 1,2-diketopyracene by reaction with phenylmagnesium bromide and oxidizing the resulting 1,2-diphenyl-1,2-pyra-

(1) Previous paper: H. J. Richter and F. B. Stocker, *J. Org. Chem.*, 24, 214 (1959).

(2) This work was supported by the National Institute of Health, Grant Cy-2997-Cy; taken from a portion of the thesis submitted by F.B.S. to the University of Colorado, in partial fulfillment of the requirements for the Ph.D. degree, 1958.

(3) M. C. Kloetzel and F. L. Chubb, *J. Am. Chem. Soc.*, 72, 150 (1950).

(4) A. G. Anderson, Jr., and R. H. Wade, *J. Am. Chem. Soc.*, 74, 2274 (1952).

(5) K. Fleischer and P. Wolff, *Ber.*, 53, 925 (1920).

(6) K. Dziewonski, W. Kahl, W. Koezoroska, and A. Wulffsohn, *Bull. intern. acad. polon.*, A, 194 (1933).

(7) R. C. Fuson, *Advanced Organic Chemistry*, John Wiley and Sons, Inc., New York, N. Y., 1950, p. 335.

(8) C. Liebermann and M. Zsuffa, *Ber.*, 44, 202 (1911).

(9) We are indebted to Prof. Anderson[4] for supplying us with a sample of pyracene.

cenediol with lead tetraacetate. A study of the glycols prepared from I is currently in progress.

EXPERIMENTAL

The reaction of oxalyl bromide and acenaphthene with aluminum chloride as the catalyst. Di-5-acenaphthyl ketone. This reaction was carried out as described by Fleischer and Wolff.[5] The crude product obtained from the reaction of 0.2 mole acenaphthene and 0.2 mole oxalyl bromide was extracted with 2 l. of boiling benzene. The benzene solution was in turn extracted with 10% aqueous sodium carbonate solution, which on acidification gave 4.56 g. of a cream colored solid, m.p. 212–214°, which was shown to be 5-acenaphthoic acid. The benzene solution was evaporated to dryness and the resulting yellow-brown residue was chromatographed on an alumina column. Elution with benzene gave a small amount of bright yellow crystals, m.p. 220–226°. Four recrystallizations from benzene raised the melting point to 237–238° (lit. 234–235°).[6] This was reported as 1,2-diketopyracene, m.p. 226°.[5]

Anal. Calcd. for $C_{25}H_{18}O$: C, 89.79; H, 5.42. Found: C, 90.23; H, 5.42.

1,2-Diketopyracene. Anhydrous aluminum bromide (62.5 g., 0.2 mole) was added in portions to a stirred solution of 0.1 mole (17.6 g.) of acenaphthene and 0.1 mole (25 g.) of oxalyl bromide in 1400 ml. of dry carbon disulfide maintained at 0°. After warming to room temperature overnight the mixture was maintained at 35° for 30 min. The carbon disulfide was decanted from the dark residue which was then hydrolyzed with cold dilute hydrochloric acid. Steam was passed through the hydrolyzed mixture to remove residual carbon disulfide. The carbon disulfide decanted from the reaction mixture did not contain any reaction product. The brown residue (20.0 g.) was extracted with hot toluene. This toluene solution was extracted with 10% aqueous sodium carbonate and then extracted exhaustively with saturated sodium bisulfite solution. A precipitate of the bisulfite addition compound formed in the aqueous layer. This was removed by filtration and treated with dilute sodium hydroxide to liberate the diketone which was combined with the precipitate obtained by treating the sodium bisulfite extract with solid sodium carbonate. There was obtained 3.85 g. (16.2%) of product m.p. 303–304°. The yields in subsequent preparations were very inconsistent. It was crystallized from methyl ethyl ketone and then from acetone to yield orange-yellow needles, m.p. 305–306°. It was found advantageous to extract with aqueous sodium bisulfite at 80° as outlined for the isolation of acenaphthenequinone.[10]

Anal. Calcd. for $C_{14}H_8O_2$: C, 80.76: H, 3.87. Found: C, 81.01; H, 3.87.

In the first preparation of this compound, oxalyl bromide (44.0 g., 0.204 mole) in 100 ml. of carbon disulfide was added dropwise during the course of 1.5 hr. to a solution of 112.0 g. (0.420 mole) of anhydrous aluminum bromide and 31.0 g. (0.201 mole) of acenaphthene in 250 ml. of dry carbon disulfide. The mixture was kept at 0° during the addition and for 6 hr. after the addition. A brown sticky mass separated which made stirring difficult. The carbon disulfide was decanted and the brown solid remaining (54.0 g.) was extracted with hot toluene. The product was isolated by bisulfite extraction. This preparation gave only 0.50 g. (1.2%) 1,2-diketopyracene, m.p. 303–304°. Evaporation of the toluene left a brown residue from which di-5-acenaphthyl ketone was obtained.

When acenaphthene dissolved in carbon disulfide was added dropwise to a solution of aluminum bromide and oxalyl bromide in the same solvent at 0° a brown solid was produced from which no di-5-acenaphthyl ketone or 1,2-diketopyracene could be isolated. At high dilution this inverse addition gave the same brown product. This substance could not be crystallized and was not investigated further.

The reaction of 1,2-diketopyracene with o-phenylenediamine. A mixture was prepared from 0.0893 g. of 1,2-diketopyracene, 0.0464 g. of *o*-phenylenediamine, and 10 ml. of glacial acetic acid. Warming for 15 min. produced a clear yellow solution. The cooled solution was poured into 200 ml. of cold water. A pale yellow precipitate formed which was removed by filtration and dried, m.p. 274–276°. The yield was quantitative. Crystallization from benzene–petroleum ether, b.p. 60–70°, gave pale yellow micro needles, m.p. 275–276°.

Anal. Calcd. for $C_{20}H_{12}N_2$: N, 10.00. Found: N, 9.76.

Pyracene. Amalgamated zinc (10 g.) was added to a mixture of 8 ml. of water, 20 ml. of concentrated hydrochloric acid, 25 ml. of toluene, and 0.50 g. of 1,2-diketopyracene. The mixture was boiled vigorously under reflux for 30 hr. Additions of 5 ml. of concentrated hydrochloric acid were made every 6 hr. The color in the toluene layer gradually changed from pale orange to yellow. The toluene layer was separated and the solvent was removed. The solid that remained was sublimed yielding very pale yellow prisms, m.p. 212–215° (sealed capillary). The sublimed solid (0.09 g., 21%) was recrystallized from cyclohexane and petroleum ether, b.p. 60–70°, to yield colorless prisms, m.p. 218–220° (sealed capillary) (lit.[2] 214.5–217.5°). The infrared spectra of an authentic sample of pyracene[9] and the compound obtained above are identical.

1,2-Diphenyl-1,2-pyracenediol. To a suspension of 1.0 g. (0.0048 mole) of 1,2-diketopyracene in 50 ml. of dry benzene was added 15 ml. of an ether solution of phenylmagnesium bromide (3.0 molar). The mixture became warm and the diketone dissolved giving an orange solution. This solution was refluxed for 29 hr. and hydrolyzed with dilute acetic acid. The benzene layer was subjected to steam distillation which left a brown oily residue. The water was decanted and the oil was dried. Attempts to crystallize the crude product were unsuccessful. An alumina column was prepared in dry petroleum ether, b.p. 60–70°, and to it was added 1.47 g. of the oil dissolved in 10 ml. of dry benzene. Elution with petroleum ether, b.p. 60–70°, removed a low melting solid (probably biphenyl). Equal portions of petroleum ether (b.p. 60–70°)–diethyl ether removed a product which separated as white needles during evaporation of the solvent. This product, m.p. 179–181° (0.67 g. 38%), was recrystallized from ethanol-water to yield white needles, m.p. 180–181°.

Anal. Calcd. for $C_{26}H_{20}O_2$: C, 85.69; H, 5.53. Found: C, 85.98; H, 5.81.

4,5-Dibenzoylnaphthalic anhydride. To a solution of 0.42 g. (0.0012 mole) of 1,2-diphenyl-1,2-pyracenediol in 20 ml. of glacial acetic acid was added 1.0 g. (0.010 mole) of chromium trioxide dissolved in a minimum of water. The mixture was heated at reflux for 2 hr. During this time a white solid separated. The cooled solution was filtered and the solid was washed with acetic acid and dried. There was obtained 0.35 g. (75%) of product, m.p. 279–283°. Crystallization from dilute acetic acid with decolorizing charcoal gave colorless prisms, m.p. 283–284°.

Anal. Calcd. for $C_{26}H_4O_5$: C, 76.84; H, 3.47. Found: C, 76.96; H 3.52.

5,6-Dibenzoylacenaphthene. To a solution of 0.12 g. (0.33 mmole) of 1,2-diphenyl-1,2-pyracenediol in 7 ml. of cold glacial acetic acid was added 0.15 g. (0.34 mmole) of lead tetraacetate and the mixture was shaken until the solid dissolved (2 to 5 min.). Colorless crystals began to separate. The mixture was allowed to stand overnight and the product was separated by filtration. The yield of crystals, m.p. 205–207°, was quantitative. One recrystallization from an alcohol-water mixture gave colorless needles, m.p. 207–208°.

Anal. Calcd. for $C_{26}H_{18}O_2$: C, 86.17; H, 5.01. Found: C, 86.32; H, 4.86.

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(10) C. F. H. Allen and J. A. Van Allen, *Organic Synthesis*, Coll. Vol. III, 1 (1955).

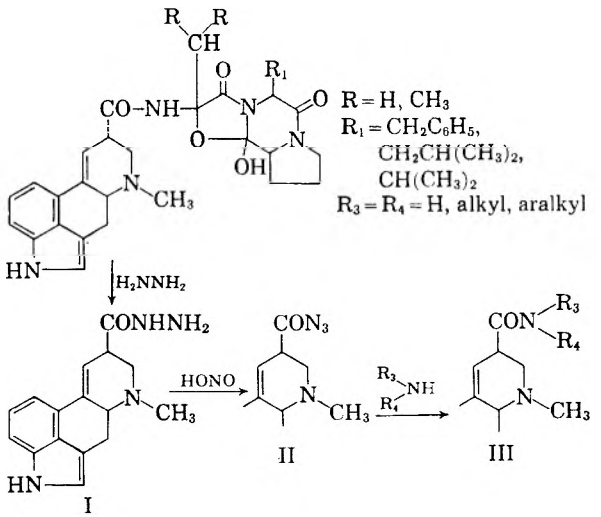
[CONTRIBUTION FROM THE DEPT. OF ORGANIC CHEMICAL DEVELOPMENT, ELI LILLY AND CO.]

Synthesis of Amides of Lysergic Acid[1]

WILLIAM L. GARBRECHT

Received September 15, 1958

Although interest in the chemistry and pharmacology of lysergic acid derivatives has remained high for many years, until recently only one useful method for converting lysergic acid into its amide derivatives has been recorded. This method as described by A. Stoll[2] consists of cleaving ergot alkaloids with hydrazine. The resulting lysergic acid hydrazide on treatment with nitrous acid is converted into the azide which may be used to prepare the desired amide by acylation of an appropriate amine.



Although this procedure is frequently capable of producing amide product in good yields, certain inherent difficulties reduce its practical value. Of these, the most important is that the necessary reaction conditions for preparing lysergic acid hydrazide result in a racemized and isomerized material, DL-isolysergic acid hydrazide. Further, the method leaves much to be desired in terms of operational ease since the azide must be collected in a relatively large volume of ether and several hours are required to carry out the acylation step.

Because optically active +-lysergic acid is readily available through aqueous alkaline cleavage of ergot alkaloids,[3] a method which utilized the free acid and caused no racemization was desired. The classical methods for preparing amides by acylation of amines with esters or acid chlorides fail when applied to lysergic acid. Thus, while the methyl[3] and ethyl[4] esters of lysergic acid are known, they fail to undergo aminolysis except in the special case already mentioned involving the use of hydrazine. On the other hand, attempts to prepare lysergic acid chloride yield only decomposition products.

Numerous new amide-forming techniques, chiefly arising from work in the peptide field, have appeared in the recent literature. Many of these were investigated with respect to lysergic acid amide synthesis. A method to be suitable for this application must operate under mild non-acidic conditions because of the sensitive nature conferred upon lysergic acid derivatives by their indole containing structure.

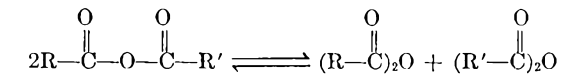
Most of the newer methods involve the application of certain mixed anhydrides. Such techniques frequently suffer from one or more of the following disadvantages:

(*a*) The reaction fails to go to completion.

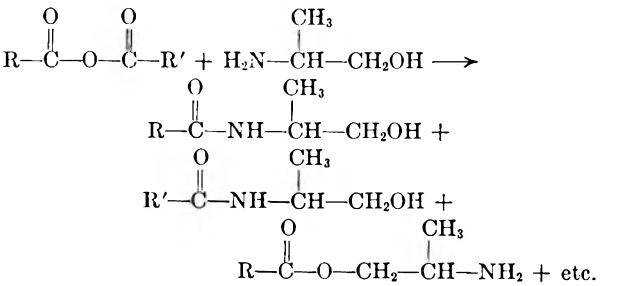
(*b*) The reaction requires higher temperatures than are compatible with the stabilities of these materials.

(*c*) The reacion system decomposes lysergic acid or its amide product because of the acidic character.

(*d*) The mixed anhydride undergoes disproportionation which contributes to reaction incompletion and/or nonspecific acylation:



(*e*) The mixed anhydride acylates in a nonspecific manner, resulting in a mixture of acylated products including esters, as well as amides where possible:



Also, two new dehydration reactions applied to peptide bond formation have been described recently, wherein an acid and an amine are caused to condense under the influence of the powerful dehydration reagents, dicyclohexylcarbodiimide and ethoxyacetylene.

(1) Presented in part before the Division of Organic Chemistry, American Chemical Society, New York, N. Y., September, 1957.

(2) A. Stoll and A. Hofmann, *Helv. Chim. Acta*, **26**, 944 (1943).

(3) W. A. Jacobs and L. C. Craig, *J. Biol. Chem.*, **104**, 547 (1934).

(4) A. Stoll and Th. Petrzilka, *Helv. Chim. Acta*, **140**, 1125 (1953).

Most of the methods examined, together with the general results obtained, are listed in Table I.

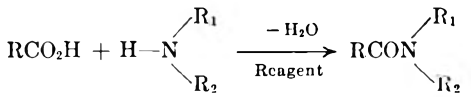
TABLE I

REACTION SYSTEMS APPLIED TO LYSERGIC ACID AMIDE SYNTHESIS

A. Mixed Anhydride Systems

Mixed Anhydride	Value of System
R—CON_3[a] (II)	Poor. Required starting material was racemized in preparation
RCOCl[b]	None. Lysergic acid decomposed
RCO_2COCF_3[c]	Good. Non-specific acylation[d]
$RCO_2CO_2C_2H_5$[e]	None. Yielded ethyl lysergate
$RCO_2PO_2C_6H_4$[f]	Poor. Low yield with decomposition
$RCO_2SO_2C_6H_4CH_3$[g]	None. Decomposed lysergic acid
$RCO_2SO_2CH_3$[h]	Fair. Moderate yield with some decomposition
RCO_2SO_3[i]	Excellent in all respects

B. Dehydration Systems



Reagent	
C_6H_5—N=C=N—C_6H_5[j]	None. Very poor yield
C_2H_5O—C≡CH[k]	None. Very poor yield

[a] A. Stoll and A. Hofmann, *Helv. Chim. Acta*, 26, 944 (1943). [b] A. Stoll and A. Hofmann, U. S. Pat. 2,090,430 (1937). [c] E. J. Bourne, S. H. Henry, C. E. M. Tatlow, and J. C. Tatlow, *J. Chem. Soc.*, 4014 (1952). [d] R. P. Pioch, U. S. Pat. 2,736,728 (1956). [e] R. A. Boissonnas, *Helv. Chim. Acta*, 34, 874 (1951). [f] G. W. Anderson and R. W. Young, *J. Am. Chem. Soc.*, 74, 5307 (1952). [g] J. H. Brewster, *J. Am. Chem. Soc.*, 77, 6214 (1955). [h] No previous reference found. [i] G. W. Kenner and R. J. Stedman, *J. Chem. Soc.*, 2069 (1952). [j] J. C. Sheehan and G. P. Hess, *J. Am. Chem. Soc.*, 77, 1067 (1955). [k] J. F. Arens, *Rec. trav. chim.*, 74, 769 (1955).

Of the methods studied, the use of the mixed anhydride of sulfuric acid and lysergic acid proved most practicable because the difficulties inherent in the other method were absent. Thus, assays for total amide produced indicated that this reaction proceeded to completion. There was no decomposition observed which could be ascribed to the reaction, since it took place readily at low temperature and at no time was the system acidic in character. Disproportionation was not encountered and no evidence of esterification was observed. The amide products were obtained free from racemization. Further, the process was carried out rapidly and with considerable experimental ease.

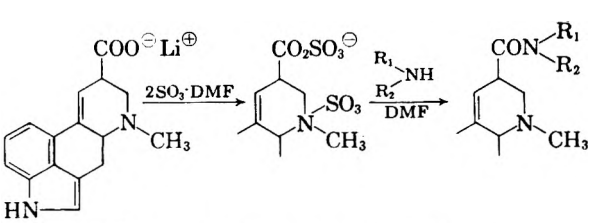
However, the yields of amide product isolated by this method were often considerably below theoretical as a consequence of the difficulties encountered in the isolation of these sensitive materials. In addition, the yield of lysergic acid amide is affected by the ever present equilibrium between the physiologically active lysergic acid series and the inactive isolysergic acid series. This equilibrium is a consequence of the possible chair conformation of ring D. Lysergic acid was deduced to possess an equatorial carboxyl group and isolysergic acid an axial carboxyl group.[5]

Fortunately, from a preparative standpoint, the amides of lysergic acid can usually be obtained as crystalline maleate or tartrate salts, while the amides of isolysergic acid generally fail to form such crystalline salts and remain in the mother liquors. Also, the equilibrium frequently favored the lysergic acid side and further amounts of it were often obtained through re-equilibration of the iso-material in the mother liquors. Thus, in spite of the difficulties cited, it was possible to obtain first crop yields of ergonovine maleate of 65%, with further amounts available through isomerization of the iso amide which remained in the mother liquor.

The stoichiometry of the reaction and the conditions necessary for its successful application were found of considerable interest. The best procedure was to dissolve +-lysergic acid monohydrate with an equivalent amount of lithium hydroxide monohydrate in methanol. The methanol was removed *in vacuo* and the residue of lithium lysergate was dissolved in dimethylformamide. A suitable amount of dimethylformamide was then distilled from the solution under reduced pressure to ensure that it was anhydrous.

The dry lithium lysergate solution was then chilled in an ice bath and a dimethylformamide solution containing two molar equivalents of sulfur trioxide was added quickly while mixing mechanically. Shortly thereafter, the reaction mixture was treated with five molar equivalents of the desired amine and then within a few minutes more a large amount of water was added and the amide product was isolated by extraction.

The success of the reaction depends very critically on the degree of adherence to the correct stoichiometry. It was for this reason that lithium hydroxide monohydrate was used, since it is nonhygroscopic and may be weighed accurately. Other alkali and alkaline earth hydroxides functioned as well but were less convenient to handle. Two molar equivalents of sulfur trioxide were required for each mole of lysergate anion, one forming the mixed anhydride and the other reacting with the piperidine nitrogen. Small deviations from the indicated ratio of sulfur trioxide to lysergate anion



(5) J. B. Stenlake, *J. Chem. Soc.*, 1626 (1955).

resulted in large decreases in the yield of amide product. Similarly, amounts of amine less than four to five molar equivalents resulted in decreased yield.

Two observations suggest that the piperidine nitrogen is complexed by the sulfur trioxide preferentially to its involvement in mixed anhydride formation: first, the stoichiometrical requirement already described, and second, the fact that the amide product can be isolated from the reaction mixture only after adding water which causes a fairly exothermic reaction to take place. This latter reaction was, doubtlessly, the hydrolysis of the sulfur trioxide complex of the tertiary nitrogen.

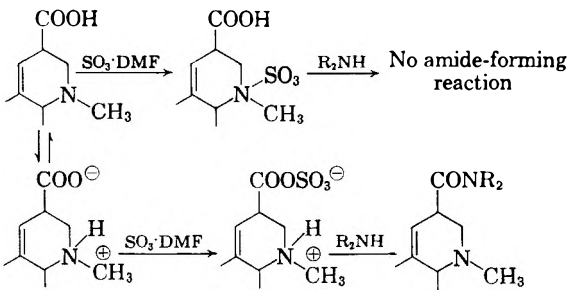
The reaction sequence was carried out very quickly since all three steps, anhydride formation, acylation, and hydrolysis, were virtually instantaneous. Reaction times from a few seconds to several hours did not materially affect the yield. Also, the reaction sequence was found to be little dependent upon temperature, proceeding well at temperatures from −20 to 35°.

Since the present work was aimed primarily towards finding a method for making the lysergic acid amide of an amino alcohol, L-2-amino-1-propanol, the fact that esters of lysergic acid were not formed from the anhydride of lysergic acid and sulfuric acid was unexpected. Not only could no trace of ester be found in this reaction, but treatment with simple alcohols failed completely to yield esters of lysergic acid.

The use of a suitable complex of sulfur trioxide was necessary to mask the extremely reactive nature of this compound and provide a convenient means of handling, storing, and measuring the reagent. Similar compounds with tertiary amines, such as *N*-ethylmorpholine or triethylamine, were found to bind the sulfur trioxide so strongly as to make it unavailable for reaction with the lysergate anion. The less stable complex with dioxane provided sulfur trioxide for reaction but was more difficult to prepare and use.

The sulfur trioxide-dimethylformamide adduct possesses nearly ideal characteristics. It readily provides sulfur trioxide for mixed anhydride formation, its solutions in excess dimethylformamide are stable in the cold for months, and dimethylformamide is the most useful solvent found for reactions involving lysergic acid. The adduct is a nicely crystalline, low melting solid which can be isolated and recrystallized from acetonitrile without decomposition.

The reaction of free lysergic acid with sulfur trioxide and subsequent treatment with excess amine gave poorer yields of amide product than those obtained with lysergate anion. Furthermore, the reaction followed a different course as was indicated by the stoichiometry. The free acid gave better yields when only one molar equivalent of sulfur trioxide was employed. The explanation probably may be found in the fact that lysergic acid, being a fairly typical amino acid, exists to some extent as the zwitterion. A representation of the reaction course is indicated below:



Although the early work was carried out using freshly prepared sulfur trioxide which was then distilled twice from phosphorus pentoxide, subsequent experimentation indicated that commercial sulfur trioxide could be added to dry dimethylformamide to give a reagent of high quality suitable for this synthesis.

EXPERIMENTAL

Sulfur trioxide-dimethylformamide complex.[6] A carefully dried, 22-liter, round bottomed flask, fitted with an ice water cooling bath, condenser, dropping funnel, and mechanical stirrer, was charged with 10 to 11 l. of dimethylformamide (freshly distilled under reduced pressure). The condenser and dropping funnel were both protected from atmospheric moisture. Two lb. of sulfur trioxide[7] were then introduced dropwise very cautiously with stirring during 4 to 5 hr. The temperature was kept at 0–5° throughout the addition. After the addition was complete, the mixture was stirred for 1–2 hr. until some separated, crystalline sulfur trioxide–dimethylformamide complex had dissolved.

The reagent was then transferred to a suitable storage vessel, such as an automatic buret system with an adequate reservoir, and kept in the cold. While the initially colorless reagent gradually becomes first yellow and then dark orange in color during storage, its efficacy remains unimpaired for at least 3 to 4 months.

The molarity of the reagent was estimated by titration. An aliquot, first diluted with a little water to convert the sulfur trioxide into sulfuric acid, was titrated to a phenolphthalein endpoint with standard aqueous alkali solution. The molarity ranged from 1.00 to 1.15.

The preparation of lysergic acid amides. General procedure. A solution of 7.15 g. of +-lysergic acid monohydrate (25.0 mmol.) and 1.06 g. of lithium hydroxide hydrate (25.0 mmol) in 200 ml. of methanol was prepared. The solvent was distilled on the steam bath under reduced pressure. The residue of glass-like lithium lysergate was dissolved in 400 ml. of anhydrous dimethylformamide. About 200 ml. of dimethylformamide was distilled at 15 mm. pressure through a 12-in. helices-packed column. The resulting anhydrous solution of lithium lysergate in dimethylformamide was cooled to 0° and, with stirring, treated rapidly with 50.0 ml. of SO_3-DMF solution (1.00 molar). The mixture was stirred in the cold for 10 min. and then 125.0 mmol. of the desired amine was added. The stirring and cooling were continued for 10 min. longer when 400 ml. of water

(6) The sulfur trioxide-dimethylformamide complex is hereinafter referred to as SO_3-DMF.

(7) Commercially available as "Sulfan B" from the General Chemical Division, Allied Chemical and Dye Corp.

was added to decompose the reaction complex. After mixing thoroughly, 200 ml. of saturated aqueous saline solution was added. The amide product was then isolated by repeated extraction with 500 ml. portions of ethylene dichloride. Tests with Van Urk reagent were used to indicate completeness of extraction.

The combined extract was dried and then concentrated to a sirup under reduced pressure. It was usually good practice to avoid heating the extract or the sirup during the concentration.

The lysergic acid amide was ordinarily isolated in a crystalline form from the sirup as a salt (maleate, tartrate, etc.), which usually crystallized readily from methanol–ether solvent mixtures. Occasionally, the product could be isolated crystalline as the free base. Sometimes it was necessary to resort to chromatography.

Lysergic acid-N-benzyl amide acid maleate. A solution of 1.62 g. of potassium +-lysergate monohydrate (5 mmol.) in 25 ml. of anhydrous dimethylformamide was prepared and carefully protected from contact with moisture. The solution was chilled in an ice water bath and then treated quickly with 7.7 ml. of SO_3-DMF solution, providing 10.0 mmol. of SO_3. The mixture was chilled with swirling for 5 min. and then 2.68 g. of benzylamine (25.0 mmol.) was added. After 5 min. more cooling and swirling, 100 ml. of 20% saline solution was added. The mixture was extracted with ethylene dichloride. The completeness of extraction was determined with Van Urk reagent. The fifth 150-ml. extract gave only a slightly blue color with the reagent.

The combined extracts were dried briefly with anhydrous magnesium sulfate and then concentrated to a sirup *in vacuo*. Care was taken to avoid heating the residual sirup. The residue was dissolved in 25 ml. of methanol, the solution made slightly acid with maleic acid and then treated with ether to a slight turbidity. After chilling for 48 hr., the product, which had crystallized in rosettes of fine, nearly colorless needles, was collected, washed with a little fresh, cold methanol-ether mixture (1:1), and dried. The crude product weighed 1.80 g.

The +-lysergic acid-*N*-benzyl amide acid maleate was purified by recrystallization from methanol and ether for characterization as follows: $[\alpha]_D^{25}$ +17.2° (c, 1 in methanol); m.p. 193° (dec.).

Anal. Calcd. for $C_{23}H_{23}N_3O.C_4H_4O_4$: C, 68.48; H, 5.74; N, 8.87. Found: C, 68.45; H, 5.83; N, 9.09.

Ergonovine acid maleate. A solution of 7.60 g. +-lysergic acid dihydrate (25.0 mmol.) and 1.06 g. of lithium hydroxide hydrate (25.0 mmol.) in 200 ml. of methanol was prepared. The solvent was distilled on the steam bath under reduced pressure. The residue of lithium lysergate was dissolved in 400 ml. of anhydrous dimethylformamide. About 200 ml. of dimethylformamide was distilled at 15 mm. pressure through a 12-inch helice-packed column. The resulting anhydrous solution of lithium lysergate in dimethylformamide was cooled to 0° and, with stirring, treated rapidly with 50.0 ml. of SO_3-DMF solution (1.00 molar). The mixture was stirred in the cold for 10 min. and then 9.40 g. of L-2-amino-1-propanol (125 mmol.) was added. The stirring and cooling were continued for 10 min. longer when 400 ml. of water was added to break the reaction complex. The mixture was acidified with tartaric acid and extracted with chloroform (three 500-ml. portions) to remove most of dimethylformamide. The aqueous mixture was treated with 80 g. of sodium chloride and 200 ml. of ethanol. The mixture was then layered with 500 ml. of ethylene dichloride and made basic with concentrated ammonium hydroxide solution. After being mixed thoroughly, the ethylene dichloride layer was separated and extraction continued with fresh portions of ethylene dichloride until all the amide product had been extracted as indicated by tests with Van Urk reagent.

The extract was concentrated *in vacuo* keeping the mixture cold at all times. The residue of sirup was collected in 50 to 75 ml. of methanol, filtered, and acidified with solid maleic acid. The solution was then carefully layered with 50 ml. of ether. After several minutes, crystallization was well under way. The mixture was treated with 200 ml. of ether and refrigerated for several hours. The crop of colorless, fine needles was collected on a Buchner funnel, washed with a cold methanol-ether mixture (1:1), and dried. The ergonovine maleate thus obtained weighed 6.75 g. (61.5%) and was identical in all respects with an authentic sample of the naturally-occurring alkaloid.

Alternatively, the free base as the stable, crystalline addition compound, ergonovine-chloroform,[8] could be isolated by triturating the residue from the ethylene dichloride extract with cold chloroform.

The crystallization mother liquor contained mainly the acid maleate of the isolysergic acid amide, ergonovinine. After removing the solvent under reduced pressure, the residue was treated with 200 ml. of 10% aqueous saline solution and excess concentrated ammonium hydroxide solution. The free base was extracted with ethylene dichloride. The extract was evaporated under diminished pressure and the residual sirup was treated with 100 ml. of alcohol and 10 ml. of 4*N* 1:1 aqueous alcoholic potassium hydroxide. This mixture was kept at room temperature for 1 to 2 hr. and then neutralized with solid carbon dioxide. After adding 400 ml. of ether, the mixture was filtered and the filtrate was concentrated. The sirup remaining was treated in the manner previously indicated for the isolation of ergonovine maleate. The second crop weighed 0.91 g. (8.3%). Further crops may be isolated by recycling the iso-material through the alkaline equilibration procedure.

Alternatively, the residual iso-material from the ethylene dichloride extract could be isolated as the crystalline ergonovinine nitrate.[9]

N-Cyanomethyl-+-lysergic acid amide. The mixed anhydride from 3.70 g. of lysergic acid hydrate, prepared as for ergonovine above, was treated with excess cyanomethylamine. After decomposing the complex with 400 ml. of saturated saline solution, the product was extracted with three 500-ml. portions of chloroform. The combined extracts were dried (anhydrous magnesium sulfate) and then concentrated under diminished pressure. The residual sirup was dissolved in 30 ml. of methanol, acidified with solid maleic acid, treated to turbidity with ether, and refrigerated for several hours. The precipitate of colorless, soft needles was collected, washed with cold ether-methanol mixture (2:1), and then dried at 50° *in vacuo*. The product weighed 2.52 g. A portion of the material was recrystallized from methanol and ether solvent mixture for analysis: $[\alpha]_D^{25}$ +42.9° (*c*, 1 in methanol); m.p. 194° (dec.) (corr.).

Anal. Calcd. for $C_{18}H_{18}N_4O.C_4H_4O_4.{}^1/_2H_2O$: C, 61.17; H, 5.48; N, 12.97. Found: C, 61.25; H, 5.70; N, 13.03.

Lysergic acid anilide. Potassium +-lysergate monohydrate (1.62 g., 5.0 mmol.) was dissolved in 25 ml. of anhydrous dimethylformamide. The solution was treated with 8.20 ml. of SO_3-DMF solution (1.21 molar) and then chilled in an ice water bath for 20 min. when 2.30 g. of aniline (25 mmol.) was added. The mixture was swirled briefly and kept cold for 1 hr. After adding 100 ml. of 10% aqueous saline solution, the amide product was extracted with ethylene dichloride until no further amount of Van Urk-positive material could be extracted. The combined extract was concentrated under reduced pressure and the sirupy residue was dissolved in 20 ml. of methanol, acidified with maleic acid, and then treated with 200 ml. of ether. After being refrigerated for several days, the crystals were collected, washed free of sirupy material with 1:1 methanol-ether mixture, and air dried. The slightly off-white product weighed 0.48 g.

The combined mother liquor and washes were concen-

(8) A. Stoll and A. Hofmann, *Z. physiol. Chem.*, Hoppe-Seyler's, **251**, 155 (1938).

(9) S. Smith and G. M. Timmis, *J. Chem. Soc.*, 1166 (1936).

trated to a sirup under reduced pressure and the residue of sirup was treated with 150 ml. of 1.0*M* methanolic potassium hydroxide. After standing for 2 hr. at room temperature, the mixture was diluted with 400 ml. of 10% aqueous saline solution and the Van Urk positive material was extracted with ethylene dichloride. The residue from the extract, after conversion to the acid maleate, yielded 0.30 g. of lysergic acid anilide acid maleate. A portion of the combined crops of product was recrystallized from methanol, yielding fine colorless needles; m.p. 200° (dec.); $[\alpha]_D^{25}$ +43.8° (*c*, 0.5 in ethanol).

Anal. Calcd. for $C_{22}H_{21}N_3O.C_4H_4O_4$: C, 67.96; H, 5.48; N, 9.15. Found: C, 68.34; H, 5.76; N, 9.11.

Ethyl +-lysergate. Potassium lysergate (3.0 g., 9.25 mmoles) was dissolved in 10 ml. of dry dimethylformamide. The solution was chilled and then 1.1 g. of ethyl chloroformate (10 mmol.) was added. The mixture was kept cold for 30 min. when 0.90 g. of morpholine (10.3 mmol.) was added. After 30 min. longer, the cold mixture was added to 50 ml. of ice water, causing a yellow, unstable solid to separate. The solid was collected in chloroform and dried with anhydrous magnesium sulfate. After evaporating the chloroform, the residue of brown sirup was dissolved in a few milliliters of methanol. The solution was then acidified with maleic acid, treated to turbidity with ether, and refrigerated for several days. The product, ethyl +-lysergate acid maleate, was obtained in the form of fine, yellow needles, which were collected, washed free of tarry material with methanol-ether solvent mixture (1:1), and dried. The needles weighed 0.78 g., m.p. 155–160° (dec.). Recrystallization from methanol and ether gave massive prisms, faintly yellow in color, m.p. 155–157° (dec.).

Anal. Calcd. for $C_{18}H_{20}N_2O_2.C_4H_4O_4$: C, 64.07; H, 5.87; N, 6.79. Found: C, 64.19; H, 5.84; N, 6.92.

Ergonovine maleate preparation via the methanesulfonic acid anhydride. Lysergic acid monohydrate (1.43 g., 5.0 mmol.) was suspended in 25 ml. of dry dimethylformamide. The mixture was chilled to 0° and a cold solution of methanesulfonic acid anhydride in dry dimethylformamide (31.4 ml. of 0.35 molar solution) was added. The lysergic acid dissolved and after 30 min. in the cold, 2.2 g. of L-2-amino-1-propanol (20 mmol.) was added. The mixture was kept cold for 1 hr. and then worked up for ergonovine in the usual manner. The yield of ergonovine maleate was 0.55 g.

Acknowledgment. I wish to thank Dr. A. L. Kranzfelder and Dr. G. H. Svoboda for many helpful discussions during the course of this work. Also, appreciation is due Mr. H. L. Bird for paper chromatographic analyses, Mr. W. L. Brown for microanalyses, Dr. H. A. Rose for X-ray diffraction data, and Dr. H. E. Boaz for infrared spectra and microtitration data.

INDIANAPOLIS, IND.

[CONTRIBUTION FROM THE RADIUM INSTITUTE OF THE UNIVERSITY OF PARIS]

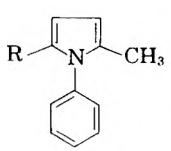
Aldehydes Derived from 1,2,5-Trisubstituted Pyrroles

RICHARD RIPS AND N. P. BUU-HOÏ

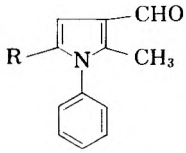
(*Received September 20, 1958*)

The formylation of 1-phenyl-2,5-dimethylpyrrole and 1,2-diphenyl-5-methylpyrrole was effected by means of dimethylformamide and phosphorus oxychloride, to give the corresponding monoaldehydes; 1-phenyl-2,3,5-trimethylpyrrole and 1,2-diphenyl-4,5-dimethylpyrrole were prepared by reduction of these aldehydes, and were also successfully formylated. A dialdehyde was also obtained from 1-phenyl-2,5-dimethylpyrrole.

In the framework of a general study on the chemical and pharmacological properties of substituted *N*-arylpyrroles,[1] we have investigated the behavior of 1-phenyl-2,5-dimethylpyrrole (I) and 1,2-diphenyl-5-methylpyrrole (II) toward dimethylformamide in the presence of phosphorus oxychloride. The formylation of a large number of derivatives of pyrrole had already been performed and the nucleus found to be highly reactive in that respect,[2] but *N*-arylpyrroles had not yet been investigated.

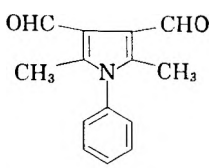


I, R = CH_3
II, R = C_6H_5

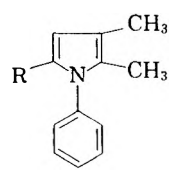


III, R = CH_3
IV, R = C_6H_5

Both pyrroles I and II readily underwent formylation to give 1-phenyl-2,5-dimethylpyrrole-3-aldehyde (III) and 1,2-diphenyl-5-methylpyrrole-4-aldehyde (IV) respectively, the best results being obtained when a diluent such as toluene was used for the reaction. In the case of 1-phenyl-2,5-dimethylpyrrole, small amounts of the corresponding *dialdehyde* (V) could also be isolated. The fact that 1,2-diphenyl-5-methylpyrrole, unlike I, gave no dialdehyde, points to a deactivating influence on the 3-position exerted by the 2-phenyl radical, and this effect justifies the assignment of structure IV to the formylation product of II. Wolff-Kishner reduction of aldehydes III and IV using Huang-



V

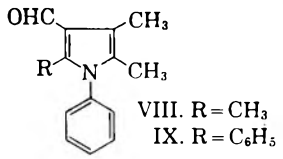


VI, R = CH_3
VII, R = C_6H_5

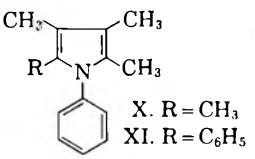
(1) N. P. Buu-Hoï, R. Rips, and R. Cavier, *J. Med. Pharm. Chem.*, in press.

(2) *Cf.* H. Fischer and H. Orth, *Die Chemie des Pyrrols*, Vol. I, Akademische Verlagsgesellschaft, Leipzig, 1934, p. 145.

Minlon's technique,[3] furnished 1-phenyl-2,3,5-trimethylpyrrole (VI) and 1,2-diphenyl-4,5-dimethylpyrrole (VII) in excellent yields, and this reaction sequence constitutes a convenient method for the preparation of such substituted 3-methylpyrroles. Formylation of these two reduction products showed a remarkable difference in their respective reactivity, 1-phenyl-2,3,5-trimethylpyrrole giving aldehyde VIII in the usual way, whilst 1,2-diphenyl-4,5-dimethylpyrrole gave aldehyde IX only when drastic experimental conditions were adopted. The relative inertia of the 3-position in the molecule of VII is further proof of the deactivating influence of the 2-phenyl substituent. Wolff-Kishner reduction was successful in both cases, and furnished the completely substituted 1-phenyl-2,3,4,5-tetramethylpyrrole (X) (this same compound was obtained by similar reduction of dialdehyde V) and 1,2-diphenyl-3,4,5-trimethylpyrrole (XI) respectively.

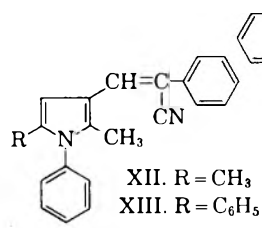


VIII. R = CH_3
IX. R = C_6H_5

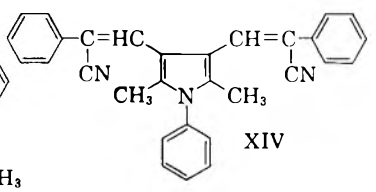


X. R = CH_3
XI. R = C_6H_5

The various monoaldehydes described gave condensation products with the usual reagents for the aldehyde group (semicarbazide, hydroxylamine, phenylhydrazine). A difference was observed, however, between the aldehydes having a free *ortho* position and the others, in their behavior toward benzyl cyanide in the presence of sodium hydroxide,[4] the former (III and IV) giving the corresponding acrylonitriles XII and XIII, whereas the latter (VIII and IX) failed to react. On the other hand, the dialdehyde V reacted with 2 moles of

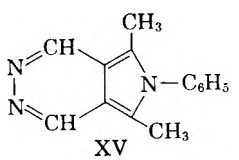


XII. R = CH_3
XIII. R = C_6H_5

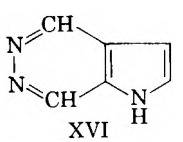


XIV

benzyl cyanide under similar conditions, to give the *bis*-acrylonitrile (XIV). With hydrazine hydrate, it gave the cyclic azine (XV), which is derived from 5,6-diazaisoindole, a heterocyclic nucleus



XV



XVI

unknown hitherto although several derivatives of the isomeric 5,6-diazaindole (XVI) have already been reported in the literature.[5] This azine belongs to a group of compounds of biological interest as potential antagonists of purine bases.

EXPERIMENTAL

Preparation of intermediates. 1-Phenyl-2,5-dimethylpyrrole and 1,2-diphenyl-5-methylpyrrole were prepared by Knorr-Paal condensation of aniline with hexane-2,5-dione and phenacylacetone respectively[6]; the condensation products were purified by vacuum-distillation, followed by recrystallization from cyclohexane.

1-Phenyl-2,5-dimethylpyrrole-3-aldehyde (III). To a well stirred solution of 25 g. (0.146 mole) of 1-phenyl-2,5-dimethylpyrrole and 16 g. (1.5 mole) of dimethylformamide in 100 ml. of dry toluene, 27 g. (1.2 moles) of phosphorus oxychloride was added in small portions. The mixture was heated on a boiling water bath for 6 hr., and then shaken for 20 min. with 300 ml. of saturated aqueous sodium acetate. The reaction product was taken up in toluene, the toluene solution washed with 10% aqueous sodium carbonate, then with water, dried over sodium sulfate, the solvent was distilled off, and the residue vacuum-fractionated. Yield: 21 g. (73%) of an aldehyde, b.p. 190°/12 mm., crystallizing in colorless plates, m.p. 92°, from aqueous methanol. Brooker and Sprague[7] obtained this compound in 25% yield by using formamide and phosphorus oxychloride in ether medium, and gave m.p. 89–90°.

The corresponding *semicarbazone* crystallized from ethanol in colorless needles, m.p. 294°.

Anal. Calcd. for $C_{14}H_{16}N_4O$: N, 21.9. Found: N, 22.0. The *oxime* crystallized from ethanol in shiny colorless prisms, m.p. 210°.

Anal. Calcd. for $C_{13}H_{14}N_2O$: N, 13.1. Found: N, 13.3.

1-Phenyl-2,5-dimethylpyrrole-3,4-dialdehyde (V). This dialdehyde was obtained by recrystallization from ethanol of the residue from the distillation of the foregoing monoaldehyde, the best yield (13%) being recorded when dimethylformamide was used in large excess (3 moles); it formed fine colorless needles, m.p. 203°, giving a yellow halochromy with sulfuric acid.

Anal. Calcd. for $C_{14}H_{13}NO_2$: C, 74.0; H, 5.8. Found: C, 74.0; H, 6.0.

1,3-Dimethyl-2-phenyl-5,6-diazaisoindole (XV). A solution of 1 g. of the foregoing dialdehyde and 1 ml. of hydrazine hydrate in ethanol was refluxed for 2 hr., and the precipitate formed on cooling was recrystallized from aqueous methanol; yield: 0.9 g. of shiny colorless prisms, m.p. 288°, giving a yellow coloration with sulfuric acid.

Anal. Calcd. for $C_{14}H_{13}N_3$: C, 75.3; H, 5.9; N, 18.8. Found: C, 75.2; H, 5.9; N, 19.0.

1-Phenyl-2,3,5-trimethylpyrrole (VI). A solution of 8 g. of aldehyde III and 3 g. of 95% hydrazine hydrate in 200 ml. of diethylene glycol was heated at 100° for 10 min.; 3.9 g. of potassium hydroxide was then added, and the mixture refluxed for 90 min., with removal of water. After cooling and acidification with dilute hydrochloric acid, the reaction product was taken up in benzene, the benzene solution washed with water and dried over sodium sulfate, the solvent was removed, and the residue vacuum-distilled. Yield: 6.4 g. (86.6%) of a compound, b.p. 140°/18 mm., crys-

(3) Huang-Minlon, *J. Am. Chem. Soc.*, **68**, 2487 (1946).

(4) For similar condensations with other nitrogen heterocyclic aldehydes, see N. P. Buu-Hoï, R. Huls, and N. D. Xuong, *J. Org. Chem.*, **20**, 1407 (1955); R. Castle and W. Seese, *J. Org. Chem.*, **20**, 987 (1955).

(5) *Cf.* for instance, H. Fischer and O. Wiedemann, *Hoppe-Seyler's Z. physiol. Chem.*, **155**, 52 (1926); H. Fischer, E. Sturm, and H. Friedrich, *Ann.*, **461**, 251 (1928); H. Fischer, H. Beyer, and E. Zaucker, *Ann.*, **486**, 61 (1931).

(6) L. Knorr, *Ann.*, **236**, 313 (1886); C. Paal, *Ber.*, **18**, 2254 (1885).

(7) L. G. Brooker and R. H. Sprague, *J. Am. Chem. Soc.*, **67**, 1869 (1945).

tallizing in colorless leaflets, m.p. 39°, from aqueous methanol.

Anal. Calcd. for $C_{13}H_{15}N$: C, 84.3; H, 8.2. Found: C, 84.2; H, 8.1.

1-Phenyl-2,3,5-trimethylpyrrole-4-aldehyde (VIII) was prepared in a manner analogous to the lower homolog of the foregoing pyrrole (VI) from 11.5 g. of the foregoing pyrrole, 6.8 g. of dimethylformamide, and 14.5 g. of phosphorus oxychloride in 100 ml. of dry toluene; yield: 11 g. (83.3%) of an aldehyde, crystallizing from methanol in long colorless needles, m.p. 134°.

Anal. Calcd. for $C_{14}H_{15}NO$: C, 78.8; H, 7.1; N, 6.6. Found: C, 78.8; H, 7.1; N, 6.6.

The *semicarbazone* crystallized from ethanol in shiny colorless prisms, m.p. 273°.

Anal. Calcd. for $C_{15}H_{18}N_4O$: N, 20.7. Found: N, 20.7.

1-Phenyl-2,3,4,5-tetramethylpyrrole (X) was prepared in the usual way from 5 g. of the foregoing aldehyde (VIII), 1.7 g. of hydrazine hydrate, and 2 g. of potassium hydroxide. This compound (3.5 g., 70%) was a colorless oil, b.p. 142°/12 mm., which darkened rapidly on exposure to air and light. The same compound was obtained by reduction of dialdehyde V.

Anal. Calcd. for $C_{14}H_{17}N$: C, 84.4; H, 8.6. Found: C, 84.1; H, 8.6.

1,2-Diphenyl-5-methylpyrrole-4-aldehyde (IV) was prepared from 15 g. of 1,2-diphenyl-5-methylpyrrole, 7 g. of dimethylformamide, and 15 g. of phosphorus oxychloride in 150 ml. of dry toluene. Yield: 16.5 g. (98%) of an aldehyde, b.p. 241–242°/13 mm., crystallizing in colorless prisms, m.p. 115–116°, from ethanol. No dialdehyde could be isolated in this reaction.

Anal. Calcd. for $C_{19}H_{15}NO$: C, 82.7; H, 5.8. Found: C, 82.8; H, 5.8.

The *oxime* crystallized from ethanol in fine colorless prisms, m.p. 198°.

Anal. Calcd. for $C_{18}H_{16}N_2O$: N, 10.1. Found: N, 10.1.

The *phenylhydrazone* crystallized from ethanol in silky colorless needles, m.p. 180°.

Anal. Calcd. for $C_{24}H_{21}N_3$: C, 81.8; H, 6.0; N, 12.0. Found: C, 81.7; H, 6.1; N, 12.2.

1,2-Diphenyl-4,5-dimethylpyrrole (VII) was prepared from 10 g. of the foregoing aldehyde (IV), 2.8 g. of hydrazine hydrate, and 3 g. of potassium hydroxide in 100 ml. of diethylene glycol. Yield: 8.2 g. (87%) of a product, b.p. 195°/12 mm., crystallizing from ethanol in colorless prisms, m.p. 79°, giving no coloration with sulfuric acid.

Anal. Calcd. for $C_{18}H_{17}N$: C, 87.4; H, 6.9. Found: C, 87.3; H, 6.9.

1,2-Diphenyl-4,5-dimethylpyrrole-3-aldehyde (IX). When the usual formylation technique was applied to the foregoing pyrrole (VII), no aldehyde was obtained, even after 30 hours' heating. The following procedure, however, furnished the expected aldehyde, in good yield. To a mixture of 5.5 g. of pyrrole VII and 2.4 g. of dimethylformamide, 4 g. of phosphorus oxychloride was added in small portions, and the sticky dark violet mass obtained was heated for 10 hr. on a water bath. After cooling, a 15% aqueous solution of sodium hydroxide was added, and the reaction product worked up in the usual way. Yield: 4.7 g. (77%) of an aldehyde, b.p. 254°/17 mm., crystallizing from cyclohexane in colorless, rhombohedric prisms, m.p. 200°.

Anal. Calcd. for $C_{19}H_{17}NO$: C, 82.9; H, 6.2; O, 5.8. Found: C, 82.9; H, 6.2; O, 5.8.

The *oxime* crystallized from ethanol in shiny colorless prisms, m.p. 238–239°.

Anal. Calcd. for $C_{19}H_{18}N_2O$: N, 9.7. Found: N, 9.7.

1,2-Diphenyl-3,4,5-trimethylpyrrole (XI) was prepared from 6 g. of the foregoing aldehyde (IX), 1.4 g. of hydrazine hydrate, and 1.4 g. of potassium hydroxide in 50 ml. of diethylene glycol. Yield: 4 g. (70%) of a compound crystallizing in shiny colorless needles, m.p. 121°, from cyclohexane or acetic acid.

Anal. Calcd. for $C_{19}H_{19}N$: C, 87.3; H, 7.3. Found: C, 87.3; H, 7.2.

α-Phenyl-β-(1-phenyl-2,5-dimethyl-3-pyrryl)acrylonitrile (XII). A solution of aldehyde III (1 mole) and benzyl cyanide (1 mole) in ethanol was refluxed for 5 min. with a few drops of aqueous sodium hydroxide (5*N*). The precipitate formed on cooling and diluting with water, was washed with water and recrystallized from ethanol, giving silky yellowish needles, m.p. 139°. Yield: 70%. Under the same experimental conditions, no condensation products were obtained with aldehydes VIII and IX.

Anal. Calcd. for $C_{21}H_{17}N_2$: N, 9.4. Found: N, 9.5.

α-Phenyl-β-(1,2-diphenyl-5-methyl-4-pyrryl)acrylonitrile (XIII). Similarly prepared from aldehyde IV and benzyl cyanide, this nitrile crystallized from ethanol in silky yellowish needles, m.p. 145°.

Anal. Calcd. for $C_{26}H_{20}N_2$: N, 7.8. Found: N, 8.1.

bis-*Acrylonitrile* (XIV). This compound, prepared from 1 mole of dialdehyde V with 2 moles of benzyl cyanide, crystallized from ethanol in pale yellow needles, m.p. 171°.

Anal. Calcd. for $C_{30}H_{23}N_3$: N, 9.9. Found: N, 9.9.

PARIS V^E, FRANCE

[CONTRIBUTION FROM THE RESEARCH DIVISION, AMERICAN CYANAMID CO., BOUND BROOK LABORATORIES]

Reactions of 2,3-Dichloro-1,4-naphthoquinone with 2-Aminopyridine and Related Amines[1]

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2,3-Dichloro-1,4-naphthoquinone reacts with 2-aminopyridine to yield a 1:1 and a 1:2 condensation product. The former is shown to have structure I, and the latter is believed to have structure X. Various substitution products of I are described, as are several analogous quinones derived from other heterocyclic amines.

During the preparation of a number of naphtho-[2,3-*b*]pyrrocolinediones *via* the convenient synthesis elaborated by Pratt *et al.*,[2,3] we became interested in the nature of the products which might

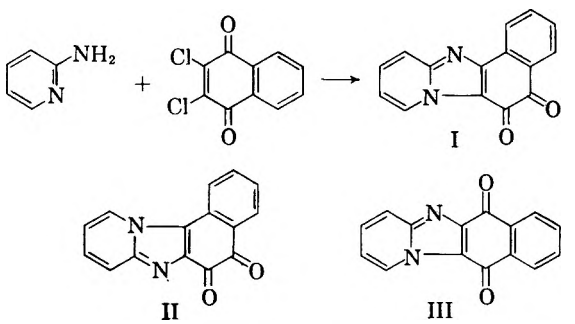
(1) Paper presented at the 133rd National Meeting of the American Chemical Society, San Francisco, Calif., April 13–18, 1958; *Abstracts*, p. 66N.

(2) E. F. Pratt, R. W. Luckenbaugh, and R. L. Erickson, *J. Org. Chem.*, **19**, 176 (1954).

(3) E. F. Pratt, R. G. Rice, and R. W. Luckenbaugh, *J. Am. Chem. Soc.*, **79**, 1212 (1957).

result from the reaction of 2,3-dichloro-1,4-naphthoquinone with 2-aminopyridine in the *absence* of an active methylene compound.

Heating an equimolecular mixture of these two reactants in ethanol was reported[4,5] to afford 3-chloro-2-(2-pyridylamino)-1,4-naphthoquinone (brown, m.p. 276–278° dec.) in 45[4] and 91%[5] yield. Despite numerous attempts, we have been unable to find any evidence for the existence of this product. Repetition of the reported[5] experimental conditions led only to mixtures of products, including 2,3-dichloronaphthoquinone. One of these products, a vattable orange quinone ($C_{15}H_8N_2O_2$, m.p. 301–302°), could be obtained in good yield as the major product of the reaction of 2,3-dichloronaphthoquinone with 2-aminopyridine in ethanol, provided a molar equivalent of sodium bicarbonate or carbonate, or a second molar equivalent of 2-aminopyridine was added initially to the reaction mixture. These reactions were normally heated for from 4–18 hours. However, when the reaction was stopped during the first hour, traces of a vattable reddish brown product ($C_{20}H_{12}N_4O$, m.p. 245.0–245.5°) could be isolated. Upon further heating of the reaction mixture, this product disappeared, and the orange quinone was the sole product isolated. If, however, four (or more) molar equivalents of 2-aminopyridine were employed initially in the reaction with 2,3-dichloronaphthoquinone, the red-brown compound was the major product. The nature of this latter substance will be discussed later (*v.i.*).

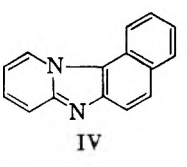


The orange quinone $C_{15}H_{18}N_2O_2$ was obtained pure, in the manner mentioned, in about 47% yield. Structures I, II, and III were considered for this product. Analogy with the naphthopyrrocolinediones[2,3] would suggest the *linear* formula III, but the *angular* structures I and II were included because of the long-known[6] reaction of 2,3-dichloro-1,4-naphthoquinone with *o*-phenylenediamines to yield derivatives of the *angular* benzo[*a*]phenazine. The formation of a phenazine derivative by reaction of the orange quinone with *o*-phenylenediamine eliminated the linear structure III from further consideration.

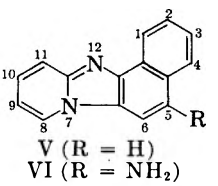
While we were seeking evidence to provide the basis for a choice between structures I and II, Truitt *et al.*[5] described the preparation, by similar reactions, of a quinone to which they assigned structure III. Evidently their failure to obtain a phenazine derivative of the quinone was a major factor in their choice of structure III. Repetition of their directions[5] for the reaction of 2-aminopyridine with dichloronaphthoquinone gave, in our hands, only traces of crude, orange quinone. However, the reaction, as reported,[5] of 2-acetamido-3-chloronaphthoquinone with 2-aminopyridine readily yielded a product identical (in infrared spectrum and other properties) with our orange quinone (I or II). The assignment[5] of structure III is, therefore, incorrect.

2-Acetamidopyridine was reported[5] not to react with 2,3-dichloronaphthoquinone, and we experienced a similar failure when the reaction was run in chlorobenzene solution. However, in methyl Cellosolve solution the reaction afforded the same orange quinone (I or II) otherwise obtained. This piece of evidence tends to support structure I over II, but is hardly conclusive as deacylation of 2-acetamidopyridine under the reaction conditions seems entirely possible. The argument in favor of structure I was strengthened somewhat when the same quinone (I or II) was obtained from the reaction of 2-aminopyridine with 3,4-dichloro-1,2-naphthoquinone.

From the reaction of 1-chloro-2,4-dinitronaphthalene with 2-aminopyridine, Morgan and Stewart[7] obtained after several steps, a product, which could be either IV or V. Without offering



IV



V (R = H)
VI (R = NH_2)

substantial evidence, they preferred structure V. The accuracy of this choice was confirmed later during work upon related compounds by Adams and Pomerantz.[8] However, by its nature, the work of the later workers corroborates that of Morgan and Stewart, and not *vice versa*, as was indicated.[8] Structure I is then merely a quinone of the established ring system V. No information is available concerning derivatives of the nucleus (IV) present in II.

Reduction of V yielded the known[7] tetrahydro compound VII, which was oxidized by chromic acid to the quinone VIII. This substance proved

(4) J. C. Calandra and E. C. Adams, *J. Am. Chem. Soc.*, **72**, 4804 (1950).

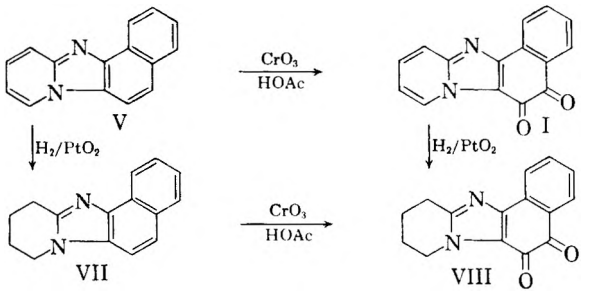
(5) P. Truitt, J. E. Cooper, and F. M. Wood, *J. Am. Chem. Soc.*, **79**, 5708 (1957).

(6) T. Zincke and M. Schmidt, *Ann.*, **286**, 27 (1895).

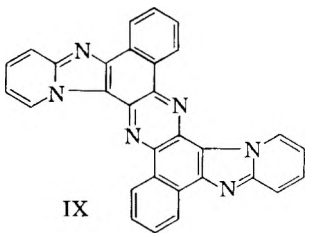
(7) G. Morgan and J. Stewart, *J. Chem. Soc.*, 1057 (1939).

(8) R. Adams and S. H. Pomerantz, *J. Am. Chem. Soc.*, **76**, 705 (1954).

to be identical with the product obtained by hydrogenating the original orange quinone ($C_{15}H_8N_2O_2$). Additional evidence for structure I also was obtained.



Oxidation of V with chromic acid gave, in low yield, a crude orange quinone, the infrared spectrum of which suggests it to be impure I. Oxidation of the amine VI with either chromic acid or lead tetraacetate yielded the phenazine IX as the sole product.


IX

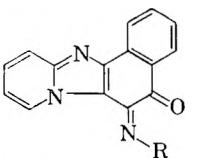
Reductive acetylation of the orange quinone I produced the hydroquinone diacetate, which upon distillation with zinc dust gave a small amount of brown oil. The oil yielded a solid picrate, the infrared spectrum of which was identical with the infrared spectrum of the picrate of V. Furthermore, the ultraviolet spectrum of the hydroquinone diacetate closely resembles that of V. The structure I for the orange quinone is thus established beyond reasonable doubt.

Oxidation of I with peracetic acid produced (at least) four products. Under either mild or vigorous oxidation conditions the major product was 2-aminopyridine (isolated as the picrate). Under mild conditions, a small yield of a substance $C_{13}H_{10}N_2O$ (m.p. 141.5–144.5°) also was obtained. The empirical formula and the presence of a carbonyl absorption at 5.88μ suggest the substance to be 2-phenylimidazo[1,2-*a*]pyridin-3(2*H*)-one. This compound was reportedly prepared by Schmidt and Gründig[9] (who give the melting point as 81.5–82°) from the reaction of 2-aminopyridine with ω-bromo-ω-nitroacetophenone. Our efforts to repeat their synthesis produced only tars. The failure of bromonitroacetophenone to yield a pyrrocoline upon reaction with 2-picoline has been recorded.[10]

Under vigorous conditions (in 40% peracetic acid), in addition to 2-aminopyridine, small amounts of two other substances (m.p. 185–186° and m.p. 226–228.5°) were isolated. The higher-melting product was identified as *N*-(2-pyridyl)-phthalimide, while the other was not identified.

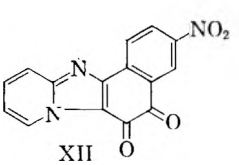
The red-brown $C_{20}H_{12}N_4O$ product. With four molar equivalents of 2-aminopyridine, in either ethanol or chlorobenzene solution, 2,3-dichloronaphthoquinone formed a vattable, reddish brown substance.[10a] The hydrochloride of this substance, mixed with unreacted dichloronaphthoquinone, was formed in a reaction with only *two* equivalents of 2-aminopyridine in *chlorobenzene* solution. The ultraviolet spectrum of the red-brown substance resembled that of the quinone I, and no OH or NH absorption was evident in the infrared spectrum. The red-brown product yielded I and 2-aminopyridine upon acid hydrolysis, but it could not be reconstituted by heating I with 2-aminopyridine in ethanol or acetic acid. Reductive acetylation afforded a colorless diacetyl derivative, the ultraviolet spectrum of which was similar to that of the hydroquinone diacetate from I.

These data, together with the other evidence, suggest that the $C_{20}H_{12}N_4O$ compound is the primary reaction product (which hydrolyzes *in situ*, under appropriate conditions, to form I), and that the pyridylimino group occupies the 6 position as shown in structure X.


X (R = 2-pyridyl)
XI (R = $COCH_3$)

The reaction of 2-acetamido-3-chloronaphthoquinone with two moles of 2-aminopyridine in hydroxylic solvents produced the quinone I. However, in chlorobenzene solution, the orange-brown acetimido compound XI is the sole product.

Related products. By the use of substituted 2-aminopyridines or substituted 2,3-dichloronaphthoquinones, several homologs of I were prepared. From 5 nitro-2,3-dichloronaphthoquinone, two mononitro derivatives of I were obtained, undoubtedly the 1- and 4-nitro compounds. A third mononitro derivative was prepared by the direct nitration of I. As it was different from each of the other


XII

(9) L. Schmidt and K. Gründig, *Monatsh.*, 84, 491 (1953).

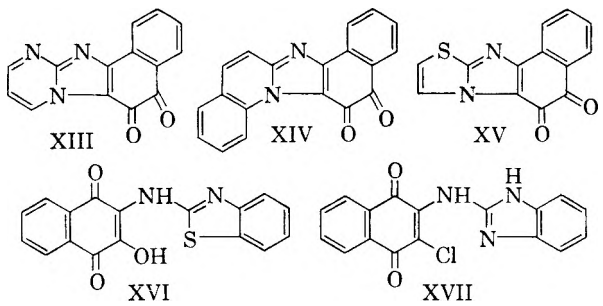
(10) E. T. Borrows, D. O. Holland, and J. Kenyon, *J. Chem. Soc.*, 1077 (1947).

(10a) These conditions were very recently reported[10b] to yield a product (m.p. 223–224°), which, after chromatography, melted at 297–298°, and was assigned structure III. It seems probable that the first substance is actually X, and was hydrolyzed to I (not III) during isolation.

(10b) M. S. Mathur and B. D. Tilak, *J. Sci. Ind. Research (India)*, 17B, 33 (1958).

two nitro derivatives, it was assigned structure XII. The use of 2,3,5,8-tetrachloronaphthoquinine led to the formation of the 1,4-dichloro derivative of I, and the 8-methyl homolog was obtained from 2-amino-6-methylpyridine.

Replacement of 2-aminopyridine with 2-aminopyrimidine in the reaction with dichloronaphthoquinone, yielded a golden yellow quinone. Like I, it formed a phenazine, and it was assigned structure XIII. Products obtained similarly from 2-aminoquinoline and 2-aminothiazole were formulated as XIV and XV, respectively, although no proof of these structures has been attempted. The reaction of dichloronaphthoquinone (in the presence of



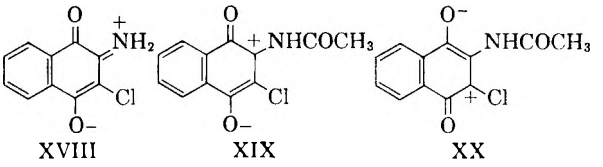
XIII XIV XV XVI XVII

sodium carbonate and ethanol) with 2-amino benzothiazole and with 2-aminobenzimidazole gave only products thought to have structures XVI and XVII, respectively.

Reaction mechanism. Insomuch as the available evidence indicates the quinoneimine X to be the precursor of the quinone I, and to form the latter by simple hydrolysis, we need consider only the mode of formation of X. The initial reaction of 2-aminopyridine with 2,3-dichloro-1,4-naphthoquinone could involve, *a priori*, attack by either the amino group or by the ring nitrogen of the pyridine, and either 1,2 or 1,4- addition to the naphthoquinone system. Evidently a complex series of reactions is required to produce X.

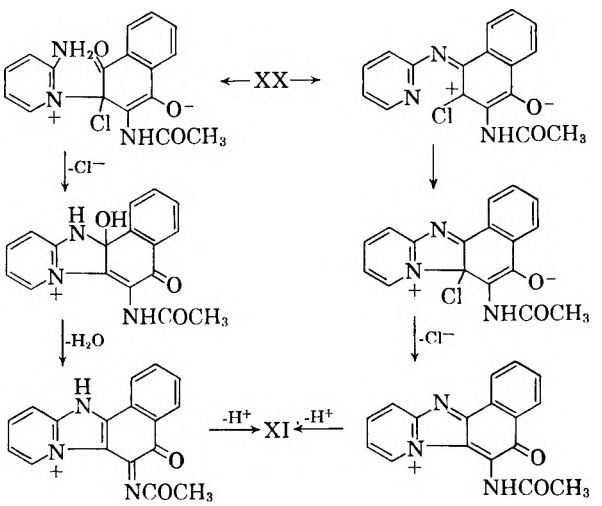
The failure of 2-acetamidopyridine to react (in *chlorobenzene* solution) with either 2,3-dichloro- or 2-acetamido-3-chloro-1,4-naphthoquinone seems to indicate involvement of the amino group of 2-aminopyridine in the initial reaction step. Now in nucleophilic displacement reactions of 2-aminopyridine upon α-haloesters, α-haloketones *etc.*, it is the ring nitrogen which is usually involved. Thus one is led to favor a 1,2- or 1,4- addition reaction to the naphthoquinone as the initial step. In this connection some related reactions in the older literature are particularly revealing.

Aniline, in ethanolic solution, reacts with 1,4-naphthoquinone to yield 2-anilino-1,4-naphthoquinone,[11] and with 2-chloronaphthoquinone to form 3-anilino-2-chloronaphthoquinone,[12] while no reaction at all occurs with 2-chloro-3-methyl-naphthoquinone.[13] These data imply 1,4- addition to the naphthoquinone. Similarly, the reaction of 2,3-dichloronaphthoquinone with ammonia (or simple amines) produces 2-amino-3-chloronaphthoquinone.[14] Further treatment of this compound with amines, even 2-aminopyridine, is without effect. A probable explanation for this lack of reactivity is the large contribution made by forms such as XVIII to the resonance hybrid. On the other hand, it is well recognized[15-18] that acylation of the amino group activates the chlorine to nucleophilic displacement. Normal amide resonance ($-CONH_2 \longleftrightarrow -O-C=NH_2$) suppresses contributions from forms such as XIX, but permits forms of type XX, and consequently reaction occurs with displacement of chlorine.



XVIII XIX XX

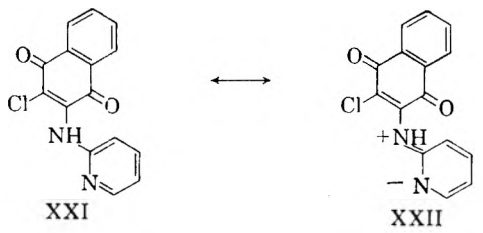
The reaction of XX with 2-aminopyridine may involve 1,2 addition of the amino group, or 1,4-addition of the ring nitrogen as follows:



Each of these sequences is capable of several variations, which, for want of evidence, it is pointless to discuss, and for the same reason a choice between the two mechanisms cannot now be made.

The formation of X may be considered to involve 1,4- addition of 2-aminopyridine to dichloronaphthoquinone, followed by loss of hydrogen chloride to produce XXI.

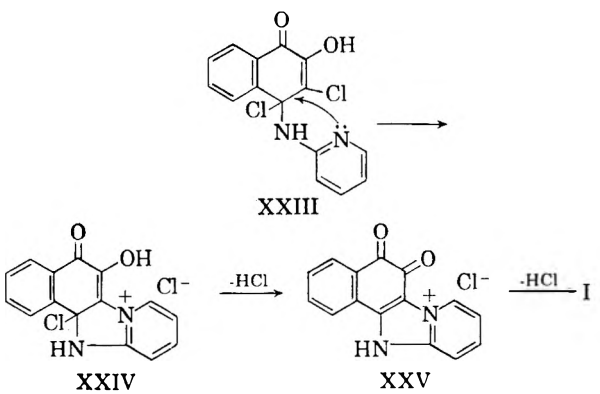
(11) T. Zincke, *Ber.*, **12**, 1641 (1879).
(12) T. Zincke, *Ber.*, **21**, 1027 (1888).
(13) K. Fries and W. Lohmann, *Ber.*, **54**, 2912 (1921).
(14) K. Fries and P. Ochwat, *Ber.*, **56**, 1291 (1923).
(15) K. Fries and K. Billig, *Ber.*, **58**, 1128 (1925).
(16) L. F. Fieser and E. L. Martin, *J. Am. Chem. Soc.*, **57**, 1844 (1935).
(17) J. R. Hoover and A. R. Day, *J. Am. Chem. Soc.*, **76**, 4148 (1954).
(18) R. Neef and O. Bayer, *Chem. Ber.*, **90**, 1137 (1957).



XXI XXII

Unlike simple 2-amino-3-chloronaphthoquinones, however, XXI may enjoy contributions from resonance forms such as XXII and thus, for the same reasons indicated for the acetamido compound XX, it contains an active chlorine and reacts rapidly with a second molecule of 2-aminopyridine. The formation of X may then occur *via* either of the two routes shown for the formation of XI.

The formation of I from 3,4-dichloro-1,2-naphthoquinone appears to be the simplest reaction of this group. Aniline is known to react with 1,2-naphthoquinone[19] and with its 3-chloro[20] or 3-nitro[21] derivatives by 1,4- addition, with the 3-substituent intact. In the present case, therefore, one may postulate an initial adduct such as XXIII, and its conversion, *via* XXIV and XXV, into I.



XXIII

XXIV XXV

In view of these conclusions, it is rather surprising that the linear quinone III was not formed by the internal cyclization of XXI. Further study of these complex reactions is required for complete elucidation of the mechanisms involved.

EXPERIMENTAL[22]

5H,6H-Benzo[e]pyrido[a]benzimidazole-5,6-dione (I).[23] (*a*) A mixture of 68.1 g. (0.30 mole) of 2,3-dichloro-1,4-naphthoquinone, 56.4 g. (0.60 mole) of 2-aminopyridine, and 500 ml. of ethanol was stirred and boiled under reflux for 8 hr. The cooled reaction mixture was filtered, washed well with ethanol, and dried. The yield of crude product was 60.6 g. (81.5%). Crystallization from *o*-dichlorobenzene gave 35.3 g. (47.4% yield) of orange quinone, m.p. 298.5–300.5°. A sample recrystallized from *o*-dichlorobenzene melted at 301–302.2°. Further recrystallization from various solvents or vacuum sublimation did not raise the melting point. λ_{max} 241, 261, 272–278, 295, 305–309 and 390 mμ (log ϵ 4.58, 4.36, 4.30, 4.21, 4.13, and 3.77).

Anal. Calcd. for $C_{15}H_8N_2O_2$: C, 72.57; H, 3.25; N, 11.29. Found: C, 72.20; H, 3.29; N, 11.60.

(*b*) A modification of the above method consists in substituting 0.30 mole of sodium carbonate for 0.30 mole of the (0.60 mole total of the) 2-aminopyridine, and heating the mixture for 18 hr. A 55.6% yield of crude product was thereby obtained, and crystallization from chlorobenzene gave a 46% yield of pure I, m.p. 299.5–301.5°.

(c) The reaction of 2-acetamido-3-chloro-1,4-naphthoquinone with 2-aminopyridine in the manner described by Truitt *et al.*[5] gave a 67.3% yield of crude orange product, which, after three recrystallizations from acetic acid, melted at 300–301.5° and possessed an infrared spectrum identical with that of I.

(*d*) The same quinone (I) also was obtained from the reaction of 1.70 g. (0.0075*M*) of 3,4-dichloro-1,2-naphthoquinone[20] with 1.41 g. (0.015*M*) of 2-aminopyridine in 25 ml. of ethanol. The purified product melted at 301–302°, and had an infrared spectrum identical with those of the samples otherwise prepared.

(*e*) A mixture of 2.27 g. (0.01 mole) 2,3-dichloro-1,4-naphthoquinone, 1.36 g. (0.01 mole) 2-acetamidopyridine, and 10 ml. of methyl Cellosolve was stirred and boiled under reflux for 24 hr. The crude product (1.31 g.) was crystallized from *o*-dichlorobenzene and recrystallized from chlorobenzene, after which it melted at 298.5–301° and was identical (by infrared spectrum) with I. In chlorobenzene, however, 2-acetamidopyridine failed to react with either 2,3-dichloro- or 2-acetamido-3-chloro-1,4-naphthoquinone.

The *hydroquinone diacetate* was obtained from I by reductive acetylation. Crystallization from benzene gave fluffy, white acicular clusters, m.p. 233–234° (lit.[5] 194°); λ_{max} 248,* 255, 276, 281,* 299, 316, 330, 340,* 355, and 370* mμ. (log ϵ 4.63, 4.67, 4.35, 4.30, 3.99, 3.94, 4.08, 3.96, 3.93, and 3.77).

Anal. Calcd. for $C_{19}H_{14}N_2O_4$: C, 68.30; H, 4.19; N, 8.39. Found: C, 68.20; H, 4.17; N, 8.19.

The *phenazine* of I was obtained by heating the quinone with a molar equivalent of *o*-phenylenediamine in acetic acid for 2 hr. The crude phenazine (92.2% yield) was recrystallized twice from chlorobenzene and once from methyl Cellosolve, giving a 50% yield of bright yellow crystals, m.p. 294.1–295.0°.

Anal. Calcd. for $C_{21}H_{12}N_4$: C, 78.73; H, 3.78; N, 17.49. Found: C, 78.90; H, 3.83; N, 17.40.

Benzo[e]pyrido[a]benzimidazole (V) was prepared by essentially the same method described by Morgan and Stewart.[7] It formed pale yellow plates, m.p. 193–195° (lit.[7] 187°), but chromatography of a benzene solution upon alumina gave very pale yellow crystals, m.p. 195.2–196.2°; λ_{max} 242–244.5, 252, 257,* 276.5, 299, 313, 326.5, 344–350, 358, and 370–372.5 mμ. (log ϵ 4.57, 4.66, 4.60, 4.37, 3.99, 3.85, 3.95, 3.94, 4.01, and 3.80).

The *picrate* was prepared in methanol and crystallized from methyl Cellosolve as fluffy yellow crystals, m.p. 258–261° dec.

Anal. Calcd. for $C_{21}H_{13}N_5O_7$: C, 56.37; H, 2.91; N, 15.66 Found: C, 56.32; H, 3.18; N, 15.64.

A mixture of 0.50 g. of the hydroquinone diacetate of I and 12.0 g. of zinc dust was distilled. The combined oily distillates from two such runs were dissolved in 0.5 ml. of methanol and treated with an excess of saturated methanolic picric acid. The resulting yellow picrate (70 mg.) was crystallized twice from methyl Cellosolve. The infrared spectrum of this material was identical with that of the picrate (*v.s.*) prepared from V.

(19) T. Zincke, *Ber.*, **14**, 1493 (1881).

(20) T. Zincke, *Ber.*, **19**, 2493 (1886).

(21) F. Brauns, *Ber.*, **17**, 1133 (1884).

(22) All melting points were taken in Pyrex capillaries using a Hershberg melting point apparatus and Anschütz thermometers. The ultraviolet spectra were measured in ethanol using a Cary recording automatic spectrophotometer and points of interest are indicated by asterisks. The infrared spectra were determined from Nujol mulls, using a Perkin-Elmer Model 321 recording spectrophotometer.

(23) This compound was first prepared in these laboratories by Dr. O. G. Birsten.

8,9,10,11-Tetrahydrobenzo[e]pyrido[a]benzimidazole (VII). To 100 mg. of benzo[e]pyrido[a]benzimidazole (V) in 25 ml. of ethanol was added 50 mg. of Adams' catalyst, and the mixture was hydrogenated at 30 p.s.i. (gage pressure) for 3 hr. The catalyst was filtered and the filtrate was stripped of ethanol to give 100 mg. of viscous oil. Trituration with cyclohexane caused crystallization, and recrystallization from cyclohexane and then from benzene gave white granular crystals, m.p. 161.5–162.5° (lit.[7] 157–158°); λ_{max} 223, 238, 256, 284.5, 308, 314.5, 322, and 328 mμ. (log ε 4.54, 4.68, 4.31, 3.73, 3.16, 3.68, 3.59, and 3.78).

Anal. Calcd. for $C_{15}H_{14}N_2$: C, 81.05; H, 6.30; N, 12.62. Found: C, 80.82; H, 6.20; N, 12.40.

The *picrate* was prepared in methanol and after crystallization from methyl Cellosolve melted at 233.5–235.2°.

Anal. Calcd. for $C_{21}H_{17}N_5O_7$: C, 55.87; H, 3.77; N, 15.53; O, 24.80. Found: C, 55.71; H, 3.70; N, 15.73; O, 24.78.

5,6,8,9,10,11-Hexahydrobenzo[e]pyrido[a]benzimidazole-5,6-dione (VIII). To a boiling solution of 0.60 g. of VII in 5 ml. of glacial acetic acid, was added dropwise a solution of 0.70 g. of chromic acid in 1 ml. of water. The mixture was cooled, diluted with water, and filtered. The crude orange quinone was crystallized twice from benzene, giving 0.50 g. of bright orange needles, m.p. 233.3–234.7°; λ_{max} 246–254,* 259.5, 266, and 305 mμ. (log ε 4.36, 4.42, 4.40, and 3.84).

Anal. Calcd. for $C_{15}H_{12}N_2O_2$: C, 71.43; H, 4.76; N, 11.10. Found: C, 71.65; H, 4.74; N, 11.22.

A slurry of 0.40 g. of the quinone I, 0.10 g. of Adams' catalyst, 50 ml. of ethanol, and a few small glass beads was shaken at 50° under hydrogen at 30 p.s.i. for several hours. The beads and catalyst were removed by filtration and the colorless filtrate was allowed to evaporate, yielding 0.32 g. of brownish orange solid. This was dissolved in benzene and chromatographed upon alumina, giving 0.11 g. of bright orange crystals, m.p. 232–233°, identical in infrared spectrum with the product (VIII) described above.

Oxidation of VI to IX was effected in boiling acetic acid by the action of either chromic acid or lead tetraacetate. The precipitated orange phenazine was boiled with acetic acid and then with methanol. Crystallization from 1-chloronaphthalene did not appear to improve the product. The use of lead tetraacetate gave a purer product. The orange phenazine melted above 360°.

Anal. Calcd. for $C_{30}H_{16}N_6$: C, 78.25; H, 3.48; N, 18.25. Found: C, 78.20; H, 3.70; N, 18.15.

Oxidation of I with peracetic acid was attempted under mild and vigorous conditions. When 10.0 g. of I were refluxed for 4.5 hr. with 90 ml. of acetic acid and 110 ml. of 6% hydrogen peroxide solution, neutralization of the resulting solution with 5% sodium carbonate solution gave 0.75 g. of crude solid. Three crystallizations from aqueous ethanol and from ethyl acetate–methyl cyclohexane gave a pale yellow substance, m.p. 141.5–144.5°, having a carbonyl absorption at 5.88 μ.

Anal. Calcd. for $C_{13}H_{10}N_2O$: C, 74.27; H, 4.79; N, 13.33. Found: C, 73.90; H, 4.84; N, 12.71.

The *picrate*, prepared in aqueous methanol, melted at 162.5–167.5°. Lack of material prevented purification.

Anal. Calcd. for $C_{19}N_{15}N_5O_7$: C, 53.65; H, 3.55; N, 16.47. Found: C, 53.00; H, 3.24; N, 16.20.

From the original, neutralized, reaction mother liquor, 2-aminopyridine was readily isolated as the picrate (m.p. 224–225°). Under more vigorous conditions, 2-aminopyridine, again isolated as the picrate, was the major degradation product.

When 1.00 g. of I was added to 4.0 ml. of 40% peracetic acid, after a minute or two a vigorous reaction ensued and the residual orange oily liquid was diluted with water and allowed to stand. The resulting pale yellow precipitate was filtered, crystallized from methanol, and then fractionally crystallized from acetonitrile. The more soluble of the two products formed colorless crystals, m.p. 226.0–228.5°, and was identified by comparison of the infrared spectrum with that of an authentic sample (m.p. 230.5–233.0°; lit.[24] 227°) of *N*-(2-pyridyl)phthalimide prepared from 2-aminopyridine and phthalic anhydride.

The less-soluble product formed white granules, m.p. 185.2–186.0°, and showed strong absorption at 3.10 and 5.85μ in the infrared spectrum. No satisfactory structure could be deduced from the spectra and microanalyses.

Anal. Found: C, 60.55; H, 3.59; N, 10.02; O, 24.96.

3-Phenyl-imidazo[1,2-a]pyridine-2(3H)-one. A solution of 2.15 g. of α-bromophenylacetic acid[25] in chloroform was converted into the acid chloride by treatment with thionyl chloride, and this was treated with a solution of 2.0 g. of 2-aminopyridine in chloroform. The solvent was allowed to evaporate and the oily residue was triturated with water. The aqueous extract was basified with ammonia, then adjusted to maximum turbidity by the addition of a few drops of acetic acid. Upon standing, the solution deposited a small quantity of yellow knobby crystals. Four recrystallizations from glycol diacetate gave 0.18 g. of pale straw-colored needles, m.p. *ca.* 246–248° dec. The melting point appears to vary somewhat with the temperature of the bath upon immersion of the sample. The carbonyl absorption at 5.80μ was visible in acetonitrile solution, but not in a nujol mull.

Anal. Calcd. for $C_{13}H_{10}N_2O$: C, 74.28; H, 4.76; N, 13.33; O, 7.62. Found: C, 74.24; H, 4.86; N, 13.00; O, 7.71.

5,6-Dihydro-5-oxo-6-(2-pyridylimino)-benzo[e]pyrido[a]-benzimidazole (X). A mixture of 22.7 g. (0.10 mole) of 2,3-dichloro-1,4-naphthoquinone, 37.6 g. (0.40 mole) of 2-aminopyridine, and 500 ml. of ethanol was stirred under reflux for 4 hr. The cooled reaction mixture was filtered and the solid was washed with ethanol, giving 22.2 g. (68.5% yield) of crude reddish brown product. A sample crystallized twice from chlorobenzene melted at 239.5–241.5°. The infrared spectrum showed a carbonyl absorption at 5.94μ, but no absorption characteristic of OH or NH stretching; λ_{max} 227, 248, 267, 308, 320.5, and 388 mμ (log ε 4.45, 4.54, 4.48, 4.20, 4.18, and 3.65).

Anal. Calcd. for $C_{20}H_{12}N_4O$: C, 74.06; H, 3.73; N, 17.28. Found: C, 74.12; H, 3.96; N, 17.14.

This product also was formed from the reaction of dichloronaphthoquinone with 4 moles of 2-aminopyridine in chlorobenzene solution. The crude product (72% yield) was crystallized from acetonitrile to give reddish brown lozenges, m.p. 245.0–245.5°.

Hydrolysis of X by heating with dilute sulfuric acid produced the quinone I, identified by melting point and infrared spectrum.

Reductive acetylation of X yielded *5-acetoxy-6-[N-(2-pyridyl)-acetamido]-benzo[e]pyrido[a]benzimidazole*, which crystallized from benzene in white granules having an instantaneous melting point of 280° dec.; if put into the melting point bath at a lower temperature the sample decomposes over a range. λ_{max} 248.5, 254, 271, 290,* 303, 320–325, 333–340, 355, and 370 mμ (log ε 4.30, 4.33, 4.01, 3.68, 3.62, 2.56, 3.67, 3.67, and 2.48).

Anal. Calcd. for $C_{24}H_{18}N_4O_3$: C, 70.25; H, 4.39; N, 13.66. Found: C, 70.41; H, 4.30; N, 13.24.

6-Acetimido-5,6-dihydro-5-oxo-benzo[e]pyrido[a]benzimidazole (XI). A mixture of 1.00 g. (0.004 mole) of 2-acetamido-3-chloro-1,4-naphthoquinone, 0.70 g. (0.008 mole) of 2-amidopyridine, and 10 ml. of dry chlorobenzene was stirred and boiled under reflux for an hour, then cooled and filtered. The resulting solid (0.81 g., 70% yield, m.p. 265–267°) was crystallized from glycol diacetate, giving 0.68 g. of orange needles, m.p. 271.5–272.5° dec.; λ_{max} 246, 265, 306, 320, and 390 mμ (log ε 4.51, 4.38, 3.13, 3.10, and 3.56).

Anal. Calcd. for $C_{17}H_{11}N_3O_2$: C, 70.58; H, 3.81; N, 14.53. Found: C, 70.43; H, 3.74; N, 14.32.

Hydrolysis of XI with hot dilute hydrochloric acid yielded

(24) E. Koenigs and H. Greiner, *Ber.*, **64**, 1049 (1931).

(25) J. M. Bruce and F. K. Sutcliffe, *J. Chem. Soc.*, 4789 (1957).

the quinone I, identified by infrared spectrum and melting point.

5,6-Dihydro-3-nitro-5,6-dioxo-benzo[e]pyrido[a]benzimidazole (XII). To a solution of 2.48 g. of I in 50 ml. of concentrated sulfuric acid was added 1.0 ml. of concentrated nitric acid. The solution was heated to 125° over a 45-min. period, then an additional 1.0 ml. of nitric acid was added and the solution was kept at 125° for an hour. The cooled solution was drowned, and the solid was filtered, washed, and dried. The crude product (2.22 g., 78.5% yield) was crystallized thrice from *o*-dichlorobenzene, giving orange crystals, m. >360° dec. The compound dyes cotton a weak green from an orange-red vat.

Anal. Calcd. for $C_{15}H_7N_3O_4$: C, 61.44; H, 2.41; N, 14.33. Found: C, 61.30; H, 2.64; N, 14.30.

5,6-Dihydro-1- and 4-nitro-5,6-dioxobenz[e]pyrido[a]benzimidazoles. A mixture of 5.98 g. (0.022 mole) of 2,3-dichloro-5-nitro-1,4-naphthoquinone (m.p. 174–175.5°), 4.14 g. (0.044 mole) of 2-aminopyridine, and 75 ml. of ethanol was stirred and boiled under reflux for 4 hr., then cooled and filtered. The yield of crude product was 3.90 g. (60.5%). Extraction with hot *o*-dichlorobenzene removed the more soluble component (1.70 g.) and recrystallization from the same solvent gave orange-red crystals, m.p. 292.5–293.5° dec., which dyed cotton a bluish red shade from a yellowish red vat.

Anal. Calcd. for $C_{15}H_7N_3O_4$. C, 61.44; H, 2.41; N, 14.33. Found: C, 61.30; H, 2.52; N, 14.20.

The fraction insoluble in *o*-dichlorobenzene (0.80 g.) was crystallized from nitrobenzene. The orange product melted at 322–324° dec., and dyed cotton a very pale pink from a brownish red vat.

Anal. Calcd. for $C_{15}H_7N_3O_4$: C, 61.44; H, 2.41; N, 14.33. Found: C, 61.40; H, 2.49; N, 14.20.

5,6-Dihydro-8-methyl-5,6-dioxobenzo[e]pyrido[a]benzimidazole, was obtained crude (m.p. 266–275°) in 20% yield from 2-amino-6-methylpyridine by procedure (*b*) described under the preparation of I. Crystallization from toluene gave yellow needles, m.p. 280.8–283.0°.

Anal. Calcd. for $C_{16}H_{10}N_2O_2$: C, 73.27; H, 3.84; N, 10.69; O, 12.20. Found: C, 73.19; H, 3.74; N, 10.56; O, 12.51.

1,4-Dichloro-5,6-dihydro-5,6-dioxobenzo[e]pyrido[a]benzimidazole, was prepared from 2,3,5,8-tetrachloro-1,4-naphthoquinone (m.p. 251–252°, prepared by Bruck's method[26]) by procedure (*a*) described under the synthesis of I, except that the heating period was reduced to 4 hr. An 83.1% yield of crude product resulted, and crystallization from *o*-dichlorobenzene afforded a 50.1% yield of the orange quinone, m.p. 319.0–320.7°.

Anal. Calcd. for $C_{15}H_6Cl_2N_2O_2$: C, 56.81; H, 1.91; Cl, 22.36; N, 8.83. Found: C, 56.60; H, 2.09; Cl, 22.40; N, 8.89.

The *phenazine* was obtained from the quinone by refluxing it with *o*-phenylenediamine in methyl Cellosolve for 16 hr. Two crystallizations from methyl Cellosolve and one from chlorobenzene gave golden crystals, m.p. 313–314.2°.

Anal. Calcd. for $C_{21}H_{10}Cl_2N_4$: C, 64.80; H, 2.59; Cl, 18.22; N, 14.39. Found: C, 64.80; H, 2.63; Cl, 18.1; N, 14.00.

5,6-Dihydro-5,6-dioxobenzo[e]pyrimido[1,2-a]benzimidazole (XIII).[27] A solution of 11.35 g. (0.05 mole) of 2,3-dichloro-1,4-naphthoquinone and 9.50 g. (0.10 mole) of 2-aminopyrimidine in 100 ml. of methyl Cellosolve was stirred and boiled under reflux for 22 hr. The cooled reaction mixture was filtered and the solid was washed well with ethanol and hot water and was dried. The yield of crude brown quinone was 6.41 g. (51.3%). Crystallization from glycol diacetate, followed by recrystallization from *o*-dichlorobenzene gave felted microneedles of the golden yellow quinone, m.p. 343.5–345.0° dec.; λ_{max} 240–248, 259.5–262, 280.5–284, 288, 300,* 315–318,* and 355–370* mμ (log ε 4.53, 4.36, 4.41, 4.46, 4.24, 4.13, and 3.71).

Anal. Calcd. for $C_{14}H_7N_3O_2$: C, 67.47; H, 2.83; N, 16.86; O, 12.84. Found: C, 67.40; H, 2.84; N, 16.76; O, 12.91.

The *phenazine* was obtained from this quinone in the usual manner. Two crystallizations from chlorobenzene gave a product melting at 343.5–346.5°.

Anal. Calcd. for $C_{20}H_{11}N_5$: C, 74.75; H, 3.43; N, 21.80. Found: C, 74.51; H, 3.54; N, 21.70.

Reductive acetylation gave the *hydroquinone diacetate.* Crystallization from chlorobenzene afforded bright yellow crystals melting at about 270° dec. (the melting point varies with the temperature of the bath upon immersion of the sample, which decomposes over a range).

Anal. Calcd. for $C_{18}H_{13}N_3O_4$: C, 64.50; H, 3.88; N, 12.54. Found: C, 64.47; H, 3.92; N, 12.49.

12,13-Dihydro-12,13-dioxobenzo[e]quinolo[1,2-a]benzimidazole (XIV), was prepared from 2-aminoquinoline by method (*b*) used to make I. The yield of crude quinone was 39.3%, and crystallization from chlorobenzene gave dull orange needles, m.p. 327.5–328.5°; λ_{max} 249, 284–290, 297, 306–308° and 328 mμ (log ε 4.46, 4.33, 4.42, 4.35, and 4.11).

Anal. Calcd. for $C_{19}H_{10}N_2O_2$: C, 76.50; H, 3.38; N, 9.39. Found: C, 76.37; H, 3.17; N, 9.31.

Reductive acetylation of the quinone gave *12,13-diacetoxybenzo[e]quinolo[1,2-a]benzimidazole* as bright greenish yellow crystals (from acetic anhydride), m.p. 217.5–218.5°; λ_{max} 236–239, 280–289, 293, 326, 341, 357, and 385 mμ (log ε 4.47, 4.57, 4.62, 3.85, 3.76, 3.86, and 3.79).

Anal. Calcd. for $C_{23}H_{16}N_2O_4$: C, 71.87; H, 4.16; N, 7.29; O, 16.66. Found: C, 71.69; H, 4.16; N, 7.55; O, 16.86.

5,6-Dihydro-5,6-dioxobenzo[e]thiazolo[3,2-a]benzimidazole (XV), was obtained from 2-aminothiazole by the method used to prepare XIII. The cooled reaction mixture was diluted with ethanol, and the precipitate was washed well with alcohol and dried. The crude quinone (33% yield) was purified by solution in *o*-dichlorobenzene and precipitation with methylcyclohexane, after which it decomposed at 273–275° when introduced into the bath at 263°.

Anal. Calcd. for $C_{13}H_6N_2O_2S$: C, 61.41; H, 2.38; N, 11.02. Found: C, 60.6; H, 2.71; N, 11.0.

2-(2-Benzothiazolylamino)-3-hydroxy-1,4-naphthoquinone (XVI), was obtained crude in 22% yield when a mixture of 11.40 g. (0.05 mole) of 2,3-dichloronaphthoquinone, 7.50 g. (0.05 mole) of 2-aminobenzothiazole, 6.0 g. of sodium carbonate, and 100 ml. of ethanol was stirred and boiled under reflux for 16 hr. Crystallization of the crude product from chlorobenzene-methylcyclohexane gave the dull violet quinone, m.p. 231.5–233.5°.

Anal. Calcd. for $C_{17}H_{10}N_2O_3S$: C, 63.34; H, 3.13; N, 8.69; O, 14.89; S, 9.95. Found: C, 63.75; H, 2.62; N, 9.24; O, 14.71; S, 10.49.

2-(2-Benzimidazolylamino)-3-chloro-1,4-naphthoquinone (XVII), was obtained by exactly the same procedure described for the preceding compound with the exception that 0.05 mole of 2-aminobenzimidazole was substituted for the aminobenzothiazole. Extraction of the crude product (29.4% yield) with boiling *o*-dichlorobenzene afforded bright violet crystals, m.p. 266.3–266.7°.

Anal. Calcd. for $C_{17}H_{10}ClN_3O_2$: C, 63.07; H, 3.11; Cl, 10.95; N, 12.98; O, 9.89. Found: C, 63.27; H, 3.27; Cl, 11.01; N, 13.26; O, 10.20.

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BOUND BROOK, N. J.

(26) W. Bruck, I. G. Farbenindustrie, A. G. in PB Report No. 70341, p. 13632.

(27) A product (m.p. 323–324°) prepared similarly, recently was assigned[10b] the structure of the linear isomer of XIII. No evidence for this structure was offered, and it is probable that the product is identical with XIII.

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, SCIENTIFIC LABORATORY OF THE FORD MOTOR COMPANY]

Coupling Reactions of Xylylene Dihalides and Trimethylchlorosilane with Magnesium in Tetrahydrofuran

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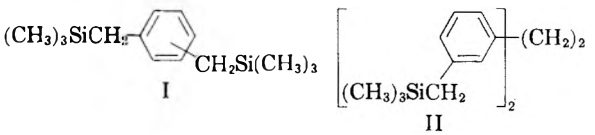
The preparation of three new organosilicon compounds—the *m*- and *p*-isomers of bis(trimethylsilyl)xylylene and 3,3'-bis(trimethylsilylmethyl)bibenzyl, from the coupling action of magnesium on the respective isomeric xylylene dihalides and trimethylchlorosilane in tetrahydrofuran, are reported.

The preparation of α,α'-disubstituted derivatives of xylene *via* the coupling of xylylene dihalides and other reactive organohalogen compounds with magnesium has received only scant attention in the chemical literature. Hersh,[1] in 1952 in a patent, described the preparation of bis-(trichlorosilyl)-*o*-xylylene (physical properties not given) by first treating *o*-xylylene dichloride with magnesium in ethyl ether followed by reaction with silicon tetrachloride. This would infer that a stable di-Grignard intermediate had been formed. Mann and Stewart,[2] in 1954, were unable to confirm Hersh's findings and isolated only poly-*o*-xylylene from the reaction of *o*-xylylene dichloride with magnesium. Attempts by these latter investigators[2] to couple *o*-xylylene dihalides with phenyldichlorophosphine by allowing them to react simultaneously with magnesium in ethyl ether likewise yielded only poly-*o*-xylylene and not the desired phenylphosphindoline. By converting the *o*- and *m*-xylylene dihalides to the respective chloromethylbenzyl ethers, Mann and Stewart[2] were able to convert only the *m*-substituted ether to a stable Grignard intermediate.

In the present instance, we wished to prepare the *m*- and *p*-isomers of bis(trimethylsilyl) xylylene (I) by an unequivocal route.



I II

Chernyshev, *et al.*[3] had reported the synthesis of an intermediate, bis(methyldichlorosilyl)-xylylene, (from reacting benzene with chloromethylmethyldichlorosilane in the presence of aluminum chloride) that could be methylated to give bis(trimethylsilyl) xylylene; however, this intermediate was a mixture of isomers whose respective concentrations and separations were not disclosed.

As a starting point, we investigated the feasibility of coupling *p*-xylylene dihalides and trimethylchlorosilane with magnesium. None of the dihalides (dichloride, dibromide, and diiodide), reacted separately, or in the presence of large excesses of trimethylchlorosilane, with magnesium in solvents such as ethyl ether, di-*n*-butyl ether or *p*-dioxane to give the desired compound but instead yielded poly-*p*-xylylene. The reaction was quite sluggish and the magnesium became coated with the insoluble polymer.

We then investigated the reaction of *m*-xylylene dibromide with magnesium and changed the solvent to tetrahydrofuran. The reaction was quite vigorous and rapid and upon completion, trimethylchlorosilane was added. The product isolated from this reaction was a low-melting polymer (molecular weight 1850–1900), containing only traces of silicon and bromine, whose elemental analysis indicated that it was poly-*m*-xylylene (consisting of approximately 18 xylene units). Since no stable di-Grignard intermediate was formed, the experiment was repeated except that the *m*-xylylene dibromide was reacted with magnesium in the presence of trimethylchlorosilane. From this latter reaction we obtained the desired bis(trimethylsilyl)-*m*-xylylene. The yield was 32–33% whether a large excess or an equivalent quantity of trimethylchlorosilane was used. A second compound was also isolated and identified as 3,3'-bis(trimethylsilylmethyl)bibenzyl (II).

Using the same technique we were also able to prepare bis(trimethylsilyl)-*p*-xylylene from coupling *p*-xylylene dichloride with trimethylchlorosilane.

Both isomers were identified by their elemental analyses and the substitutions verified by their respective infrared absorption spectra (reproduced in Figs. 1 and 2). The meta isomer was a liquid and the para isomer a low melting (61–63°) solid.

These reactions clearly demonstrate the versatility of tetrahydrofuran, over other ethereal solvents, for conducting coupling reactions of the type illustrated. Although no stable di-Grignard intermediates of *m*- and *p*-xylylene dihalides could be prepared for subsequent reactions, the tetrahydrofuran enables one to force a coupling reaction in the desired direction to a much greater extent

(1) J. M. Hersh, U. S. Patent **2,615,033** (1952).

(2) F. G. Mann and F. H. C. Stewart, *J. Chem. Soc.*, 2826 (1954); F. G. Mann, I. T. Millar, and F. H. C. Stewart, *J. Chem. Soc.*, 2832 (1954).

(3) E. A. Chernyshev, M. E. Dolgaya and P. Egorov, *Zhur. Obshchei Khim.*, **27**, 2676 (1957).

Fig. 1. Bis(trimethylsilyl)-*p*-xylylene

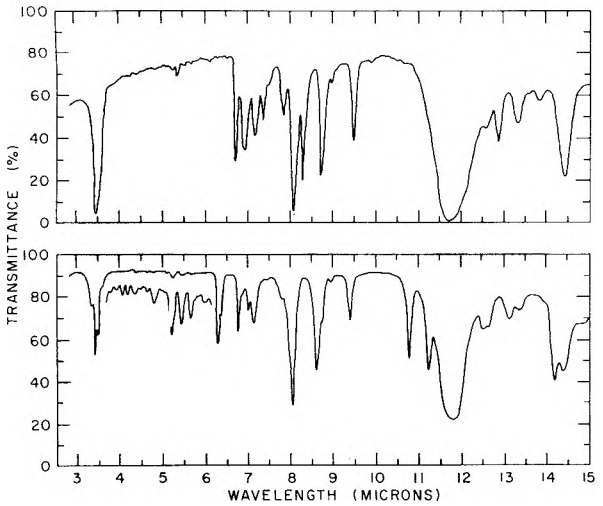


Fig. 2 Bis(trimethylsilyl)-*m*-xylylene

than was possible in the other ethereal solvents tried and thus provides a convenient and unequivocal route to the preparation of otherwise difficult-to-prepare α,α'-disubstituted xylenes.

EXPERIMENTAL

Starting materials: m-Xylylene dibromide. Eastman Kodak (Practical Grade). Recrystallized from ethanol, m.p. 76–77°. *p-Xylylene dichloride.* Eastman Kodak (White Label). *Trimethylchlorosilane.* Dow Corning. Redistilled through a 36-in. packed column and stored over Molecular Sieves, Type 4A. *Tetrahydrofuran.* Matheson, Coleman and Bell.

Further purification by distillation from lithium aluminum hydride and stored over calcium hydride. Traces of moisture or hydroxy compounds must be rigidly excluded due to reaction with the chlorosilane and subsequent reaction with the tetrahydrofuran.

Apparatus. All subsequent reactions were carried out in a 3-necked, round bottom flask equipped with a condenser, stirring assembly, addition funnel, and nitrogen inlet. All reactions were conducted under a dry nitrogen flush and protected from moisture.

Reaction of m-xylylene dibromide with magnesium in tetrahydrofuran followed by addition of trimethylchlorosilane. A solution of 61 g. (0.23 mole) of *m*-xylylene dibromide in 200 ml. of tetrahydrofuran was added to a stirred suspension of 11 g. (0.45 g.-atom) of magnesium chips (previously activated with iodine vapor) in 50 ml. of tetrahydrofuran. Reaction started immediately and the solution added at a rate sufficient to maintain gentle reflux. After stirring and refluxing for 2 hr., 50 g. (0.46 mole) of trimethylchlorosilane was added (little or no heat of reaction was noted) and the mixture stirred and refluxed for 3 hr. Upon cooling, 100 ml. of benzene was added, the mixture washed with water, the organic layer dried over Molecular Sieves, Type 4A, filtered, and distilled to remove solvents and low boiling materials.

The residue solidified upon cooling and extraction with acetone left an insoluble residue that melted at 65–75°. Attempts to crystallize the material from solvent mixtures were unsuccessful and yielded a viscous oil that solidified only after all traces of solvent were removed.

The elemental analysis and molecular weight agree with that calculated for poly-*m*-xylylene containing approximately 18 xylene units.

Anal. Calcd. for $C_{144}H_{146}$: C, 92.16; H, 7.84; mol. wt. 1877. Found: C, 91.41, 91.50; H, 8.02, 8.11; Si, trace; Br, trace; mol. wt., 1850, 1900.

The infrared spectrum of the polymer verified meta substitution and also exhibited weak bands at 8.05 and 11.80–11.90μ characteristic of Si—CH_3 and Si—C linkages, due probably to trimethylsilyl end groups.

Bis(trimethylsilyl)-m-xylylene. A. *Reaction of m-xylylene dibromide, in the presence of an excess of trimethylchlorosilane, with magnesium.* A mixture of 40 g. (0.15 mole) of *m*-xylylene dibromide and 130.3 g. (1.2 mole) of trimethylchlorosilane was reacted with 7.3 g. (0.3 g.-atom) of magnesium as described in the preceding experiment. After refluxing for 2 hr., the mixture was concentrated to remove unreacted trimethylchlorosilane and a portion of the solvent at which time the magnesium halide salts separated. The liquid portion was decanted from the salts and the latter washed with ethyl ether. The decanted liquid and washings were combined and distilled to remove solvents and the residue fractionated at reduced pressures. Five liquid fractions were collected of which fractions 3 and 4 constituted 11.9 g. (32% yield), b.p. 73–74° (0.6 mm.), n_D^{20} 1.4919 and 1.4920 respectively.

Anal. Calcd. for $C_{14}H_{26}Si_2$: C, 67.13; H, 10.46; Si, 22.40. Found: Fraction 3: C, 67.24; H, 10.20; Si, 22.60. Fraction 4: C, 67.13; H, 10.43; Si, 22.50.

The residue, a viscous, dark-colored oil, weighed 6.0 g.

B. *Reaction of m-xylylene dibromide, in the presence of an equivalent quantity of trimethylchlorosilane, with magnesium.* A solution of 52.1 g. (0.20 mole) of *m*-xylylene dibromide in 180 ml. of tetrahydrofuran was added to 9.6 g. (0.40 g.-atom) of magnesium chips suspended in a solution of 42.9 g. (0.40 mole) of trimethylchlorosilane and 200 ml. of tetrahydrofuran over a period of 2 hr. followed by refluxing for 19.5 hr.

Water, 200 ml., was added to the reaction mixture followed by 300 ml. of toluene. The organic layer was separated, dried, filtered; the solvents removed, and the residue fractionated. The fraction boiling at 66–66.5° (0.3 mm.) weighed 16.6 g. (33.7% yield), n_D^{20} 1.4919. The infrared absorption spectrum of this product was identical with that from (A).

Anal. Calcd. for $C_{14}H_{26}Si_2$: C, 67.13; H, 10.46; Si, 22.40. Found: C, 67.41, 67.48; H, 10.22, 10.29; Si, 22.85, 22.56.

Further distillation of the residue (17.0 g.) yielded 3.5 g. of liquid, b.p. 139–142° (0.65 mm.), n_D^{20} 1.5270, whose elemental analysis agreed with that calculated for 3,3′-bis(trimethylsilylmethyl)bibenzyl (II). The infrared absorption spectrum also supported the structure indicated by II.

Anal. Calcd. for $C_{32}H_{34}Si_2$: C, 74.51; H, 9.66; Si, 15.83. Found: C, 74.84; H, 9.20; Si, 16.04.

Bis(trimethylsilyl)-p-xylylene. A mixture of 35 g. (0.20 mole) of *p*-xylylene dichloride and 174 g. (1.6 mole) of trimethylchlorosilane in 200 ml. of tetrahydrofuran was added to 9.7 g. (0.40 g.-atom) of magnesium chips suspended in 50 ml. of tetrahydrofuran and reacted in the manner described in the preceding experiments.

The precipitated magnesium chloride was removed by centrifugation and the filtrate distilled to remove solvent and unreacted trimethylchlorosilane. The residue, partially crystalline upon cooling, was dissolved in hot ethanol, treated with charcoal, and filtered. Upon cooling, white needle-like crystals separated; however, these melted over a wide range and the crude product was distilled at reduced pressures. The fraction collected at 73–74° (0.3 mm.) melted at 61–63°.

Anal. Calcd. for $C_{14}H_{26}Si_2$: C, 67.13; H, 10.46; Si, 22.40. Found: C, 67.20, 67.06; H, 10.42, 10.30; Si, 22.14, 22.31.

Infrared spectra. The infrared spectra, reproduced in Figs. 1 and 2, were recorded on a Perkin-Elmer Infracord, Model 137. The spectrum of the *m*-isomer was taken from a film and a capillary (0.05 mm.) to resolve the 5–6μ region and the spectrum of the *p*-isomer was taken from a Nujol mull.

Acknowledgments. The preparation of these compounds was conducted under the sponsorship of the United States Air Force under Contract AF 33(600)-32448, monitored by Materials Laboratory, Director of Laboratory, Wright Air Development Center, Wright-Patterson AFB, Ohio. The authors also wish to express their gratitude to Dr. Harold Rosenberg for his helpful advice.

DEARBORN, MICH.

[RESEARCH DIVISION CONTRIBUTION NO. 275, JACKSON LABORATORY ORGANIC CHEMICALS DEPARTMENT, E. I. DU PONT DE NEMOURS AND CO., INC.]

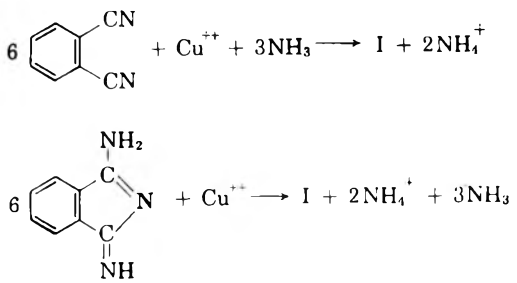
Chemistry of Copper Phthalocyanine Precursor

R. A. BROOKS, J. G. BURT, B. F. SKILES, AND M. S. WHELEN

Received October 1, 1958

The preparation and properties of a precursor of formula $C_{48}H_{25}N_{13}Cu$ which generates copper phthalocyanine upon reduction are discussed. A structure for the precursor is proposed.

Copper phthalocyanine precursor is the name given to a buff colored compound I of empirical formula $C_{48}H_{25}N_{13}Cu$ which generates copper phthalocyanine (II) upon reduction. I is formed by reaction under oxidizing conditions of phthalonitrile, ammonia and a cupric salt in dimethylformamide at about 90° or by reaction of 1-amino-3-iminoisoindolenine and a cupric salt under similar conditions. The yield by the phthalonitrile route is improved by the addition of a small amount of *N*-methylglucamine, the role of which has not been determined.



I is very soluble in dimethylformamide and in alcoholic solvents such as ethylene glycol monoethyl ether. It has limited solubility in benzene and is insoluble in aliphatic hydrocarbons. I is usually amorphous but can be crystallized from benzene. Stirring in a small amount of methyl alcohol also converts the amorphous material to a crystalline form[1] the x-ray diffraction pattern of which is reproduced in Fig. 1.

Unlike II, which is highly colored, I exhibits only very weak absorption in the visible region of the spectrum. The ultraviolet and infrared spectra are reproduced in Figs. 2 and 3, respectively.

When in crystalline form, I is quite stable and can be stored for long periods at room temperature. Its solutions decompose in a few days, especially in sunlight, to give copper phthalocyanine and other products of lower molecular weight.

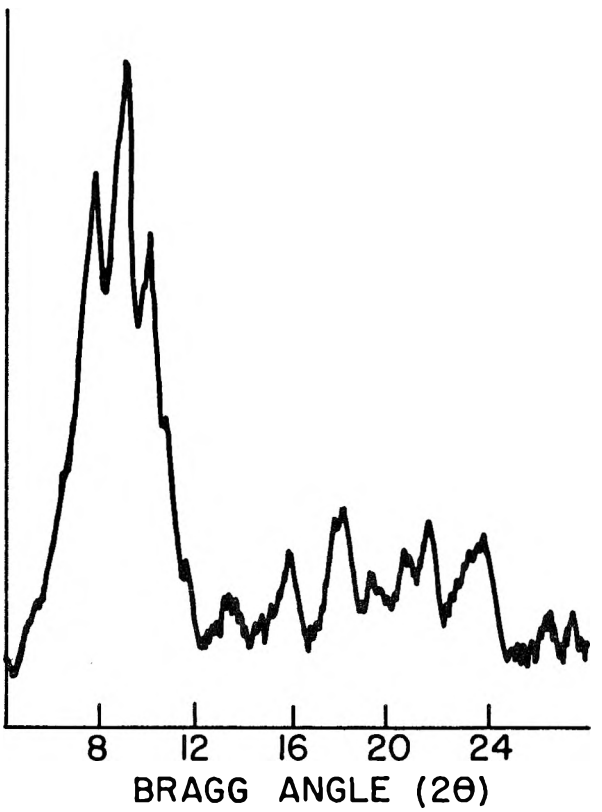


Fig. 1. X-ray diffraction pattern of copper phthalocyanine precursor

Reduction of I is easily effected with a large number of agents. The weight yield of II is 68%, the remaining weight being accounted for as ammonia and derivatives of phthalic acid. Hydrogenation over palladium indicates that reduction is a 2 electron process. Reduction with hot, alkaline glucose shows that 5 moles of ammonia are liberated. Pyrolysis of I at 180° gives about a 65% yield of II with liberation of 1 mole of ammonia and 2 moles of phthalonitrile. The slightly lowered

(1) M. S. Whelen, U.S. Patent 2,795,586, June 11, 1957; *Chem. Abstr.*, 51, 17184 (1957).

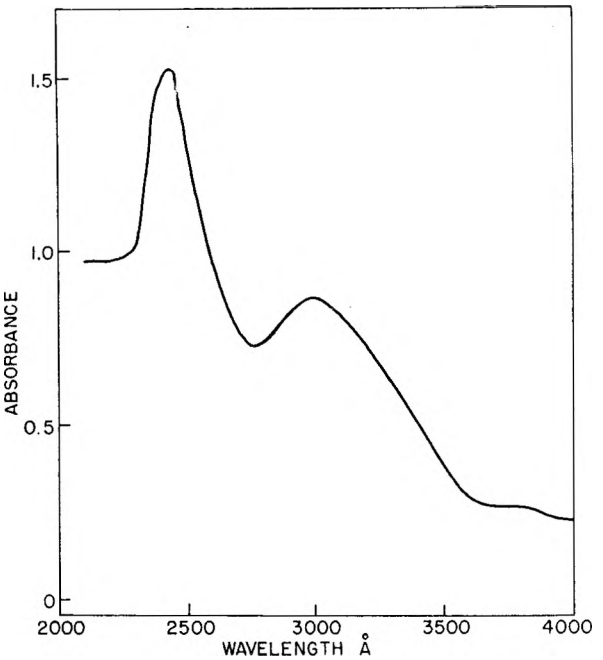


Fig. 2. Ultraviolet spectrum of copper phthalocyanine precursor. Chloroform solvent, 0.0134 mg./ml.

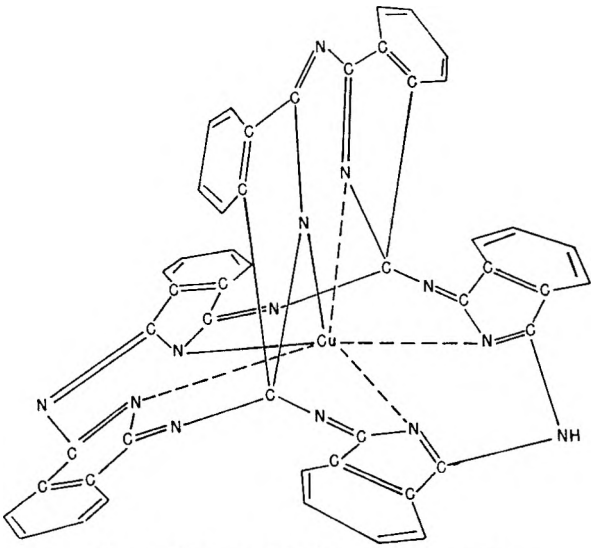


Fig. 4. Copper phthalocyanine precursor

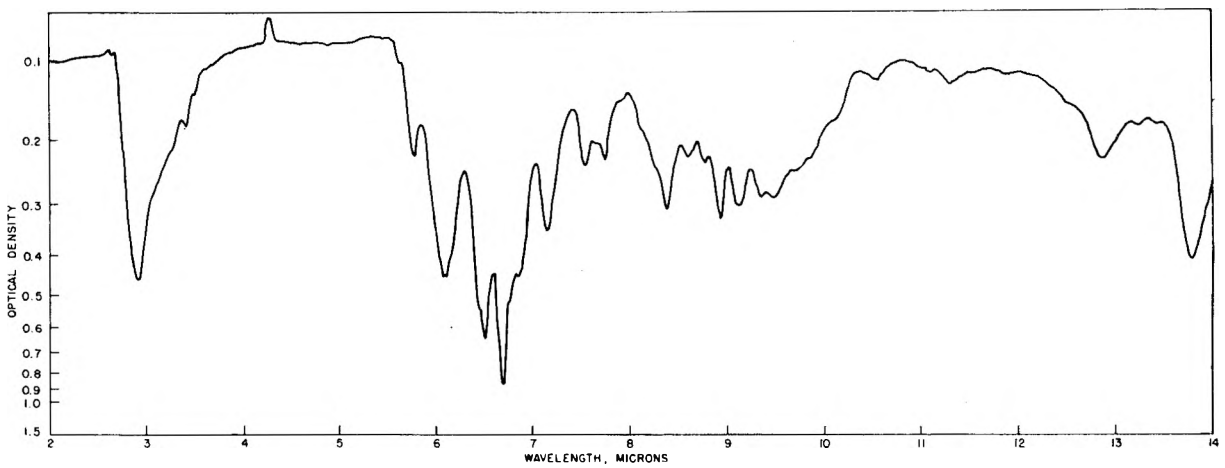


Fig. 3. Infrared spectrum of copper phthalocyanine precursor, KBr disk, NaCl prism

yield of II suggests that autoreduction has taken place.

On the basis of its reactions and a study of molecular models, it is concluded that I is a condensation polymer of 1-amino-3-iminoisoindolenine containing bound copper. A triplanar structure, as shown in Fig. 4, has been suggested[2] to explain the solubility and weak color. This structure cannot be considered as proven and alternatives can be written, for example, an open chain structure. It is felt, however, that the triplanar cage structure is supported by all known facts and serves best to explain the properties of I. A similar structure has been proposed for a pyridine complex of a copper-containing polymer of 1-amino-3-iminoisoindolenine.[3]

EXPERIMENTAL

Copper phthalocyanine precursor (I) was prepared from phthalonitrile by the method of Barnhart, Skiles, and Stevenson.[4] The product was obtained as a buff colored powder which slowly turned green upon heating over 100° but had no definite melting point. A sample was crystallized from benzene.

Anal. Calcd. for $C_{48}H_{25}N_{13}Cu$: C, 68.0; H, 2.97; N, 21.5; Cu, 7.50. Found: C, 67.5, 67.7; H, 2.84, 3.21; N, 21.5, 21.4; Cu, 7.43, 7.77.

Reduction of 0.760 g. (0.0009 mole) of I over palladium in methanol required 24.1 ml. (0.0009 mole) of hydrogen at 25°. The reduction products included 0.520 g. (0.0009 mole) of copper phthalocyanine (II) and 0.015 g. (0.0009 mole) of ammonia.

(2) G. Barnhart, B. F. Skiles, and A. C. Stevenson, French Patent 1,068,092, June 22,1954.

(3) F. Baumann, B. Bienert, G. Rosch, H. Vollmann, and W. Wolf, *Angew. Chem.*, 68, 133 (1956).

(4) G. Barnhart, B. F. Skiles, and A. C. Stevenson, British Patent 745,359, Feb. 22, 1956; *Chem. Abstr.*, 50, 12491 (1956).

Reduction of 8.47 g. (0.01 mole) of I with excess alkaline glucose at 80° gave 5.77 g. (0.01 mole) of copper phthalocyanine (II) with the liberation of 0.85 g. (0.05 mole) of ammonia. A fluorescein test on the residue indicated the presence of phthalic acid or a derivative.

Pyrolysis of 8.47 g. (0.01 mole) of I at 180° gave 5.50 g. (0.0009 mole) of copper phthalocyanine (II) and 0.17 g. (0.01 mole) of ammonia. Phthalonitrile, m.p. 141°, sublimed and was collected; yield 2.56 g. (0.02 mole).

1-Amino-3-iminoisoindolenine. Phthalonitrile (128 g., 1.0 mole) and liquid ammonia (119 g., 7.0 moles) were placed in a 400-ml. stainless steel pressure vessel sealed with an aluminum gasket. The vessel was heated to 150° and shaken at that temperature for 5 hr. at about 500 p.s.i.g. It was then cooled, vented, and the product was discharged; yield 145 g. (100%). Titration with hydrochloric acid to an endpoint at *p*H 5.25, assuming monobasicity, indicated a purity of 99%.

Anal. Calcd. for $C_8H_7N_3$: C, 66.2; H, 4.83; N, 28.9. Found: C, 65.7, 65.9; H, 4.88, 4.76; N, 28.3; 28.2.

A sample of 1-amino-3-iminoisoindolenine was converted to I by the method of Brooks.[5] The product was identical to that prepared from phthalonitrile.

WILMINGTON 99, DEL.

(5) R. A. Brooks, U.S. Patent 2,772,285, Nov. 22, 1956; *Chem. Abstr.*, 50, 17464 (1956).

[CONTRIBUTION FROM THE MCPHERSON CHEMISTRY LABORATORY OF THE OHIO STATE UNIVERSITY]

New Reactions on Decomposition of a Hindered α-Diazoketone[1]

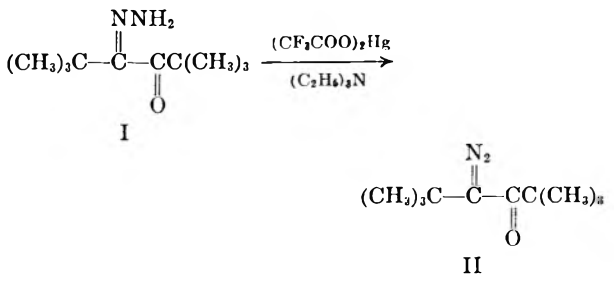
MELVIN S. NEWMAN AND A. ARKELL[2]

Received October 6, 1958

A new procedure for the conversion of monohydrazones of α-diketones to α-diazoketones by oxidation of the hydrazone with mercuric trifluoroacetate in acetonitrile in the presence of triethylamine is described. The rearrangements of 4-diazo-2,2,5,5-tetramethyl-3-hexanone under several conditions are described. The main product of these rearrangements is 2,2,4,5-tetramethyl-4-hexen-3-one, a product in which a methyl migration has occurred.

In connection with work on the synthesis of highly hindered aliphatic compounds we wished to prepare a quantity of di-*t*-butylacetic acid as it represents a disubstituted acetic acid with a *six number*[3] of eighteen. One method which appeared promising was the pyrolysis of 4-diazo,2,2,5,5-tetramethyl-3-hexanone, II, to di-*t*-butylketene (III)[4] a compound which would be expected to yield di-*t*-butylacetic acid on hydration.

The preparation of II was accomplished by a new method which involved oxidation of the monohydrazone of dipivaloyl (I) with mercuric trifluoroacetate and triethylamine in acetonitrile at room temperature. During this treatment about 20% of the theoretical amount of nitrogen to be expected from the diazoketone was evolved.



I

II

The entire reaction mixture thus obtained was then treated by three methods in attempts to obtain III. However, only minute amounts (0–3%) of ketene (III) were obtained by heating, either alone or in solvents, by treatment with boron trifluoride etherate, or by irradiation with ultraviolet light at 40°. The small amount of III obtained in any experiment precluded its isolation in sufficient quantity for analysis. However, by means of gas chromatography a homogeneous fraction was isolated which was undoubtedly the ketene (III) as judged by strong infrared absorption bands at 4.83μ and 5.80μ. This ketene III appears to be much more stable than other aliphatic ketenes, as no great tendency to dimerization was apparent. Because of the low yields of III obtained in spite of many attempts at improvement, this method for the synthesis of di-*t*-butylacetic acid was abandoned.[5]

Although the original purpose was not attained, the rearrangements of the diazoketone, II, produced results of interest. These are outlined in Chart 1.

The major product of pyrolysis (or irradiation, or acid-catalyzed rearrangement) was 2,2,4,5-tetramethyl-4-hexen-3-one (IV). In addition small amounts of 2,2,4,5-tetramethyl-5-hexen-3-one (V) and of a saturated (hence cyclic) ketone, $C_{10}H_{18}O$- (VI) were formed. In both IV and V a carbon skele-

(1) The material herein presented was taken from the Ph.D. thesis, Ohio State University, 1958, of A. Arkell.

(2) This research was supported in part by the United States Air Force under Contract No. AF33(616)-3412, monitored by the Aeronautical Research Laboratory, Wright Air Development Center.

(3) M. S. Newman, *J. Am. Chem. Soc.*, 72, 4783 (1950); K. L. Loening, A. B. Garrett, and M. S. Newman, *J. Am. Chem. Soc.*, 74, 3929 (1952).

(4) For an example of the rearrangement of a *t*-butyl group in the decomposition of a diazoketone, see K. B. Wiberg and T. W. Hutton, *J. Am. Chem. Soc.*, 76, 5367 (1954).

(5) The synthesis of di-*t*-butylacetic acid in good yield by another method will soon be reported.

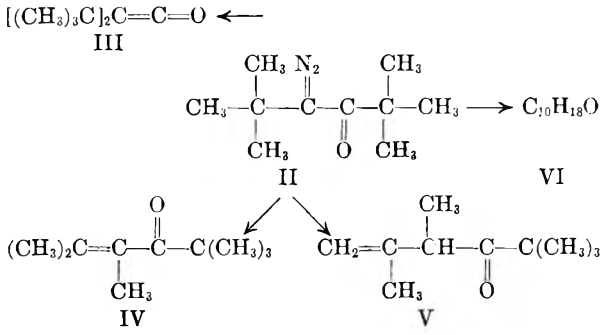


CHART I

tal rearrangement, involving migration of a methyl group to the carbon which held the diazo group, has occurred.[6] The structure of VI is in doubt as infrared spectral studies favor a polymethylated cyclopentanone structure, 2,2,4,4,5-pentamethylcyclopentanone, whereas a study of the NMR spectrum[7] favors formulation as *t*-butyl 2,2-dimethylcyclopropyl ketone, but neither line of evidence seems conclusive. We do not propose to study this compound further since the main purpose of the pyrolysis was the synthesis of di-*t*-butylketene.

The structure, 2,2,4,5-tetramethyl-4-hexen-3-one (IV) was assigned to the major product (near 80%) of the decompositions of II on the basis of the following facts. Analysis of a homogeneous sample, obtained by gas chromatography, indicated a formula of $C_{10}H_{18}O$. The ultraviolet absorption spectrum showed a maximum at 245 mμ (ϵ_{max}, 900), which compares with a maximum at 243 mμ (ϵ_{max}, 1400) for 2,6,6-trimethyl-1-acetylcyclohexene.[8] The very low intensity is typical of hindered α,β-unsaturated ketones.[9] In the present example, IV, the hindrance to coplanarity is severe because of the *t*-butyl group, whereas in other ketones under discussion[8] methyl ketones were involved. Compound IV absorbed strongly at 5.95μ in the infrared and formed a liquid 2,4-dinitrophenylhydrazone. No double bond absorption in the 6.0–6.4 or 11.1–11.3μ regions was observed.

The structure, 2,2,4,5-tetramethyl-5-hexen-3-one (V) present as a minor constituent (1–5%) in the products of decomposition of II by the methods described above, was assigned on the basis of the following facts. Analysis and gas chromatographic characteristics indicated that V was isomeric with IV. The ultraviolet absorption spectrum showed a maximum at 296.5 mμ (ϵ_{max}, 81). As compared to hexamethylacetone which has a maximum[10] at 295 mμ (ϵ_{max}, 20). The absorption maximum for a ketone having an isolated double bond should occur at about the same position as that of the corresponding saturated ketone.[11] In addition a strong band at 11.2μ in the infrared is characteristic of compounds having a terminal methylene group. V formed a 2,4-dinitrophenylhydrazone.

The following facts were obtained by a study of a small amount of VI which appeared homogeneous by gas chromatographic separation. Analysis indicated the formula, $C_{10}H_{18}O$, isomeric with IV and V. No hydrogen was absorbed on an attempted hydrogenation. The ketone, VI, absorbed at 286 mμ (ϵ_{max}, 59)[12] and its 2,4-dinitrophenylhydrazone absorbed at 360 mμ (ϵ_{max}, 20,600).[13] The infrared absorption was puzzling as there was a medium band at 5.65μ and a strong band at 5.90μ. Split carbonyl absorption bands have been observed before[14] but in no case has the spread been so large. The band at 5.90μ might be explained by a structure of *t*-butyl 2,2-dimethylcyclopropyl ketone[15] for VI, but one would expect an absorption at a higher wave length for this ketone since methyl cyclopropyl ketone absorbs at 5.87μ and polymethyl substitution in ketones generally increases the wave length of the carbonyl absorption.[16] In view of the latter effect, a structure of 2,2,4,4,5-pentamethyl cyclopentanone appears attractive for VI, except that the NMR evidence rules against this structure.[7]

EXPERIMENTAL[17]

2,2,5,5-Tetramethyl-4-hexanol-3-one (pivaloin). To a sodium dispersion prepared by rapid stirring of 93 g. of sodium and 2 g. of oleic acid in 300 ml. of dry toluene was added 850 ml. of toluene and then 260 g. of ethyl pivalate during a 3.5-hr. period. After stirring an hour, an ice cold solution of 210 g. of sulfuric acid in 350 ml. of water was added during 1 hr.

(6) The formation of an α,β-unsaturated ketone with unrearranged carbon skeleton has been reported by V. Franzen, *Ann.*, **602**, 199 (1957). The rearrangement of triphenylmethyl diazomethane to triphenylethylene has been reported by L. Hellerman and R. L. Garner, *J. Am. Chem. Soc.*, **57**, 139 (1935).

(7) We thank Dr. George V. D. Tiers, Minnesota Mining and Manufacturing Co., for the NMR study and interpretation.

(8) H. B. Henbest and G. Woods, *J. Chem. Soc.*, 1150 (1952).

(9) For examples, see E. A. Braude and C. J. Timmons, *J. Chem. Soc.*, 3766 (1955); E. A. Braude and F. Sondheimer, *J. Chem. Soc.*, 3755 (1955); G. D. Hedden and W. G. Brown, *J. Am. Chem. Soc.*, **75**, 3744 (1953); N. J. Leonard and E. R. Blout, *J. Am. Chem. Soc.*, **72**, 434 (1950).

(10) F. O. Rice, *J. Am. Chem. Soc.*, **42**, 727 (1920).

(11) A. E. Gillam and E. S. Stern, *Electronic Absorption Spectroscopy*, Edward Arnold Ltd., London (1954), pp. 62–3.

(12) R. C. Cookson, *J. Chem. Soc.*, 282 (1954) reports that camphor absorbs at 289.5 mμ (ϵ_{max}, 32).

(13) A. Kergomard and C. Sandris, *Bull. soc. chim.*, 1260 (1954) report that the 2,4-dinitrophenylhydrazone of camphor absorbs at 365 mμ (ϵ_{max} 23,100).

(14) See J. L. Hales, J. I. Jones, and W. Kynaston, *J. Chem. Soc.*, 618 (1957), for a discussion of split carbonyl absorption bands. Also P. Yates, N. Yoda, W. Brown, and B. Mann, *J. Am. Chem. Soc.*, **80**, 202 (1958).

(15) This suggestion was made by Dr. Tiers, ref. 7.

(16) P. D. Bartlett and M. Stiles, *J. Am. Chem. Soc.*, **77**, 2809 (1955).

(17) All melting points uncorrected unless otherwise noted.

The washed and dried toluene layer was cooled at −70° to yield pivaloin, m.p. 80–81°, in 86.5% yield.[18]

2,2,5,5-Tetramethyl-3,4-hexanedione (pivalil). After considerable study the following oxidative procedure was found to give excellent yields of pure pivalil. A pivaloin solution, A, was prepared from 86.2 g. of pivaloin, 210 ml. of acetic acid, 50 ml. of water, and 25 ml. of concentrated sulfuric acid (total volume, 380 ml.). A chromic acid solution, B, was prepared from 50 g. of chromic oxide, 100 ml. of acetic acid, and 50 ml. of water (total volume, 170 ml.). Ten similar small scale oxidations were run. In each 38 ml. of solution A was heated to 75° and with gentle stirring 17 ml. of solution B was added all at once. A vigorous reaction set in and quickly subsided. The hot mixture was then immediately poured on ice. The combined reaction mixtures were extracted with Skellysolve B (petroleum ether, b.p. 65–70°) and the extracts washed with 2% sodium hydroxide, saturated salt solution, and dried by filtration through magnesium sulfate. After removal of solvent and distillation 74.0 g. (87%) of pivalil, b.p. 66–67° and 19–20 mm., n_D^{20} 1.4163, was obtained.[19]

2,2,5,5-Tetramethyl-3,4-hexanedione monohydrazone, I. After refluxing a mixture of 85.2 g. of pivalil, 250 ml. of alcohol, 500 ml. of benzene, 100 g. of 98% hydrazine, and 2 ml. of acetic acid into a column equipped with a phase-separating head for 42 hr., no more aqueous phase was being formed. The reaction mixture was diluted with water and the organic layer distilled to yield 46.0 g. (50%) of solid I and 30.9 g. (36%) of recovered pivalil. A sublimed sample of I melted at 43.4–45.0° and was colorless.[20]

Anal. Calcd. for $C_{10}H_{20}N_2O$: C, 65.2; H, 10.9; N, 15.2. Found:[21] C, 65.2; H, 10.9; N, 15.2.

When a solution of I was passed through a column of alumina, I was absorbed. On elution with aqueous acetone crystals of a colorless compound, m.p. 43.8–44.2° were obtained in about 80% yield based on I. Absence of the NH band at 3.0μ and depression of melting point when mixed with I showed that a new compound had been formed. We believe this to be the acetone azine of I.

Anal. Calcd. for $C_{13}H_{24}N_2O$: C, 69.6; H, 10.8; N, 12.5. Found: C, 69.6; H, 10.6; N, 12.9.

Preparation and decomposition of 2,2,5,5-tetramethyl-4-diazo-3-hexanone, II. A filtered solution of 42.7 g. of mercuric trifluoroacetate (made by dissolving mercuric oxide in anhydrous trifluoroacetic acid) in 130 ml. of acetonitrile was added dropwise during 7 hr. to a magnetically stirred solution of 18.4 g. of I and 30 g. of triethylamine in 25 ml. of acetonitrile in a flask fitted to an azotometer. During this period, approximately 20% of the theoretical nitrogen was evolved. The filtered solution diluted with low boiling petroleum ether was washed with cold dilute 2% hydrochloric acid until neutral. After drying over magnesium sulfate the solvent was removed under reduced pressure and aliquots of the residual oil treated in one of the following ways: (*A*) heating 1- to 2-g. samples of II at 60–90°; (*B*) irradiation of 5.0 g. of II in 100 ml. of dry tetrahydrofuran for 15 hr. at 24–40°; and (*C*) catalytic decomposition by cuprous chloride in acetonitrile solution (3.0 g. of crude II in 15 ml.) at 24–26° during 12 hr. The products of pyrolysis were analyzed by gas chromatography.[22] By methods *A* and *B* the chief product was 2,2,4,5-tetramethyl-4-hexen-3-one (IV) which was present in 80–90% yield based on starting I. The amounts of di-*t*-butylketene (III) present were too small to allow for more than an infrared absorption spectral analysis which, however, was conclusive as a strong band at 4.83μ indicated the ketone function.[23] The analytical sample of IV had n_D^{20} 1.4424, λ_{max} 245, ϵ_{max} 900. The 2,4-dinitrophenylhydrazone, an oil, had λ_{max} 364, ϵ_{max} 23,200.

Calcd. for $C_{10}H_{18}O$: C, 77.9; H, 11.8. Found: C, 77.8, 77.6; H, 11.6, 11.6. Calcd. for $C_{16}H_{22}N_4O_4$: C, 57.5; H, 6.6; N, 16.8. Found: C, 57.6; H, 6.6; N, 16.8.

The analytical sample of V had n_D^{20} 1.4324, λ_{max} 296.5, ϵ_{max} 81. The 2,4-dinitrophenylhydrazone of V was not obtained in quantities sufficient for analysis, but spectral analysis showed λ_{max} at 361 mμ, ϵ_{max} 23,200.

Anal. Calcd. for $C_{10}H_{18}O$: C, 77.9; H, 11.8. Found: C, 77.6; H, 11.8.

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(18) Previously reported yields were 77% (in xylene), H. J. Backer, *Rec. trav. chim.*, **57**, 967 (1937); and 52–60% (in ether), J. M. Snell and S. M. McElvain, *Org. Syntheses* **13**, 36 (1933).

(19) N. J. Leonard and P. M. Mader, *J. Am. Chem. Soc.*, **72**, 5388 (1950) report for pivalil n_D^{20} 1.4144 (50% yield) in an oxidation by chromic acid at 14°. G. F. Hennion and T. F. Banigan, Jr., *J. Am. Chem. Soc.*, **68**, 1202 (1946) report n_D^{20} 1.4157 by oxidation of di-*t*-butylacetylene. Our sample of pivalil, on chromatography or vapor phase chromatography, was homogeneous and had n_D^{20} 1.4163.

(20) This compound was first prepared by G. R. Kahle, Ph.D. Thesis, Ohio State University, 1956, p. 66.

(21) All microanalyses by Galbraith Microanalytical Laboratory, Knoxville, Tenn.

(22) We acknowledge with thanks the valuable assistance of Mr. W. E. Lee and Dr. E. Malmberg in developing this analytical procedure.

(23) A. K. Bose and P. Yates, *J. Am. Chem. Soc.*, **74**, 4703 (1952).

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NORTHWESTERN UNIVERSITY]

Preparation of Acyclic Imides

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Bisphenylacetimide is produced from benzamide and phenylacetyl chloride or phenylacetic anhydride by way of *N*-benzoylphenylacetamide. The mechanism appears to involve acyl carbonium ions. The same acylating agents do not convert methyl phenaceturate to an imide. Phenyl isocyanate and ethyl isocyanatoacetate were found to react with a number of acid anhydrides, both cyclic and acyclic, to yield imides with evolution of carbon dioxide. This reaction is useful in preparing imides that contain a substituent on the nitrogen. A mechanism for this reaction is suggested.

The preparation of diacyl derivatives of ammonia or alkylamines has received considerable attention in recent years, especially the direct acylation of amides. In many instances an amide $RCONH_2$ may be acylated to the imide $(RCO)_2NH$ in good yields by reaction with an acid anhydride or acyl chloride. Such catalysts as hydrogen chloride,[2] acyl chloride,[2] or sulfuric acid[3] are helpful with acid anhydrides, and pyridine has been used with acyl halides.[4,5] As an example, dipropionimide[6] was made in good yields[3] from propionic anhydride, propionamide, and sulfuric acid. Some amides, however, take a different course, examples being benzamide which reacted with benzoic anhydride to give 33 times more benzonitrile[3] than dibenzimide, and acetanilide which reacted with benzoyl chloride and pyridine to give *N*-phenyldibenzimide[4] instead of *N*-benzoylacetanilide. The unpredictability of such reactions is witnessed again in the contrasting behavior of aceturic and phenaceturic esters: The former[7] was readily acetylated by acetic anhydride to yield diacetimidoacetic ester Ac_2NCH_2COOR, whereas the latter[8] ($PhCH_2CONHCH_2COOCH_2Ph$) was nonacylated by phenylacetic anhydride or phenylacetyl chloride alone or in the presence of bases. Thus, the objective of the present work was to study various methods of synthesis of acyclic imides, with especial reference to diacetimido esters and analogous compounds, $(RCO)_2NCH_2COOR'$.

Preliminary experiments substantiated in general the findings of other investigators. For example, when a mixture of benzamide and acetic anhydride was heated for 3 min. in the presence of concentrated sulfuric acid, a 61% yield of *N*-acetylbenzamide was obtained. Similarly, a 52% yield of *N*-acetylbenzamide was obtained. Similarly, a 52% yield of *N*-benzoylphenylacetamide resulted from heating (160–180°) a mixture of phenylacetic anhydride and benzamide for only 2 min. in the presence of sulfuric acid; but a similar mixture containing 2 equivalents of phenylacetic anhydride and heated for 10 minutes produced bisphenylacetimide, $(C_6H_5CH_2CO)_2NH$, in 60% yield. The same compound was obtained in 96% yield when benzamide was heated with an excess of phenylacetyl chloride at 80° for 24 hr. No bisphenylacetimide resulted on heating pure phenylacetamide at 180° for 6 hr. but an 11% yield was obtained together with unchanged amide if the heating was done in the presence of a trace of sulfuric acid.

The formation of the mixed imide, *N*-benzoylphenylacetamide, is a simple acylation of benzamide, but the continued reaction to form bisphenylacetimide is interesting from a standpoint of mechanism. The fact that the latter is formed from either phenylacetic anhydride or phenylacetyl chloride is evidence for the phenylacetyl carbonium ion as intermediate, since it is common to both the anhydride and chloride. This mechanism would account for the findings:

$$PhCONH_2 \xrightleftharpoons{PhCH_2\overset{+}{C}O} PhCO\overset{+}{N}H_2COCH_2Ph \rightleftharpoons$$

$$Ph\overset{+}{C}O + PhCH_2CONH_2 \xrightarrow[-H^+]{PhCH_2\overset{+}{C}O} (PhCH_2CO)_2NH$$

The benzoyl carbonium ion arising in this sequence of steps is less active than the phenylacetyl carbonium ion for it is stabilized by resonance with the aromatic nucleus. The greater reactivity of the latter, therefore, explains why the reaction progresses so nearly to completion in forming the symmetrical imide.

Methyl phenaceturate was the next amide

(1) This work was done during 1953–1954 when one of us (A.G.P.) held a Swift and Co. Fellowship. The material is abstracted from part of a doctoral dissertation submitted to Northwestern University by A.G.P. in 1955.

(2) J. B. Polya and P. L. Tardrew, *J. Chem. Soc.*, 1081 (1948); J. B. Polya and T. M. Spotswood, *Rec. trav.chim.*, **67**, 927 (1948); P. Dunn, E. A. Parkes, and J. B. Polya, *Rec. trav. chim.*, **71**, 676 (1952).

(3) D. Davidson and H. Skovronek, *J. Am. Chem. Soc.*, **80**, 376 (1958).

(4) A. W. Titherley, *J. Chem. Soc.*, 85, 1673 (1904).

(5) Q. E. Thompson, *J. Am. Chem. Soc.*, **73**, 5841 (1951).

(6) The compound $(C_2H_5CO)_2NH$ has been named both dipropionamide and dipropionimide. Our preference for and usage of the latter follows the practice of the London Chemical Society: A. D. Mitchell, *British Chemical Nomenclature*, E. Arnold, London, 1948, p. 66.

(7) (a) R. H. Wiley, O. H. Borum, and L. L. Bennett, Jr., *J. Am. Chem. Soc.*, **71**, 2899 (1949); (b) R. H. Wiley and O. H. Borum, *J. Am. Chem. Soc.*, **72**, 1626 (1950).

(8) J. C. Sheehan and E. Corey, *J. Am. Chem. Soc.*, **74**, 4555 (1952).

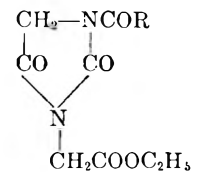
studied. Neither it nor glycine ethyl ester hydrochloride reacted in pyridine solution with phenylacetyl chloride at −60° (conditions resembling those used by Thompson[5] for acylating amides and amines). Also, no product other than unused anhydride could be isolated from the red oil that was obtained on refluxing a mixture of ethyl phenaceturate, phenylacetic anhydride, and pyridine. Heating a mixture of glycine ethyl ester hydrochloride and phenylacetic anhydride at 160° did induce monoacylation to form ethyl phenaceturate.

Another approach tested was to heat a mixture of sodium bisphenylacetimide, ethyl chloroacetate, and a trace of potassium iodide at 140°, with or without xylene as solvent. A viscous red oil was obtained from which phenylacetamide and sodium chloride were isolated but no ethyl bisphenylacetimidoacetate.

A promising approach to the synthesis of diacylated amines was reaction of isocyanates and acid anhydrides. Although this reaction has been known for over a century it has not been generally appreciated. A recent paper,[9] for example, lists a dozen reactions of isocyanates without including acid anhydrides. Wurtz[10] discovered the reaction when he heated acetic anhydride and ethyl isocyanate at 180–190° and obtained *N*-ethyldiacetimide, $(CH_3CO)_2NC_2H_5$. Brunner[11] produced diacetimide by heating acetic anhydride with potassium cyanate at 100°. A few reactions at elevated temperatures are on record between acid anhydrides and ureas, which may be regarded as precursors of isocyanates, as are a few reactions between acid anhydrides and isothiocyanates.[12] The reaction[13] of phthalic anhydride and an acid azide (precursor of isocyanate) yielding an *N*-substituted phthalimide has been reported.

To test this reaction with simple materials, phthalic anhydride was treated with phenyl isocyanate (rather than diphenylurea or benzazide). *N*-Phenylphthalimide was formed in 85% yield on heating in a bath at 180°. A lesser yield (63%) resulted by refluxing in pyridine, and a still smaller yield (27%) at 140° in the presence of a trace of perchloric acid. Dains[12] reported the formation of *N*-phenylphthalimide from phthalic anhydride and phenyl isothiocyanate without listing details or yield. We obtained 83% yield when this mixture was refluxed in pyridine.

Acyclic acid anhydrides were found to react comparably with isocyanates. Thus, from acetic anhydride and phenyl isocyanate there was produced *N*-phenyldiacetimide in 71% yield, together with a little acetanilide. About the same yields (70–74%) of ethyl diacetimidoacetate and ethyl dioctanimidoacetate, $(C_7H_{15}CO)_2NCH_2COOC_2H_5$, were obtained from ethyl isocyanatoacetate and acetic or octanoic anhydrides. As would be expected, propionic anhydride reacted similarly but the resulting ethyl dipropionimidoacetate was difficult to separate completely from ethyl 1-propionyl-3-hydantoinacetate (IB) that was formed concurrently. Some ethyl 1-octanoyl-3-hydantoinacetate (IC) was isolated also as a minor product



I. A. R = CH_3
B. R = C_2H_5
C. R = C_7H_{15}

from octanoic anhydride. At 200°, benzoic anhydride yielded ethyl dibenzimidoacetate but at 195° or lower there was no evolution of carbon dioxide and there was recovery of reagents.

Two reactions of ethyl diacetimidoacetate may be mentioned at this point. One is the quantitative hydrolysis of both acetyl groups by refluxing with concentrated potassium hydroxide solution. The other is reaction with phosphorus pentachloride, an exothermic process accompanied by evolution of gas. Further heating of the reaction mixture resulted in extensive decomposition and the distillation of acetyl chloride. The amount of acetyl chloride was 50% more than the amount expected if only one of the acetyl groups had been cleaved. Hence, both acetyl groups were attacked by the phosphorus pentachloride. A very small amount of acetamide was produced also. A similar result has been observed before[14] when gaseous hydrogen chloride was passed into molten *N*-phenyldiacetimide at 150–170°. Both acetyl chloride and acetanilide were obtained.

One anhydride studied, phenylacetic anhydride, failed to yield an imide in its reaction with phenyl isocyanate. Only monoacylation was noticed. The product was phenylacetanilide in high yield.

Two by-products were observed in the reaction between acetic anhydride and ethyl isocyanatoacetate, namely, ethyl *N*,*N*′-carbonylbis(aminoacetate), a urea $CO(NHCH_2COOC_2H_5)_2$, and ethyl 1-acetyl-3-hydantoinacetate, IA. The first of these compounds probably results from the presence of traces of water in the original isocyanate as well as of small amounts of acetic acid in the anhydride, even though reasonable precautions were made to start with pure anhydride and to maintain anhydrous conditions. A small amount of *sym*-diphenylurea also was obtained in the experiments with phenyl isocyanate. Compound IA undoubtedly

(9) S. Petersen, *Ann.*, **562**, 205 (1949).
(10) A. Wurtz, *Ann. Chim. Phys.*, [3], **42**, 54 (1854).
(11) K. Brunner, *Monatsh.*, **36**, 517 (1915).
(12) P. Kay, *Ber.*, **26**, 2848 (1893); F. B. Dains, *J. Am. Chem. Soc.*, **22**, 186 (1900); J. Dubsky and C. Graenacher, *Ber.*, **50**, 1689 (1917).
(13) M. Aeberli and H. Erlenmeyer, *Helv. Chim. Acta*, **31**, 470 (1948).
(14) A. W. Chapman, *J. Chem. Soc.*, **127**, 2819 (1925).

came from the urea by cyclization and subsequent acetylation by the acetic anhydride. Precedent for this is the formation of hydantoin on pyrolysis (140°) of ethyl ureidoacetate,[15] $H_2NCONHCH_2COOC_2H_5$; in turn, the hydantoin was converted into 1-acetylhydantoin on refluxing with acetic anhydride. Similarly, ethyl 3-hydantoinacetate was obtained[16] by heating ethyl *N*-(ureidoacetyl)-aminoacetate hydrochloride,

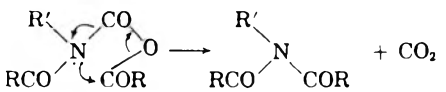
$$HCl \cdot NH_2CONHCH_2CONHCH_2COOC_2H_5$$

at 180–190° *in vacuo*, or by heating ethyl *N,N'*-carbonylbis(aminoacetate) in a saturated solution of hydrochloric acid in ethanol.[17]

To explain the formation of imides in this reaction it is assumed that there is an initial addition of anhydride to the isocyanate, resulting from partial polarization of both molecules at the temperature required by the reaction:

$$R'N{=}C{=}O + RCO{-}OCOR \longrightarrow R'N(COR){-}C(OCOR){=}O$$

The resulting mixed acid anhydride is unstable and loses carbon dioxide by readjustment of electrons in the molecule:



In support of this mechanism it may be pointed out that mixed carboxylic-carbamic anhydrides have been actually isolated[18] and characterized.[19] Moderate heating (80–100°) of these mixed anhydrides produced a carboxylic anhydride and a symmetrically disubstituted urea. Stronger heating (160–170°) of the mixed anhydrides caused evolution of carbon dioxide and the production of an amide. Evidence that the carbon dioxide comes from the carbonyl attached to the nitrogen is supplied by the fact that in the reaction of isothiocyanates the gas evolved is carbon oxysulfide,[20] and by the liberation of ordinary carbon dioxide[21] from the reaction of phenyl isocyanate and acetic-1-C^{14} acid: $CH_3C^{14}OOH + PhNCO \rightarrow [CH_3C^{14}O{-}O{-}CONHPh] \rightarrow CH_3C^{14}ONHPh + CO_2$.

EXPERIMENTAL

Reagents. Ethyl isocyanatoacetate, b.p. 72–73° (14 mm.), was prepared[22] in 83% yield by reaction of glycine ethyl ester hydrochloride[23] with phosgene. Octanoic anhydride,[24] b.p. 136–140° (1.5 mm.); m.p. −1°, was prepared in 82% yield from octanoic acid and acetic anhydride. Benzoic anhydride, m.p. 43°, was prepared in 81% yield by the reaction of benzoic acid with benzoyl chloride[25] in pyridine.

We tested two syntheses of phenylacetic anhydride. The reaction of phenylacetic acid and acetic anhydride gave 67–70% yield of material, m.p. 71–72°, compared to the stated yield[26] of 80%. A better yield was obtained by reaction of phenylacetyl chloride and acetic anhydride, adapting a procedure recommended[27] for other acid anhydrides. A mixture of 51 g. (0.33 mole) of phenylacetyl chloride and 35 g. (0.33 mole or 100% excess) of 97% acetic anhydride was heated gently until acetyl chloride started distilling off. This distillation lasted 12 hr. All material boiling up to 140° (1 mm.) was then removed from the mixture, and the residue of phenylacetic anhydride was recrystallized from benzene-hexane; m.p. 71–72°; yield, 37 g. (88.4%).

Phenaceturic acid, m.p. 142–143°, was prepared in 64% yield by the reaction[28] of glycine with methyl phenylacetate and sodium methoxide. Its methyl ester, m.p. 87–88°, was prepared in 85% yield by reaction of the acid with diazomethane, and in 78% yield by esterification of the acid with 4 parts of methanol in ethylene dichloride together with a little concentrated sulfuric acid.

N-Acetylbenzamide. A solution of 1.21 g. (0.01 mole) of benzamide in 2.04 g. (0.02 mole) of acetic anhydride was treated with two drops (0.1 ml.) of concentrated sulfuric acid, and heated to 135–140° for 3 min. The reaction mixture was poured into 50 ml. of cold water. The precipitate was collected, washed with ethanol, and recrystallized from dilute ethanol; weight, 1.0 g. (61%); m.p. 117–118° (lit.[29] m.p. 116–117°).

N-Benzoylphenylacetamide. An equimolar (0.02 mole) mixture of phenylacetic anhydride and benzamide was fused. Two drops of concentrated sulfuric acid were added to the yellow-red melt. The mixture was heated at 160–180° for 2 min. It was left to solidify during 12 min. and the solid was remelted and poured into water. The separated solid was collected and triturated with water. In the aqueous filtrate there were a few drops of a colored oil, heavier than water, with the odor of a nitrile. The solid was recrystallized from 95% ethanol; weight 2.5 g. (52%); m.p. 129–130°, and mixed melting point with benzamide, 105–120° (lit.[30] m.p. 129–130°).

Bisphenylacetimide. (*A*) *From anhydride and benzamide.* A mixture of 5.1 g. (0.02 mole) of phenylacetic anhydride and 1.2 g. (0.01 mole) of benzamide, containing two drops of concentrated sulfuric acid, was heated at 160–180° for 10 min. After cooling it was poured into 30 ml. of water. The precipitated bisphenylacetimide was separated and recrystallized twice from 95% ethanol; weight 1.5 g.; m.p. 190–192° (lit.[31] m.p. 192°).

(*B*) *From acid chloride and benzamide.* A mixture of 9.2 g. (0.076 mole) of benzamide and 36 g. (0.233 mole) of phenylacetyl chloride was heated at 80–82° for 24 hr. A very

(15) C. Harries and M. Weiss, *Ann.*, **327**, 369 (1903).
(16) C. Graenacher and H. Landolt, *Helv. Chim. Acta*, **10**, 799 (1927).
(17) R. Loquin and V. Cherchez, *Compt. rend.*, **188**, 177 (1929).
(18) W. Dieckmann and F. Breest, *Ber.*, **39**, 3052 (1906).
(19) C. Naegeli and A. Tyabji, *Helv. Chim. Acta*, **17**, 931 (1934); **18**, 142 (1935).
(20) F. Kraft and H. Karstens, *Ber.*, **25**, 452 (1892).
(21) A. Fry, *J. Am. Chem. Soc.*, **75**, 2686 (1953).
(22) W. Siefken, *Ann.*, **562**, 105 (1949).
(23) C. S. Marvel, *Org. Syntheses*, Coll. Vol. II, 310 (1943).
(24) D. Holde and R. Gentner, *Ber.*, **58**, 1422 (1925).
(25) H. Adkins and Q. E. Thompson, *J. Am. Chem. Soc.*, **71**, 2242 (1949).
(26) W. Autenrieth and G. Thomae, *Ber.*, **57**, 431 (1927).
(27) F. Zetzsche, F. Enderlin, C. Fluetsch, and E. Menzi, *Helv. Chim. Acta*, 9, 181 (1926); N. O. V. Sonntag, J. R. Trowbridge, and I. J. Krems, *J. Am. Oil Chem. Soc.*, **31**, 151 (1954).
(28) J. H. Ford, *J. Am. Chem. Soc.*, **71**, 3842 (1949).
(29) A. W. Titherley and T. H. Holden, *J. Chem. Soc.*, **101**, 1871 (1912).
(30) R. H. Wiley and W. B. Guerrant, *J. Am. Chem. Soc.*, **71**, 981 (1949).
(31) C. E. Colby and F. D. Dodge, *Am. Chem. J.*, **13**, 1 (1891).

small amount of hydrogen chloride was evolved. All the volatile material was then removed by rapid distillation at a bath temperature of up to 139° and 10 mm. The solid nonvolatile cake was triturated with pentane and collected on a filter; yield, 18.5 g.; m.p. 190–192°, after two recrystallizations from benzene and glacial acetic acid.

(*C*) *From phenylacetamide.* Two portions of phenylacetamide weighing 2.0 g. (0.016 mole) each were heated in an open tube at 180° for 6 hr. Five drops (0.2 ml.) of concentrated sulfuric acid had been added to only one of the tubes at the beginning of the reaction. The contents of the tube without the acid were readily soluble in slightly warm 95% ethanol. The solid obtained from this solution on cooling was phenylacetamide; m.p. and mixed m.p. 154–155°. Part of the contents (a few mg.) of the tube with the acid was insoluble in warm 95% ethanol. It did not melt up to 290° and possibly was cyanuric acid.[32] Fractional crystallization of the ethanolic solution yielded 0.2 g. of bisphenylacetimide (m.p. 193–194°) and 1.7 g. of unreacted phenylacetamide (m.p. 154–155°).

Ethyl phenaceturate. A mixture of 0.75 g. (0.0054 mole) of glycine ethyl ester hydrochloride and 4.1 g. (0.016 mole) of phenylacetic anhydride was heated at 165° for 3 hr. A slow stream of nitrogen was passed through the melt throughout this period. All volatile material was removed at a bath temperature up to 190° and 2 mm. Repeated extraction of the residue with boiling hexane produced 0.6 g. of ethyl phenaceturate; m.p. and mixed m.p. 81–82°.

In contrast, there was no reaction after 23 hr. when 1.4 g. of glycine ethyl ester hydrochloride was added to a cold (−60°) solution of 4 g. of phenylacetyl chloride, 100 ml. of dry chloroform, 25 ml. of dry methylene chloride, and 2.8 g. of dry pyridine. After processing, 1.35 g. of glycine ethyl ester hydrochloride was recovered, m.p. and mixed m.p. 142–143°.

Attempts to acylate phenaceturic esters. From an original 2.07 g. of powdered methyl phenaceturate 1.6 g. was recovered (m.p. and mixed m.p. 86–87°) after treatment for 21 hr. at −65° in a mixture containing 3.1 g. of phenylacetyl chloride, 100 ml. of dry, alcohol-free chloroform, 25 ml. of dry methylene chloride, and 1.8 g. of dry pyridine.

A mixture of 1.11 g. of ethyl phenaceturate and 6.35 g. of phenylacetic anhydride in 2 g. of dry pyridine was refluxed gently for 5.5 hr. Volatile materials were removed by heating the mixture up to 150° at 2-mm. pressure. Repeated extractions of the dark red oily residue with boiling hexane yielded only phenylacetic anhydride; m.p. and mixed m.p. 75–76°.

Sodium bisphenylacetimide and ethyl chloroacetate. A solution of 3.0 g. of sodium bisphenylacetimide in dry xylene was mixed with 1.35 g. of ethyl chloroacetate and a small crystal of potassium iodide. The mixture was refluxed with stirring for 1 hr., and the xylene was distilled off slowly. Ether extraction of the colored oily residue yielded 1 g. of phenylacetamide; m.p. and mixed m.p. 154.5–155.5°. Treatment of the viscous red oil with various other solvents failed to extract any solid material. Extraction with water produced sodium chloride.

The same reaction was repeated without solvent. The mixture was heated at 155° for 3 hr. The only product isolated by extraction was again 1 g. of phenylacetamide.

N-Phenylphthalimide. (*A*) *From phenyl isocyanate.* A mixture of 1.5 g. (0.01 mole) of phthalic anhydride and 1.2 g. (0.01 mole) of phenyl isocyanate was heated by a bath at 180° for 19 hr. Treatment of the solidified mixture with ethanol produced 1.9 g. of *N*-phenylphthalimide (85% yield); m.p. 204–205° (from 95% ethanol), (lit.[33] 205°); mixed melting point with phthalic acid, 185–189°.

(*B*) *From phenyl isocyanate and perchloric acid.* The same mixture as in (A) was treated with two drops of 70% perchloric acid, and it was heated at 135° for 20 min. Carbon dioxide gas was evolved and the melt turned green, then red, and finally violet. Extraction with boiling ethanol yielded 0.6 g. of *N*-phenylphthalimide; m.p. 204–205°.

(*C*) *From phenyl isocyanate and pyridine.* The same mixture as in (A) was dissolved in 40 ml. of dry pyridine and it was refluxed for 5 hr. The pyridine was then removed (35 mm.) and the residue was dissolved in boiling 95% ethanol. Pure *N*-phenylphthalimide crystallized on cooling; weight 1.4 g.; m.p. 204–205°.

(*D*) *From phenyl isothiocyanate and pyridine.* A solution of 3.0 g. (0.02 mole) of phthalic anhydride and 2.7 g. (0.02 mole) of phenyl isothiocyanate (*cf.* Dains[12]) in 50 ml. of dry pyridine was refluxed for 20 hr. The solvent was then removed at reduced pressure, and the residue was dissolved in 95% ethanol. The *N*-phenylphthalimide precipitated in fine needles on cooling; weight 3.85 g. (86%); m.p. 204–205°.

N-Phenyldiacetimide. A mixture of 5.95 g. (0.05 mole) of phenylisocyanate and 5.10 g. (0.05 mole) of acetic anhydride (98%) was heated at 175° for 11 hr. The system was provided with a reflux condenser, and it was protected from moisture. The unreacted acetic anhydride and phenyl isocyanate were removed at 12.5-mm. pressure. The *N*-phenyldiacetimide distilled over at 142–146° (12.5 mm.), and it crystallized slowly by long chilling; weight, 6.3 g. (72% yield); m.p. 36–37° (lit. 37°).

Extraction of the distillation residue with boiling ligroin yielded 1 g. of acetanilide; m.p. 113.5–114°. About 0.15 g. of *sym*-diphenylurea was obtained by chilling the forerun; m.p. 238–239°.

Phenylacetanilide. (*A*) *From phenyl isocyanate and pyridine.* A solution of 2.54 g. of phenylacetic anhydride and 1.19 g. of phenyl isocyanate in 50 ml. of dry pyridine was refluxed for 15 hr. The pyridine was removed at reduced pressure. The oily residue was very soluble in warm 95% ethanol. Removal of the ethanol and treatment of the residue with boiling hexane yielded 1.3 g. of phenylacetanilide; m.p. 115–117° (lit.[34] 117°); mixed melting point with an authentic sample, 116–117°.

(*B*) *From phenyl isothiocyanate at 180°.* A mixture of 2.54 g. of phenylacetic anhydride and 1.35 g. of phenyl isothiocyanate was heated at 180° for 4.5 hr. The product was crystallized from boiling ligroin (86–100°); yield, 2 g.; m.p. and mixed m.p. 116–117°.

(*C*) *From phenyl isothiocyanate at 215°.* The same mixture was heated, in a tube protected from moisture, at 215° for 15 hr. Again the only solid isolated was 1.8 g. of phenylacetanilide; m.p. 115–116°.

Ethyl diacetimidoacetate. An equimolar mixture of 10.7 g. of acetic anhydride (98%) and 12.9 g. of ethyl isocyanatoacetate was protected from moisture and heated at 185° for 12 hr. Fractional distillation at 2.5-mm. pressure yielded 13.75 g. (73.5%) of ethyl diacetimidoacetate; b.p. 122.5–123° (2.5 mm.); n_D^{25} 1.4490 (lit.[7b] 106–110° (2 mm.), n_D^{25} 1.4525).

When a comparable mixture was heated for only 6 hr. half of the acetic anhydride and considerable of the isocyanate were recovered. The yield of ethyl diacetimidoacetate was 6 g., but in addition two solid fractions were obtained: 0.45 g. of ethyl *N,N'*-carbonylbis(aminoacetate), m.p. and mixed m.p. 145° (lit.[35] 144–146°), and 0.52 g. of ethyl 1-acetyl-3-hydantoinacetate, m.p. 87–88°, which was analyzed.

The acetic anhydride used in the last run was distilled over phosphorus pentoxide before use but the presence of these byproducts suggests that still greater precautions would be necessary to guard against the presence of water or acetic acid in the reactants.

Anal. (of the hydantoin) Calcd. for $C_9H_{12}N_2O_5$: C, 47.37; H, 5.30; N, 12.28. Found: C, 47.18; H, 4.91; N, 12.74.

Reactions of ethyl diacetimidoacetate. (*A*) *Acetyl determination.* A mixture of 3.00 g. of ethyl diacetimidoacetate and

(32) *Cf.* O. Diels, *Ber.*, **36**, 740 (1903); C. S. Venable and F. J. Moore, *J. Am. Chem. Soc.*, **39**, 1750 (1917).

(33) O. Doebner, *Ann.*, **210**, 267 (1881).

(34) A. W. Hofmann, *Ber.*, **13**, 1225 (1880).

(35) E. Fischer, *Ber.*, **34**, 440 (1901).

6.5 ml. of a 50% potassium hydroxide solution was refluxed for 6 hr. The solution was then acidified with dilute sulfuric acid, diluted with water to 100 ml., and distilled. When two thirds of the liquid had distilled, 50 ml. of water was added and the distillation was resumed. The combined distillates were titrated with *N* sodium hydroxide solution.

Anal. Calcd. for $C_8H_{13}NO_4$: Acetyl, 45.9. Found: Acetyl, 45.3.

(*B*) *Phosphorus pentachloride.* Addition of 4.16 g. (0.02 mole) of phosphorus pentachloride to 3.74 g. (0.02 mole) caused an exothermic reaction to take place, with evolution of a gas. Further heating up to 150° produced 2.45 g. (0.031 mole) of acetyl chloride, b.p. 50–53°, which gave acetanilide, m.p. 115–116°, on reaction with aniline.

Ethyl dipropionimidoacetate. A mixture of 6.45 g. (0.05 mole) of ethyl isocyanatoacetate and 5.62 g. (0.043 mole) of propionic anhydride was heated in a bath at 200° for 6 hr. Carbon dioxide was evolved. The mixture was distilled and a fraction weighing 6.0 g., b.p. 125–150° (2 mm.), was separated and distilled again. The middle fraction was ethyl dipropionimidoacetate, b.p. 109° (0.2 mm.); n_D^{25} 1.4512; weight, 4.0 g.

Anal. Calcd. for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.51. Found: C, 54.42; H, 7.87; N, 7.08.

The discrepancy in the analysis suggests the presence of small amounts of ethyl 1-propionyl-3-hydantoinacetate, and some was actually isolated from the main fraction.

Ethyl 1-propionyl-3-hydantoinacetate. A total of 2.5 g. of this ester was extracted from the above distillation residue with boiling ligroin (86–100°). It melted at 117–118°.

Anal. Calcd. for $C_{10}H_{14}N_2O_5$: C, 49.58; H, 5.83; N, 11.57; neut. equiv., 242.2. Found: C, 50.03; H, 6.00; N, 11.77; neut. equiv., 242.

Ethyl dioctanimidoacetate. (A) A mixture of 10.3 g. (0.038 mole) of octanoic anhydride and 4.90 g. (0.038 mole) of ethyl isocyanatoacetate was heated in a bath at 175° for 10 hr. Distillation of the mixture yielded crude ethyl dioctanimidoacetate, which was purified by two redistillations. The final product weighed 9.5 g. (70% yield); b.p. 177–179° (0.9 mm.).

Anal. Calcd. for $C_{20}H_{37}NO_4$: C, 67.57; H, 10.49. Found: C, 67.36; H, 10.19.

Ethyl 1-octanoyl-3-hydantoinacetate. Repetition of the above experiment at 197° and with a 10% excess of the isocyanate, followed by prolonged chilling at 0° of the crude fraction of ethyl dioctanimidoacetate produced 0.3 g. of ethyl 1-octanoyl-3-hydantoinacetate, m.p. 93.5–94.5° (acetone-water).

Anal. Calcd. for $C_{15}H_{24}N_2O_5$: C, 57.67; H, 7.74; N, 8.97. Found: C, 57.84; H, 7.62; N, 9.33.

Ethyl dibenzimidoacetate. A mixture of 6.78 g. (0.03 mole) of benzoic anhydride and 3.87 g. (0.03 mole) of ethyl isocyanatoacetate was heated in a bath kept at 200° for 8.5 hr., and then distilled. The fraction distilling at 160–190° (0.15 mm.) was a very viscous liquid, which by repeated alternate chilling to 0°, and thawing, was made to crystallize in part. The crystalline material weighed 6.5 g., and melted at 96–99°. Three recrystallizations from methanol produced pure ethyl dibenzimidoacetate, m.p. 103.5–104°.

Anal. Calcd. for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50. Found: C, 69.10; H, 5.50.

In another experiment with the same reagents it was observed that when the bath temperature was below 195° there was no evolution of carbon dioxide from the mixture. The evolution would start again as soon as the bath temperature was over 195°. From a reaction mixture kept at 177° for 6 hr., 98.7% of the benzoic anhydride, and 83% of the isocyanate were recovered.

Ethyl phenaceturate. A mixture of 9.7 g. (0.038 mole) of phenylacetic anhydride and 4.9 g. (0.038 mole) of ethyl isocyanatoacetate was heated in a bath at 175° for 9 hr. Carbon dioxide evolution was observed at temperatures over 160°. Distillation of the mixture at 1.5-mm. pressure yielded 10 g. of a fraction distilling at 170–195°, and 2.4 g. of a residue. The main fraction was ethyl phenaceturate, m.p. 77–78° (ether), mixed melting point with pure ethyl phenaceturate of m.p. 80–81.5° was 78–80°. Its nitrogen content by analysis was 6.35% (theory, 6.33). Extraction of the residue with various solvents failed to yield any other material.

Acknowledgment. The microanalyses were made by Miss Hilda Beck.

EVANSTON, ILL.

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF CALIFORNIA]

The Grignard Reaction with 2-(β-Cyanoethyl)-2-ethylhexanal and Further Conversions of the Reaction Products. Limitations of Anisole as Solvent for the Grignard Reaction

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Reaction of *n*-butylmagnesium bromide with an approximately equimolar amount of 2-(β-cyanoethyl)-2-ethylhexanal at 0° in diethyl ether as solvent yields about equal amounts of the reduction product, 2-(β-cyanoethyl)-2-ethyl-1-hexanol (II), and the addition product, 6-(β-cyanoethyl)-6-ethyl-5-decanol (III). There could be detected no product resulting from reaction of the nitrile grouping. Yields were similar, whether normal addition or inverse addition was used in the reaction. In anisole as solvent, considerable quantities of two unidentified by-products could be detected by gas phase chromatography, and the yield of the addition product, III, was somewhat lower. With inverse addition in anisole, the amount of reduction was much greater than observed when diethyl ether was the solvent. The addition product, the cyano alcohol III, was hydrolyzed to a lactone which was transesterified with methanol to yield a mixture of unsaturated esters. Ozonolysis of these esters indicates the mixture expected from rearrangement of the carbonium ion resulting from alkyl-oxygen fission of the lactone, and development of the double bond at less substituted positions as well as the most substituted position.

The reaction of *n*-butylmagnesium bromide with an equimolar amount of 2-(β-cyanoethyl)-2-ethylhexanal (I) has been examined, partly in order to evaluate the relative reactivities of the nitrile and the highly hindered aldehyde, and partly to supply for futher study compounds containing the highly

hindered quaternary carbon atom. There have already been reported[1] reactions of this cyano aldehyde with excess of Grignard reagent. The observed products were hydroxy nitriles (homologous to III) and dihydropyrans resulting from cyclization and dehydration of hydroxy ketones resulting from further reaction of the hydroxy nitriles with Grignard reagent.

The Grignard reaction in diethyl ether with an equimolar amount of cyano aldehyde I, at 0°, whether by normal addition of the cyano aldehyde to the Grignard reagent or inversely, gave no significant amount of product resulting from reaction with the nitrile. Further, the yields of products resulting from reaction with the aldehyde were similar for the two methods of addition. The only identified reaction products were the primary alcohol (II), resulting from reduction of the starting material, and the secondary alcohol (III), resulting from addition of the Grignard reagent to the aldehyde. Average yields are recorded in Table I.

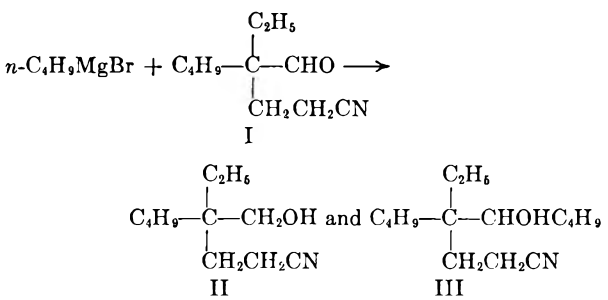


TABLE I

REACTION OF *n*-BUTYLMAGNESIUM BROMIDE WITH 2-(β-CYANOETHYL)-2-ETHYLHEXANAL

Solvent	Mode of Addition	Yields, % Pri. alc. II	Sec. alc. III
Diethyl ether	Normal	30	33
Diethyl ether	Inverse	26	33
Anisole	Normal[a]	21	25
Anisole	Inverse[b]	42	23

[a] In this run there was also observed a 17% yield of product of slightly shorter retention time in gas chromatography than II, and an 11% yield of product with retention time between II and III; *cf.* Table II. [b] In this run, yields of products mentioned in Note *a* were respectively 10% and 7%.

It has been reported[2] that the reducing action of a Grignard reagent is less favored when a less basic ether is used as solvent for the reaction. Specifically, less reduction was found when anisole was the solvent than was the case when diethyl ether was the solvent. Although the yield of Grignard reagent is poor in anisole, this is a rather minor disadvantage when the other component of the reaction is relatively expensive; therefore, the effect of anisole was examined in the Grignard reaction with 2-(β-cyanoethyl)-2-ethylhexanal. When the products of the reaction in anisole were isolated by fractional distillation, there appeared to be an increase in the yield of product III resulting from addition to the carbonyl group, as would be expected from the previous work[2]; however, the intermediate fraction between the primary and secondary alcohols seemed rather large, and isolation of pure products was difficult. When the reaction mixture was subjected to gas phase chromatography, nine bands appeared in the recorder tracing, and two of these were almost as large as the bands for alcohols II and III. In runs carried out in diethyl ether, these large by-product bands were entirely absent, or barely visible; indeed, for runs in diethyl ether, the two alcohols accounted for about 90% of the total area under all bands. There are recorded in Table II representative results of the chromatography of runs in which normal addition was used. From the data in Tables I and II, it may be noted that use of anisole as solvent reduces the yield of addition product, results in large amounts of by-products, and with inverse addition increases the yield of reduction product. The by-products may have resulted in part from the small excess of Grignard reagent used in the runs in anisole, but it seems improbable that this is a major factor.

TABLE II

GAS CHROMATOGRAPHY OF PRODUCTS OF GRIGNARD REACTIONS IN DIETHYL ETHER AND IN ANISOLE[a]

Diethyl Ether Solvent		Anisole Solvent	
Retention time[b] (min., sec.)	% of total area under bands	Retention time[b] (min., sec.)	% of total area under bands
1′ 45″	0.2	1′ 45″	0.1
		3′ 10″	5.5
6′ 15″	4.6	6′ 32″	2.2
		7′ 40″	0.6
10′ 06″	0.4	10′ 10″	2.2
12′ 27″[c]	4.4		
		15′ 25″	17.8
20′ 07″[d]	34.4	19′ 30″	20.0
32′ 32″	0.7	33′ 50″	15.1
49′ 52″[e]	55.3	48′ 25″	36.5

[a] A solution in the appropriate ether of *n*-butylmagnesium bromide, assayed by titration, was treated at −5 to 0° with a solution of an approximately equimolar amount of 2-(β-cyanoethyl)-2-ethylhexanal. [b] Retention time was taken as time elapsing between injection of sample and the peak of the band. A smaller area under the band gives a slightly shorter retention time; for a similar size of band, reproducibility of retention time is about 0.5 min. for a time of 30 min. Values in this table were determined by injection of 70–80 λ of the reaction product into a 3 m. × 15 mm. O.D. column, at 226°, with helium flow of 145 ml./min. [c] Retention time of 2-(β-cyanoethyl)-2-ethylhexanal. [d] Retention time of primary alcohol II. [e] Retention time of secondary alcohol III. Injection of smaller amounts resolved this band into two overlapping bands with peaks at 44 min., 00 sec. and 45 min., 55 sec. These are believed to represent diastereoisomers.

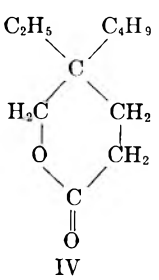
(1) N. Rabjohn, M. J. Latina, and L. V. Phillips, *J. Org. Chem.*, 21, 285 (1956).

(2) R. N. Lewis and J. R. Wright, *J. Am. Chem. Soc.*, 74, 1253 (1952).

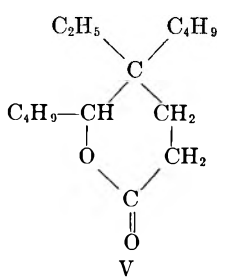
The significant by-products observed in the runs in anisole have not been identified; in fact, re-chromatography of the material from the band appearing between the alcohols gave several new bands, so cracking at the chromatography temperature of 226° (or on passing the heated detector) is indicated. The byproduct with shorter retention time than the primary alcohol (II) showed a single sharp band in the same position on rechromatography. Analysis indicated a ratio of one oxygen to about fifteen carbons, consistent with a dihydropyran as reported by Rabjohn and co-workers[1]; however, the infrared spectrum exhibited a significant carbonyl band, so it is presumed that this fraction is not a single compound, and its investigation has not been pursued further.

Evidence has been presented that the Grignard reaction with the carbonyl group is second order with respect to Grignard reagent,[3] while the reaction with a nitrile is first order[4] with respect to Grignard reagent. If this be the case, inverse addition of the Grignard reagent should favor reaction with the nitrile, since the lower concentration of this reagent would enter the rate equation only once for the nitrile reaction. Failure to isolate or detect any product from reaction with the nitrile for either method of addition, however, prevents utilization of the present data for a test of the validity of these reaction mechanisms. It is possible that nitrile is too unreactive to compete significantly with aldehyde, even when favored by a low concentration. On the other hand, failure of inverse addition in diethyl ether to favor reduction is surprising if, indeed, the reduction is first order in respect to Grignard reagent,[5] and the addition reaction is second order.[3] It is the case that twice as much reduction was obtained with inverse addition in anisole; however, this increased reduction was at the expense of the uncharacterized side products observed in anisole. The yield of addition product in anisole was the same for normal or inverse addition (*cf.* Table I).

The primary alcohol, 2-(β-cyanoethyl)-2-ethylhexanol, II, was characterized by hydrolysis to γ-butyl-γ-ethyl-δ-valerolactone, IV, previously prepared by Bruson and Riener.[6] The liquid lactone was further characterized by oxidation with permanganate in alkaline sclution to yield the known[6] α-butyl-α-ethylglutaric acid of melting point 78–80°.

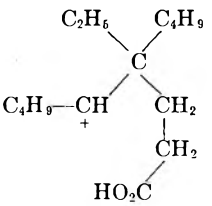


IV

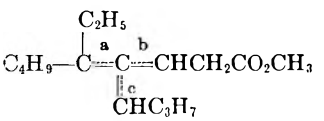


V

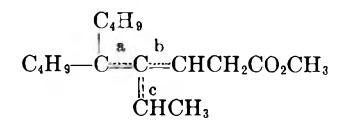
The secondary alcohol, 6-(β-cyanoethyl)-6-ethyl-5-decanol, III, was similarly characterized by hydrolysis to lactone V. When this lactone was transesterified with methanol in presence of hydrogen chloride, the product was not the ester of a hydroxy acid but the ester of an unsaturated acid containing the same number of carbons as the starting lactone. The presence of the double bond was established by the ultraviolet spectrum, hydrogenation, bromination, and oxidation. Molecular weight was established by quantitative hydrogenation and equivalent weight of the corresponding acid. The most plausible route to an unsaturated ester would probably involve[7] attack of a proton on the ring oxygen of the lactone, followed by opening of the ring to give the carbonium ion, VI. Although this ion might go directly to alkene by loss of a proton from the carbon adjacent to the charge, such an ion would be expected to rearrange



VI



VII



VIII

rapidly by migration of one of the groups on the quaternary carbon adjacent to the charge. Indeed, rearrangement and ring opening may be concerted. Since a butyl group is present on each of the adjacent carbons involved in the rearrangement, there would result the two carbon skeletons shown in formulas VII and VIII after rearrangement, loss of a proton, and esterification. Since it has been well demonstrated[8] that steric strain resulting from substitution of large groups on a double bond can render the more substituted position for the double bond the position of higher energy, generation of structures VII and VIII by the route proposed

(3) C. G. Swain and H. B. Boyles, *J. Am. Chem. Soc.*, **73**, 870 (1951).

(4) C. G. Swain, *J. Am. Chem. Soc.*, **69**, 2307 (1947).

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

(6) H. A. Bruson and T. W. Riener, *J. Am. Chem. Soc.*, **66**, 56 (1944).

(7) For a discussion of unimolecular acid-catalyzed ester hydrolysis involving alkyl-oxygen fission, reference may be made to E. R. Alexander, *Principles of Ionic Organic Reactions*, John Wiley and Sons, Inc., New York, 1950, pp. 226, 230; or to J. Hine, *Physical Organic Chemistry*, McGraw-Hill Book Co., Inc., New York, 1956, pp. 270–272.

(8) H. C. Brown and I. Moritani, *J. Am. Chem. Soc.*, **77**, 3607 (1955); R. B. Turner, D. E. Nettleton, Jr., and M. Perelman, *J. Am. Chem. Soc.*, **80**, 1430 (1958).

would be expected to give compounds with unsaturation in each of the positions *a*, *b*, and c.

Since gas phase chromatography of the unsaturated ester gave a single symmetrical band, separation of a mixture of the six compounds represented by formulas VII and VIII would appear to be impractical or impossible; however, partial separation of the products of ozonolysis of the mixture has proved possible. The appearance of eight major bands in the chromatogram of the ozonolysis product attests to the complexity of the mixture ozonized. Several known compounds were chromatographed in order to locate the approximate positions of the expected degradation products. In Fig. 1 are tabulated the bands observed in the chromatography carried out at 200°, and the positions on the scale of the known compounds are indicated. As noted in the legend to this figure, bands are observed at the positions expected for all of the keto esters and ketones. If any unsaturated ester should have been formed directly from ion VI, without rearrangement, an ozonolysis product would be methyl 4-ethyl-4-formyloctanoate whose retention time in gas chromatography would be expected to be similar to that of the keto ester from VIIc. The small size of the band at 24 min. in Fig. 1 suggests no more than traces of unrearranged ester. No effort was made to recover the low molecular weight aldehydes that would result from VIIc and VIIIc, and the methyl formylacetate from VIIb and VIIIb would be expected to condense with itself or an aldehyde. The unidentified bands at about 12 min. and 16 min. may be due to these condensation products.

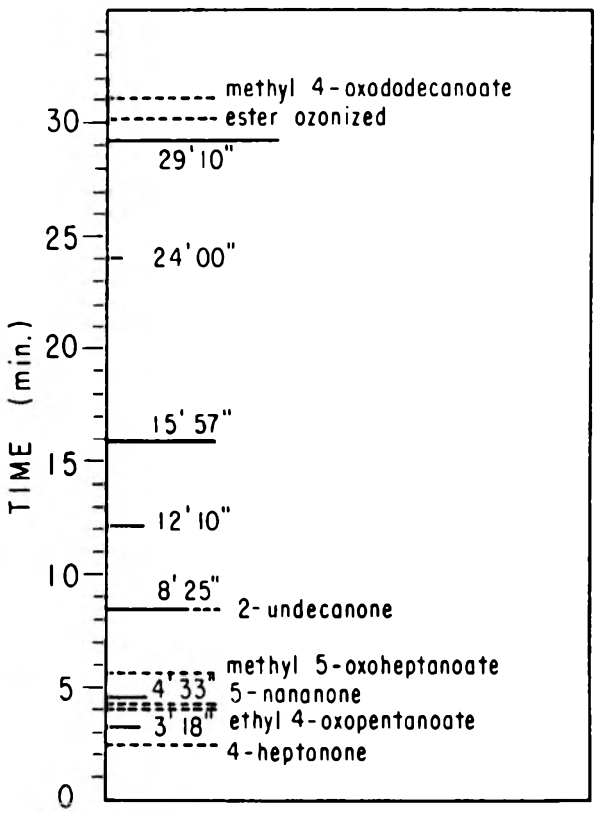


Fig. 1. Gas chromatography of ozonolysis products of the mixed unsaturated esters (Formulas VII and VIII). Chromatography was at 200° in the 3 meter × 15 mm. O.D. column with high vacuum silicone grease as partitioning agent; helium pressure of 16.4 cm. of mercury gave a flow rate of approximately 180 ml./min. The dotted lines indicate the positions observed for known compounds. The solid lines indicate the positions of bands in the chromatogram of the ozonolysis mixture, and the lengths of the lines are proportional to the areas under the bands. Ozonolysis products whose retention times would correspond to those of the observed bands are as follows:

3′ 18″ band: 3-heptanone from VIIa; in chromatography of the series of octadecanones, retention time became shorter as the keto approached the center of the chain

4′ 33″ band: 5-nonanone and methyl 4-oxohexanoate from VIIIa

8′ 25″ band: methyl 4-oxooctanoate from VIIa and the branched C_{12} ketones from VIIb and VIIIb. Chromatography at 190° gave resolution of this band into two overlapping bands with peaks at 15′ 18″ and 17′ 10″, and 2-undecanone appeared at 16′ 55″

12′ 10″ and 15′ 57″ bands: possibly condensation products of methyl formylacetate from VIIb and VIIIb

24′ 00″ band: methyl 4-oxo-5-ethylnonanoate from VIIc

29′ 10″ band: methyl 4-oxo-5-butylnonanoate from VIIIc Any of the starting ester not ozonized would also appear in this band.

When the unsaturated ester was formed by methanolysis of lactone V, lactone recovered from the reaction amounted to about 25% of the starting material. This recovered lactone had an index of refraction differing somewhat from that of lactone V, showed infrared bands characteristic of a γ-lactone (5.66 μ) as well as a δ-lactone (5.76 μ), and in gas chromatography showed a band at the correct position for starting lactone as well as one at a somewhat shorter retention time. Further, heating with 2*N* sulfuric acid of the unsaturated acid, obtained by saponification of the ester from methanolysis, converted about 10% of it to neutral material with infrared absorption at 5.66 and 5.76 μ. Thus, all the characteristics of the unsaturated ester and its formation are consistent with conversion of lactone V *via* the carbonium ion VI (or a concerted reaction) to a mixture of unsaturated esters of structures indicated in formulas VII and VIII.

EXPERIMENTAL[9]

Reaction of n-butylmagnesium bromide with 2-(β-cyanoethyl)-2-ethylhexanal. Average yields under the several conditions are recorded in Table I. These data were determined by quantitative gas phase chromatography of the total reaction product distilled from a Claisen flask at about 0.5 mm. pressure and a bath temperature up to about 200°. Direct comparisons of area were made for alcohols II and III by injection of 0.06-ml. volumes of 2.5% benzene solutions of pure samples of the alcohols separated by fractional distillation. Known samples were run on each occasion that quantitative work was done, and the unknowns were run without any alteration of the bridge current. Precision of the data is regarded as approximately ± 3%. Yields of the unidentified compounds giving major bands were calculated on the assumptions that they have molecular weights similar to alcohols II and III, which occur near them in the chromatograph, and that area under the tracings is related to

molecular weight as reported by Eastman.[10] Results obtained on fractional distillation of one run gave excellent agreement with the chromatography data; however, the distillation data are subject to the uncertainty of estimating composition of intermediate fractions. In the gas chromatography, the tracing went to baseline between the major bands.

A. *Normal addition in diethyl ether solvent.* A Grignard reagent was prepared in 75 ml. of anhydrous ether from 13.7 g. (0.1 mole) of *n*-butyl bromide (b.p. 100–101°, n_D^{22} 1.4389) and 2.43 g. (0.1 g.-atom) of magnesium turnings. Titration of aliquots of several runs indicated yields of 80–83% of Grignard reagent. The stirred solution of Grignard reagent was cooled to −5°, then there was added as rapidly as consistent with keeping the temperature of the reaction mixture in the range −5° to 0° a solution in 50 ml. of benzene of 14.5 g. (0.08 mole) of 2-(β-cyanoethyl)-2-ethylhexanal[6] (b.p. 125–128°/4 mm., n_D^{22} 1.4528). After addition had been completed (about 15 min.), stirring was continued at about 0° until a negative Gilman test for Grignard reagent had been obtained (45–90 min.). The reaction mixture was finally treated with ice and 50 ml. of 6*N* sulfuric acid, most of the ether was distilled with stirring, and the mixture was heated under reflux with stirring for an additional hour in order to ensure hydrolysis of any imine that may have been formed by reaction of the nitrile grouping. The organic phase was separated, the aqueous phase was extracted with two portions of ether, and the organic phase and extracts were washed in sequence with two portions of water. After solvent had been distilled the product was distilled from a Claisen flask and the total distillate collected up to a b.p. of 170°/0.5 mm., weight 13.1 g.

By quantitative gas chromatography and comparison with known quantities of the primary and secondary alcohols, this distillate was determined to contain, in addition to 5.5% of the starting cyano aldehyde (I), 31% of primary alcohol II and 44% of secondary alcohol III. Thus, the yield of primary alcohol was 4.1 g. (28%) and that of secondary alcohol was 5.8 g. (30%). In the 2 m. × 9 mm. O.D. gas chromatography column, at 200°, helium flow rate of 145 ml./min., retention times for compounds I, II, and III were respectively 2′ 35″ (min., sec.), 3′ 45″ and 9′ 10″.

As a check on the results of gas chromatography, 13.0 g. of the above run was fractionated through the 60-cm. column at 3.4 mm. pressure, to yield the following fractions: (1) b.p. 77–140°, wt. 1.0 g.; (2) b.p. 140–147°, wt. 0.5 g.; (3) alcohol II, b.p. 147–151°, wt. 3.7 g.; (4) b.p. 151–165°, wt. 1.5 g.; (5) alcohol III, b.p. 165–167°, wt. 4.5 g. If it be assumed that the intermediate fraction is one third the lower-boiling primary alcohol and two thirds the higher-boiling secondary alcohol, the mixture distilled is calculated to have contained about 32% primary alcohol and 42% secondary alcohol.

An analytical sample of *2-(β-cyanoethyl)-2-ethyl-1-hexanol*, II, was collected as a center cut in a fractional distillation, b.p. 143.7°/3 mm., n_D^{28} 1.4608.

Anal. Calcd. for $C_{11}H_{21}ON$: C, 72.08; H, 11.55; N, 7.64. Found: C, 71.68; H, 11.66; N, 7.66.

An analytical sample of *6-(β-cyanoethyl)-6-ethyl-5-decanol*, III, was collected as a center cut in a fractional distillation, b.p. 171.5°/4 mm., n_D^{28} 1.4641.

Anal. Calcd. for $C_{15}H_{29}ON$: C, 75.25; H, 12.21; N, 5.85. Found: C, 75.19; H, 12.14; N, 6.06.

B. Inverse addition in diethyl ether solvent. The procedure was the same as described for normal addition, except that the solution of Grignard reagent was forced under nitrogen pressure into a separatory funnel, and the solution of cyano aldehyde I was placed in the flask and stirred as the Grignard solution was added during 30–45 min. After completion of addition, stirring at −5 to 0° was continued until a negative Gilman test was obtained. Work-up and assay of the yields by gas chromatography was as described for normal addition.

C. *Reactions in anisole as solvent.* For preparation of the Grignard reagent from 0.2 mole of butyl bromide, the magnesium was placed in 25 ml. of anisole (dried over sodium, distilled; n_D^{20} 1.5170), and this mixture was stirred at 75–80° as the bromide solution in 75 ml. of anisole was added during 30–45 min. After addition was complete, stirring was continued at 75–80° for 3 hr. Titration indicated yields of Grignard reagent of about 50%. There was used 0.08 mole of cyano aldehyde I dissolved in 50 ml. of anisole. Other details of procedure were the same as described for the diethyl ether runs, except for omission of the period of heating with sulfuric acid after decomposition of the Grignard complex with water. It was found that omission of this step did not result in any product with the properties of an imine sulfate.

γ-Butyl-γ-ethyl-δ-valerolactone (IV) was obtained by hydrolysis of an 11.7-g. sample of alcohol II by heating under reflux with stirring for 5 hr. with a solution of 4.25 g. of potassium hydroxide in 45 ml. of water. On acidification of the reaction mixture and extraction, the lactone was obtained in a yield of 73.5%, b.p. 145–147°/7 mm., n_D^{26} 1.4634. Bruson and Riener[6] reported for this lactone b.p. 124°/3.5 mm., n_D^{25} 1.4635.

For more positive identification of the lactone by oxidation, an 8.4-g. sample was dissolved by warming to 50° in a solution of 3.6 g. of potassium hydroxide in 125 ml. of water. During 15 min., there was added 10.5 g. of solid potassium permanganate at such a rate as to keep the temperature of the reaction mixture at 50–55°. Stirring was continued at 55–60° for 1.75 hr., at which time the permanganate color had disappeared. After the manganese dioxide had been removed by suction filtration, it was extracted with 25 ml. of boiling water, and the total aqueous filtrate was clarified with Supercel. Acidification of the clear solution gave a heavy oil, which slowly crystallized to give 7.9 g. (80.5%) of slightly waxy *α-butyl-α-ethylglutaric acid*. After one crystallization from nitromethane, hard white crystals were obtained, m.p. 78–80°, no depression on mixing with an authentic sample.[11]

γ-Ethyl-γ,δ-dibutyl-δ-valerolactone (V) was obtained by hydrolysis of the secondary alcohol, III, in the manner described for hydrolysis of alcohol II to lactone IV. The yield of product of b.p. 142–143°/1.5 mm. was 83.5%. For analysis there was used a center cut, b.p. 142.7°/1.5 mm., n_D^{26} 1.4681. Infrared absorption was at 5.76 μ, and gas phase chromatography gave a single symmetrical band.

Anal. Calcd. for $C_{15}H_{28}O_2$: C, 74.94; H, 11.74. Found: C, 75.06; H, 11.60.

Methanolysis of lactone V. There was heated under reflux for 5 hr. a solution of 6.0 g. (0.025 mole) of lactone V in 8.0 g. of methanol which had been saturated with hydrogen chloride gas at 0°. The cooled reaction mixture was added to 100 ml. of water, and the product was extracted with three portions of ether. The extracts were washed in sequence

(9) Gas phase chromatography was carried out on a 3 m. × 15 mm. O.D. column except for a part of the quantitative work recorded in Table I, which utilized a 2 m. × 9 mm. O.D. column. The packing material was Chromosorb, 30–60 mesh, impregnated with 4 parts of high vacuum silicone grease for 10 parts of Chromosorb. Carrier gas was helium, and detection was by a thermistor in a bridge circuit. Rate of gas flow and temperature are indicated in each instance where data are cited.

Distillations, unless otherwise specified, were carried out in a 60-cm. Podbielniak type column with simple tantalum wire spiral, heated jacket, and partial reflux head. Boiling points are uncorrected and melting points are corrected. Ultraviolet spectra were determined with a Beckman DU spectrophotometer, and infrared spectra were recorded on a Baird spectrophotometer. Microanalyses were by the Microanalytical Division, Department of Chemistry, University of California, Berkeley.

(10) R. H. Eastman, *J. Am. Chem. Soc.*, **79**, 4243 (1957).

(11) J. Cason, *J. Org. Chem.*, **13**, 227 (1948).

with water, sodium carbonate solution, water, and saturated sodium chloride solution, then dried by filtering through a layer of anhydrous sodium sulfate. The product recovered from the extracts was fractionated at 4 mm. pressure to yield: (1) 0.9 g., b.p. 126–130°, n_D^{25} 1.4508; (2) 2.5 g., b.p. 130°, n_D^{25} 1.4508; (3) 1.6 g., b.p. 159–163°, n_D^{25} 1.4610.

Fractions 1 and 2 were taken as the yield of unsaturated esters (VII and VIII), wt. 3.4 g. (55%). For analysis, there was used a center cut, b.p. 130°/4 mm., n_D^{25} 1.4508.

Anal. Calcd. for $C_{16}H_{30}O_2$: C, 75.33; H, 11.89. Found: C, 75.64; H, 11.78.

On quantitative hydrogenation in acetic acid, with platinum oxide catalyst, consumption of hydrogen was one millimole per 254 mg. of ester (calcd. mol. wt. is 254). The ultraviolet spectrum showed a rapidly rising absorption as the wave length was decreased below 220 mμ until at 200 mμ, ε was 6280. Carbonyl absorption in the infrared was at 5.75 μ. In gas chromatography, a single symmetrical peak was observed (*cf.* data below on recovered lactone).

The principal constituent of Fraction 3 in the above distillation was starting lactone, but there was also present some unsaturated ester and a third component which appears to have the γ-lactone structure. Infrared absorption was at 5.66 μ and at 5.76 μ. In gas phase chromatography in the 2 m. × 9 mm. column at 226°, helium flow of 145 ml./min., three bands with the following retention times and per cents of total area were observed: 10′ 00″ (18.5%), 14′ 04″ (18.0%), 17′ 51″ (63.5%). For the unsaturated ester, retention time was 9′ 50″, and for the starting lactone retention time was 17′ 50″; so the intermediate band presumably represents γ-lactones.

Ozonolysis of unsaturated ester mixture. Ozone, flowing at the rate of 0.29 mmole/min., was passed for 4.2 min. into a dichloroethylene solution of 305 mg. (1.2 mmole) of the unsaturated ester mixture. Temperature of the reaction was −20°. After the reaction had stood for about 20 min., water was added, and the mixture was heated at 80° with stirring for 30 min.[12] The organic phase was separated, solvent was distilled, and the residue was used for gas phase chromatography in the 3 m. × 15 mm. column. Chromatograms were recorded at 190°, 200°, and 227°, but results at 200° recorded in Fig. 1 were most informative.

Saponification of the unsaturated ester mixture. A 2.0-g. sample of the unsaturated ester mixture was saponified by heating under reflux for 2.5 hr. with 3*M* equivalents of potassium hydroxide in 10% solution in ethanol. The reaction mixture was diluted with water, acidified and extracted. Distillation of the product at 4-mm. pressure yielded 0.3 g., b.p. 156–161.5°, n_D^{25} 1.4591, and 0.9 g., b.p. 161.5–163.5°, n_D^{25} 1.4592. Both fractions absorbed bromine in carbon tetrachloride solution and showed infrared absorption at 5.86 μ. Titration gave an equivalent weight of 240, which is the calculated value for the unsaturated acid.

A mixture of 0.5 g. of the unsaturated acid and 60 ml. of 2*N* sulfuric acid was heated to boiling for 2 min. The cooled solution was extracted with three portions of ether, and the extracts were washed with water and sodium carbonate solution. Material recovered from the ether after carbonate extraction amounted to 50 mg. and showed infrared absorption at 5.66 μ, 5.77 μ, and 5.86 μ. Acid recovered from the sodium carbonate extract showed an infrared spectrum identical with that of the starting material.

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(12) Experiments in these laboratories on methyl oleate by Dr. Peter Tavs have shown that this procedure gives a high yield of carbonyl compounds from the ozonide, with 5% or less of acids.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Twofold Alkylations of Sodium Diphenylmethide with Methylene Halides to Form Bisbenzhydrylmethylene Hydrocarbons. Alkylations of Sodium Triphenylmethide[1]

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Sodium diphenylmethide in liquid ammonia entered into a twofold type of alkylation with methylene chloride and certain higher methylene halides to form the corresponding bisbenzhydrylmethylene hydrocarbons in good yields. These results are of both theoretical and practical interest. Similar results were obtained with sodium triphenylmethide and certain methylene halides.

It has recently been shown[2] that sodium diphenylmethide, prepared from diphenylmethane and sodium amide in liquid ammonia and ether, can be alkylated in excellent yields with various alkyl halides in this medium. The reaction may be illustrated with benzyl chloride, which rapidly discharged the red color of the reagent (Equation 1).

$$(C_6H_5)_2CH_2 \xrightarrow[\text{liq. } NH_3 \text{ (ether)}]{NaNH_2} (C_6H_5)_2CHNa \text{ (red)} \xrightarrow{C_6H_5CH_2Cl} (C_6H_5)_2CHCH_2C_6H_5 \quad (1)$$

It has now been found that sodium diphenylmethide can enter into a twofold alkylation with certain methylene halides to form the corresponding bisbenzhydrylmethylene derivatives in good yields. For example, treatment of this reagent with half of a molecular equivalent of methylene chloride produced hydrocarbon I in 72% yield. This reaction presumably involves the intermediate formation of the corresponding monohaloalkyl derivative (Equation 2).

(1) Supported by the Office of Ordnance Research, U. S. Army.

(2) C. R. Hauser and P. J. Hamrick, Jr., *J. Am. Chem. Soc.*, 79, 3142 (1957). Also see C. B. Wooster and N. W. Mitchell, *J. Am. Chem. Soc.*, 52, 688 (1930); C. B. Wooster and J. F. Ryan, *J. Am. Chem. Soc.*, 54, 2419 (1932).

TABLE I

BISBENZHYDRYLMETHYLENE HYDROCARBONS FROM SODIUM DIPHENYLMETHIDE AND METHYLENE HALIDES

Hydrocarbon	Yield,[a] %	M.P., °C.	Lit., M.P.	Analysis Calcd. C	Calcd. H	Found C	Found H	Molecular Weight Calcd.	Molecular Weight Found
I	72	141–142[b]	135[c]	93.05	6.94	92.87	6.64	348	344
II	93	124–125[d]	120–121[c]	92.77	7.23	92.65	7.21	362	360
III	85	74–75[b]	74–75[e]	92.51	7.49	92.48	7.30	377	371
IV	90	123–125[b]	123–124[f]	92.26	7.74	92.31	7.68	391	389

[a] In general, these yields were based on the combined weights of several fractions, each of which melted at the recorded value or slightly lower. [b] Recrystallized from 95% ethanol. [c] Ref. 3. [d] Recrystallized from 1:4 benzene–petroleum ether. [e] Ref. 5. [f] Ref. 6.

$$(C_6H_5)_2CHNa \xrightarrow[\text{liq. } NH_3\ (\text{ether})]{ClCH_2Cl} (C_6H_5)_2CHCH_2Cl \xrightarrow{(C_6H_5)_2CHNa} (C_6H_5)_2CHCH_2CH(C_6H_5)_2 \quad (2)$$
I

Similarly, sodium diphenylmethide underwent the twofold type of alkylation with ethylene chloride, trimethylene bromide, and tetramethylene chloride to give hydrocarbons II, III, and IV in yields of 93%, 85%, and 90%, respectively. The results are summarized in Table I.

$(C_6H_5)_2CH(CH_2)_2CH(C_6H_5)_2$ II $(C_6H_5)_2CH(CH_2)_3CH(C_6H_5)_2$ III

$(C_6H_5)_2CH(CH_2)_4CH(C_6H_5)_2$ IV

The hydrocarbons I–IV have previously been obtained by various methods. Hydrocarbon I was produced in unreported yield by the reduction of 1,1,3,3-tetraphenylpropene with sodium in liquid ammonia and in practically quantitative yield, by the reduction of tetraphenylallene with this reagent.[3] Hydrocarbon II was formed as a by-product (best yield 35%) in the reduction of 1,1-diphenylethylene with certain metals in liquid ammonia.[4] Hydrocarbon III was prepared in over 50% yield by the reduction of 1,1,5,5-tetraphenylpentadiene-1,4 with phosphorous and iodine.[5] Hydrocarbon IV was obtained in unreported yield from 1,1,6,6-tetraphenylhexanediol-1,6 through its dimethyl ether which was cleaved with sodium-potassium alloy in ether, followed by hydrolysis.[6]

It can be seen from Table I that the melting points of our products III and IV agreed with the literature values but that the melting points of our products I and II were slightly higher than the earlier values. It is to be noted that the melting points of the homologous series I to IV pass through a minimum.

It can further be seen from Table I that our products gave satisfactory analyses and molecular weights.

(3) C. B. Wooster and J. F. Ryan, *J. Am. Chem. Soc.*, **56**, 1133 (1934).

(4) H. Gilman and J. C. Bailie, *J. Am. Chem. Soc.*, **65**, 267 (1943).

(5) G. Wittig and B. Obermann, *Ber.*, **68B**, 2214 (1935).

(6) B. Wittig and M. Leo, *Ber.*, **63A**, 943 (1930).

It seems unlikely that any of the products isolated were *o*- or *p*-ring derivatives which might have arisen from alkylations involving *o*- or *p*-resonance forms of the diphenylmethide ion, since such derivatives were evidently not obtained in the previous alkylations with benzyl chloride and other alkyl halides.[2]

The present type of two-alkylation of sodium diphenylmethide furnishes a convenient method for the synthesis of the homologous series of hydrocarbons I–IV and presumably for that of certain higher members of this series. With the exception of the reaction with methylene chloride where a red color was still present after 40 min., the reactions studied appeared to be completed within a few minutes as indicated by the discharge of the characteristic red color of the diphenylmethide ion.

It is of interest that, although ethylene chloride and especially the intermediate monohalide represented in Equation 2 have relatively reactive β-hydrogens, these halides underwent largely the substitution type of reaction to form the alkylation products and not much dehydrohalogenation (β-elimination). These observations further illustrate the considerable tendency of sodium diphenylmethide to exhibit nucleophilic displacement on carbon rather than β-elimination even though the diphenylmethide ion is a relatively strong base.[7]

Alkylations of sodium triphenylmethide. Like sodium diphenylmethide, sodium triphenylmethide may be prepared from triphenylmethane and sodium amide in liquid ammonia and ether and alkylated in this medium. As an example of a simple alkylation, this reagent was benzylated to form hydrocarbon V in 99% yield (Equation 3).

$$(C_6H_5)_3CH \xrightarrow[\text{liq. } NH_3\ (\text{ether})]{NaNH_2} (C_6H_5)_3CNa\ (\text{red}) \xrightarrow{C_6H_5CH_2Cl} (C_6H_5)_3CCH_2C_6H_5 \quad (3)$$
V

Hydrocarbon V has previously been obtained in equally high yield from benzylmagnesium chloride and triphenylchloromethane.[8]

(7) See ref. 2 and C. R. Hauser, C. F. Hauser, and P. J. Hamrick, Jr., *J. Org. Chem.*, **23**, 1713 (1958).

(8) M. Gomberg and L. H. Cone, *Ber.*, **39**, 1461 (1906).

TABLE II

BISTRIPHENYLMETHYLMETHYLENE HYDROCARBONS FROM SODIUM TRIPHENYLMETHIDE AND METHYLENE HALIDES

Hydrocarbon	Yield,[a] %	M.P., °C.	Lit., M.P.	Calcd. C	Calcd. H	Found C	Found H
VI	78	94–95[b]	..	93.34	6.66	93.45	6.67
VII	84	150–151[c]	..	93.14	6.86	93.12	6.67
VIII	49	207–208[d]	189[e]	92.94	7.06	92.99	6.86

[a] In general these yields were based on the combined weights of several fractions, each of which melted at the recorded value or slightly lower. [b] Recrystallized from 95% ethanol. [c] Recrystallized from 1:4 ethyl acetate–ethanol. [d] Recrystallized from 1:2 ethyl acetate–ethanol. [e] Ref. 9.

Also, sodium triphenylmethide evidently underwent the twofold type of alkylation with ethylene chloride, trimethylene bromide, and tetramethylene chloride to give hydrocarbons VI, VII, and VIII in yields of 78%, 84%, and 49%, respectively. The results are summarized in Table II.

$(C_6H_5)_3C(CH_2)_2C(C_6H_5)_3$ VI $(C_6H_5)_3C(CH_2)_3C(C_6H_5)_3$ VII

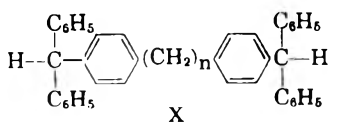
$(C_6H_5)_3C(CH_2)_4C(C_6H_5)_3$ VIII

Apparently hydrocarbons VI and VII have not previously been described. Hydrocarbon VIII has been prepared[9] from the 1,4-addition of triphenylmethyl radicals to 1,3-butadiene followed by reduction over Adams catalyst. The yields in these two steps were 10% and 80%, respectively.

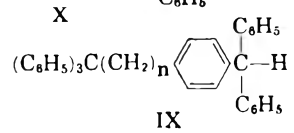
It can be seen from Table II that the melting point of our product VIII was considerably higher than the earlier value.

It can further be seen from Table II that all three of our products VI–VIII gave acceptable analyses. Unfortunately these hydrocarbons were too insoluble in the ordinary solvents for satisfactory molecular weight determinations by the boiling point elevation method.

It was possible that one or more of our products VI–VIII were in reality *o*- or *p*-ring–substituted derivatives such as IX or X, which might have arisen from alkylations involving a *p*-resonance form of the triphenylmethide ion.



X



IX

This now seems doubtful, however, since the addition of these products to sodium amide in liquid ammonia failed to produce colors which might have been expected had they had the active methinyl hydrogen of structures IX and X. On the other hand, the addition of the hydrocarbons I–IV to sodium amide in liquid ammonia produced red colors.

The twofold alkylations with sodium triphenylmethide appeared to be completed somewhat more slowly than the corresponding twofold alkylations with sodium diphenylmethide as indicated by the time of fading of the characteristic red colors of the two reagents.

Moreover, whereas sodium diphenylmethide gave a good yield of hydrocarbon I with methylene chloride, sodium triphenylmethide failed to undergo satisfactorily the corresponding twofold alkylation with this halide under similar conditions. The latter reagent may have formed the monohaloalkyl derivative XI, since several workers[10] have observed that this halide can be obtained in good yield by the action of methylene chloride on an ethereal solution of sodium triphenylmethide prepared from triphenylchloromethane and sodium or sodium amalgam.

$(C_6H_5)_3CCH_2Cl$ XI

It should be mentioned that the monochlorides, $(C_6H_5)_3CCH_2CH_2Cl$ and $(C_6H_5)_3CCH_2CH_2CH_2Cl$, have also apparently been obtained by Charlton, Dostrovsky, and Hughes[10] from ethereal sodium triphenylmethide and ethyl chloride and trimethylene chlorobromide, respectively. The former monochloride and the bromide corresponding to the latter monochloride were presumably formed as intermediates in our preparations of hydrocarbons VI and VII, respectively.

EXPERIMENTAL[11]

Twofold alkylations of sodium diphenylmethide with methylene halides. To a stirred suspension of 0.1 mole of sodium amide in 300 ml. of commercial, anhydrous liquid ammonia[12] was added 16.8 g. (0.1 mole) of diphenylmethane in 50 ml. of anhydrous ether. The resulting dark red sodium diphenylmethide solution was stirred for 10 min. To this stirred reagent was added 0.05 mole of methylene chloride,

(9) J. B. Conant and B. F. Chow, *J. Am. Chem. Soc.*, 55, 3475 (1933).

(10) J. Charlton, I. Dostrovsky, and E. Hughes, *Nature*, 167, 987 (1951); E. Grovenstein, Jr., *J. Am. Chem. Soc.*, 79, 4985 (1957); H. E. Zimmerman and F. J. Smentowski, *J. Am. Chem. Soc.*, 79, 5455 (1957).

(11) Melting points were taken on a Fisher-Johns melting point apparatus. Analyses are by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

(12) See C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. Reactions*, VIII, 122 (1954).

ethylene chloride, trimethylene bromide, or tetramethylene chloride in 100 ml. of anhydrous ether, and the stirring continued for 35–40 min. In the experiment with methylene chloride, the reaction mixture was still deeply colored (cherry red) after this time but in the experiments with the other three halides the red color faded and a yellow or tan suspension was produced within a few minutes. The liquid ammonia was evaporated on the steam bath as an equal volume of ether was added. The resulting ethereal suspension was cooled and shaken with water. The two layers were separated. The aqueous layer was extracted with ether and the ethereal extract combined with the original ethereal layer. The ethereal solution was dried over Drierite, and the solvent removed. The residue was recrystallized from appropriate solvents to give the hydrocarbons I–IV. The data for these compounds are summarized in Table I. The molecular weights were estimated by boiling point elevations in chloroform solution.[13]

Benzylation of sodium triphenylmethide. This reagent (0.1 mole) was prepared as described below, and its alkylation with a molecular equivalent of benzyl chloride was effected essentially as described recently[2] for the corresponding alkylation of sodium diphenylmethide. There was obtained a 99% yield of 1,1,1,2-tetraphenylethane (V), m.p. 143–144° after recrystallization from benzene and petroleum ether. The reported melting point for this hydrocarbon is 144°.[8]

Twofold alkylations of sodium triphenylmethide with methylene halides. To a stirred suspension of 0.1 mole of sodium amide in 300–400 ml. of liquid ammonia[12] was added 24.4 g. (0.1 mole) of triphenylmethane in 50–100 ml. of anhydrous ether. The resulting dark red solution was stirred for 10 min. To this stirred reagent was added 0.05 mole of ethylene chloride, trimethylene bromide, or tetramethylene chloride in 50–100 ml. of anhydrous ether, and the stirring continued for 50–90 min. (Dry Ice condenser). The red color of the reagent was discharged within 15–45 min. The reaction mixture was worked up as described above for the experiments with sodium diphenylmethide. The results are summarized in Table II.

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(13) We are indebted to Mr. W. F. Owens, Jr., of Wake Forest College for these determinations.

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND THE ENGINEERING EXPERIMENT STATION, GEORGIA INSTITUTE OF TECHNOLOGY]

Synthesis of Some Octenoic Acids

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The preparation and properties of *trans*-4- and -6- and of *cis*-3-, -4-, and -6-octenoic acids are reported in this paper. The previously reported isomers, *trans*-3- and *cis*-2-octenoic acids, are also reported in this paper. The *cis* acids were prepared by the catalytic semihydrogenation of the corresponding octynoic acids. The *trans* acids were obtained either directly or indirectly starting with a *trans* alkenoic acid obtained by a Knoevenagel condensation. Physical properties, including infrared spectra, were determined for all of the acids and most of the intermediates. The infrared spectra of the *trans* compounds showed strong absorption in the region of 10.2–10.35 microns. None of the *cis* compounds showed absorption in this region.

The isomeric unbranched octenoic acids were needed in a study of the ionization constants of unsaturated fatty acids. Of the eleven isomers, the following acids are reported in the literature: *trans*-2-,[2,3] *trans*-3-,[4] *trans*-5-,[5] *cis*-2,[2] *cis*-5-[5] and 7-octenoic acid.[6,7] The preparation and properties of the unreported isomers, *trans*-4- and -6- and *cis*-3-, -4-, and -6-octenoic acids, are presented in this paper. Due to the method of preparation of *trans*-3-octenoic acid and the lack of agreement of physical constants for *cis*-2-octenoic acid, the preparation and properties of these acids are also included. The physical properties of the acids are given in Table I.

The *cis* octenoic acids were prepared by catalytic semihydrogenation of the corresponding octynoic acids. Hydrogenation of acetylenic compounds in the presence of catalytic substances is reported to give predominantly *cis* ethylenic compounds.[8–11] This method has been used to prepare unsaturated acids[5,6] and hydrocarbons[12] having a *cis* configuration. In this work, W-5 Raney nickel[13] which had been aged five to six months was used as the catalyst, and dry thiophene-free benzene was found to be the most suitable solvent. In previous studies[5,14] a sharp decrease in the rate of hydrogenation was reported to occur after one molar equivalent of hydrogen had been absorbed. In

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TABLE I

PHYSICAL PROPERTIES OF OCTENOIC ACIDS

Octenoic Acid	Boiling Point, °C.	Melting Point, °C.	n_D^{20}	Density, 20°	Molar Refraction	Analyses, Found	
						Carbon	Hydrogen
cis-2-[a]	89 (0.9 mm.)	−6	1.4441	0.9234	40.91[b]	67.1[c]	9.75
cis-3-	96 (0.5 mm.)	−25	1.4433	0.9352	40.33	67.4	9.82
cis-4-	96 (0.8 mm.)	−35	1.4417	0.9301	40.43	67.3	9.84
cis-6-	88 (0.8 mm.)	−17	1.4441	0.9378	40.29	67.2	9.70
trans-3-[d]	92 (1.4 mm.)	1	1.4452	0.9378	40.37	67.0	9.82
trans-4-	93 (1.5 mm.)	−4	1.4441	0.9313	40.57	67.5	9.89
trans-6-	90 (1.2 mm.)	6	1.4454	0.9422	40.20	67.3	9.93

[a] Bourguel, *Bull. soc. chim. France*, **45**, 1067 (1929), reported for *cis*-2-octenoic acid, b.p. 127° at 15 mm., n_D^{20} 1.456, density 0.940 at 15°. [b] Calculated molar refraction of octenoic acid, 40.26. The atomic and multiple bond refraction constants were taken from A. Weissberger, *Physical Methods of Organic Chemistry*, Vol. I, Interscience Publishers, Inc., New York, N. Y., 1945, pp. 672–80. [c] Calculated for octenoic acid: C, 67.6; H, 9.92. Microanalyses by Weiler and Strauss, Microanalytical Laboratory, 164 Banbury Road, Oxford, England. [d] Delaby and Leccmte, *Bull. soc. chim. France*, **4**, 1007 (1937), reported for *trans*-3-octenoic acid, b.p. 142° at 19 mm., n_D^{20} 1.4456, density 0.942 at 20°.

this work there was in no instance a sharp break in the rate of hydrogenation. After the approximate theoretical volume of hydrogen was absorbed, there was observed a gradual decrease in the rate of hydrogenation. Therefore, the most likely impurities in the *cis*-octenoic acids prepared in this manner are the parent acetylenic acid and octanoic acid.

Catalytic semihydrogenation of 2-octynoic acid gave the *cis*-2-octenoic acid.

cis-3-Octenoic acid was prepared by the semihydrogenation of 3-octynoic acid which was synthesized by the following route rather than by a published method[15] since use of the latter gave an impure product. The 3-octyn-1-ol which had been

$$C_4H_9C{\equiv}CH \xrightarrow{C_2H_5MgBr} C_4H_9C{\equiv}CMgBr \xrightarrow[(2)\ H_2O,\ H+]{(1)\ (CH_2)_2O}$$

$$C_4H_9C{\equiv}CCH_2CH_2OH \xrightarrow{CrO_3,\ H_2SO_4} C_4H_9C{\equiv}CCH_2COOH$$

obtained in 21% yield by Newman and Wotiz[15] from 1-hexynylsodium and ethylene oxide in liquid ammonia, and in 25% yield in the present investigation from 1-hexynylmagnesium bromide and ethylene oxide in ethyl ether, was obtained in markedly improved yield, 81%, by carrying out the Grignard reaction in benzene. The use of benzene in place of ether allows a higher reflux temperature thus enabling the thermal rearrangement of the first formed, weakly bound oxonium complex[16] to take place. Oxidation of normal C_4, C_5, and C_6 acetylenic primary alcohols has been reported[17,18] to give the corresponding acetylenic acids in yields of 11 to 50%. Oxidation of the 3-octyn-1-ol gave a 21% yield of 3-octynoic acid when a mixed solvent of water and acetone was used, whereas with water alone the yield was only 2.3%.

cis-4- and *cis*-6-Octenoic acids were prepared by catalytic semihydrogenation of the corresponding octynoic acids, prepared as previously reported.[15]

The *trans*-octenoic acids were prepared by utilizing the Knoevenagel condensation. Evidence that the acids produced by a Knoevenagel condensation, as well as the alcohols and bromides obtained from these acids, have a *trans* configuration is supported by the strong infrared absorption of these compounds in the 10.3-micron region.[19] The Knoevenagel condensation in the presence of pyridine yields the *trans*-2-alkenoic acid whereas in the presence of triethanolamine, the *trans*-3-alkenoic acid is formed.[20]

The reported preparation of *trans*-3-octenoic acid[4] involved an allylic rearrangement of 1-hepten-3-ol to 1-bromo-2-heptene during bromination of the alcohol with phosphorus tribromide. In view of the fact that the conversion of secondary allylic alcohols to bromides with phosphorus tri-

(15) M. S. Newman and J. H. Wotiz, *J. Am. Chem. Soc.*, **71**, 1292 (1949).

(16) M. S. Kharasch and O. Reinmuth, *Grignard Reactions of Non-Metallic Substances*, Prentice Hall, Inc., New York, 1954, p. 961.

(17) I. Heilbron, E. R. H. Jones, and F. Sondheimer, *J. Chem. Soc.*, 604 (1949).

(18) G. Eglinton and M. C. Whiting, *J. Chem. Soc.*, 3052 (1953).

(19) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley and Sons, Inc., New York, 1954, p. 31.

(20) S. E. Boxer and R. P. Linstead, *J. Chem. Soc.*, 740 (1931).

bromide is reported[21] to give, under ordinary preparative conditions, an equilibrium mixture containing mainly the primary bromide along with 10 to 20% of the secondary bromide, it seems likely that the previously reported *trans*-3-octenoic acid contained isomeric impurities. *trans*-3-Octenoic acid was prepared by the condensation of *n*-hexaldehyde and malonic acid in triethanolamine.

trans-4-Octenoic acid was prepared by the following series of reactions:

$$C_4H_9CHO \xrightarrow[\text{Triethanolamine}]{CH_2(COOH)_2} C_3H_7CH{=}CHCH_2COOH \xrightarrow[(2)\ PBr_3]{(1)\ LiAlH_4} C_3H_7CH{=}CHCH_2CH_2Br \xrightarrow[(3)\ H_2O,\ H^+]{(1)\ Mg;\ (2)\ CO_2} C_3H_7CH{=}CHCH_2CH_2COOH$$

trans-6-Octenoic acid was synthesized by the following series of reactions:

$$CH_3CH_2CHO \xrightarrow[\text{Triethanolamine}]{CH_2(COOH)_2} CH_3CH{=}CHCH_2COOH \xrightarrow[(2)\ PBr_3]{(1)\ LiAlH_4} CH_3CH{=}CHCH_2CH_2Br \xrightarrow[(3)\ H_2O,\ H^+]{(1)\ Mg;\ (2)\ (CH_2)_2O} CH_3CH{=}CHCH_2CH_2CH_2CH_2OH \xrightarrow{PBr_3} CH_3CH{=}CH(CH_2)_4Br \xrightarrow[(3)\ H_2O,\ H^+]{(1)\ Mg;\ (2)\ CO_2} CH_3CH{=}CH(CH_2)_4COOH$$

EXPERIMENTAL

Boiling points and melting points are uncorrected.

cis-2-Octenoic acid.[2] 2-Octynoic acid,[22] b.p. 101° at 1 mm., was prepared in 58% yield by the carbonation of the Grignard reagent of 1-heptyne.

A 16.2-g. (0.12 mole) sample of 2-octynoic acid was semihydrogenated catalytically using 5 g. of W-5 Raney nickel,[13] aged for 5 to 6 months, and 100 ml. of benzene. The reaction was allowed to proceed until a 10% excess of hydrogen was taken up. After removal of the catalyst and benzene, rectification of the crude acid gave a 61% yield of *cis*-2-octenoic acid.

cis-3-Octenoic acid. 3-Octyn-1-ol. The Grignard reagent from 2.51 moles of ethyl bromide, using 2.66 g.-atoms of magnesium and 700 ml. of dry ether, was prepared in the usual manner. Seven hundred milliliters of dry, thiophene-free benzene was added to the ethereal solution of the Grignard reagent, and then a total of 700 ml. of solvent (mostly ether) was removed by distillation. The Grignard reagent was cooled to 10°, and a solution of 2.0 moles of 1-hexyne in 35 ml. of benzene was added over a period of 95 min. The reaction mixture, after refluxing for 5 hr., was a smooth grayish suspension. Ethylene oxide (2.82 moles) was passed onto the surface of the stirred 1-hexynylmagnesium bromide, which was cooled in an ice bath. The reaction mixture, after standing overnight, was refluxed for 4 hr. Six hundred milliliters of solvent was removed by distillation, and after cooling, the addition complex was decomposed by adding cold water and then cold 20% sulfuric acid. The organic layer was separated, dried over magnesium sulfate, and rectified The yield of 3-octyn-1-ol, b.p. 87° at 9 mm., n_D^{20} 1.4541, was 81%. Reported values of 3-octyn-1-ol are b.p. 97° at 15 mm. and n_D^{25} 1.4542.[23]

3-Octynoic acid. An oxidizing solution was prepared by dissolving 1.23 moles of chromium trioxide in 370 g. of conc. sulfuric acid and diluting with water to give 770 ml. of solution. A mixture of 110 g. (0.86 mole) of 3-octyn-1-ol, 160 ml. of water, and 350 ml. of acetone was cooled in an ice bath, and the oxidizing solution was added over a period of 4 hr. After stirring for an additional 4 hr. at 0°, the organic material was extracted with ether. The crude acid was freed of neutral impurities by extraction of the acid from the ethereal solution using potassium hydroxide solution. The free acid, recovered by acidification of basic solution, was dried over magnesium sulfate and then rectified. The acid was colorless when freshly distilled but turned yellow upon standing overnight. A yield of 21% of 3-octynoic acid, b.p. 85° at 0.4 mm., m.p. 19°, n_D^{20} 1.4573, was obtained. Recorded values for 3-octynoic acid are b.p. 110° at 2 mm., m.p. 18°, and n_D^{25} 1.4577.[15]

cis-3-Octenoic acid was prepared by semihydrogenating 21.5 g. (0.15 mole) of 3-octynoic acid using 16 g. of W-5 Raney nickel, aged for 5 to 6 months, and 70 ml. of benzene. After the theoretical quantity of hydrogen was taken up, the catalyst and solvent were removed, and an 82% yield of *cis*-3-octenoic acid was obtained upon fractional distillation of the crude acid.

cis-4-Octenoic acid. In essentially the same manner as described by Newman and Wotiz,[16] 4-octynoic acid, m.p. 49°, was prepared starting with 1-pentyne. Semihydrogenation of 0.096 mole of 4-octynoic acid using 7 g. of W-5 Raney nickel, aged 5 to 6 months, and 100 ml. of benzene gave a 69% yield of *cis*-4-octenoic acid.

cis-6-Octenoic acid. 6-Octynoic acid was prepared according to the procedure described by Newman and Wotiz.[15] The crude acid, purified by recrystallization from diethyl ether, had a m.p. of 44° whereas the reported value is 37°. A 0.143-mole sample of 6-octynoic acid was semihydrogenated using 13 g. of W-5 Raney nickel, aged 5 to 6 months, and 100 ml. of benzene. After the removal of the catalyst and benzene, the crude acid was rectified, giving a 71% yield of *cis*-6-octenoic acid.

trans-3-Octenoic acid. *trans*-3-Octenoic acid was prepared in a 35% yield by the condensation of *n*-hexaldehyde with malonic acid in the presence of triethanolamine in a manner similar to that described by Linstead and Noble[24] for the preparation of *trans*-3-hexenoic acid.

trans-4-Octenoic acid. *trans*-3-Heptenoic acid[25] was prepared by condensing 0.77 mole of 1-pentanal with 0.8 mole of malonic acid in the presence of 0.8 mole of triethanolamine. The yield was 18%; b.p. 77° at 0.5 mm., n_D^{20} 1.4410.

trans-3-Hepten-1-ol was prepared by the reduction of *trans*-3-heptenoic acid using lithium aluminum hydride.[26,27] The yield of the alcohol, b.p. 66° at 9 mm., n_D^{20} 1.4393, was 83%.

1-Bromo-*trans*-3-heptene was prepared, using the procedure of Crombie and Harper,[27] in a 59% yield. The product had a b.p. of 66° at 20 mm. and n_D^{20} 1.4687.

trans-4-Octenoic acid was prepared in a 38% yield by carbonation of the Grignard reagent from 26.1 g. (0.15 mole) of 1-bromo-3-heptene.

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trans-6-Octenoic acid. *trans*-3-Pentenoic acid[24] was prepared by condensing 5.20 moles of freshly distilled propionaldehyde with 5.20 moles of malonic acid in 5.20 moles of triethanolamine. The acid, obtained in a 13% yield, had a b.p. of 54° at 1 mm. and n_D^{20} 1.4357.

trans-3-Penten-1-ol[28] was prepared by the reduction of 1.28 moles of *trans*-3-pentenoic acid using 1.71 moles of lithium aluminum hydride. The alcohol, yield 81%, had a b.p. of 47° at 13 mm. and n_D^{20} 1.4334.

1-Bromo-*trans*-3-pentene was prepared in a 71% yield using 1.00 mole of *trans*-3-penten-1-ol, 0.41 mole of phosphorus tribromide, and 0.36 mole of dry pyridine in 75 ml. of carbon tetrachloride. The bromide, obtained in a 71% yield, had a b.p. of 80° at 152 mm. and n_D^{20} 1.4686.

trans-5-Hepten-1-ol was prepared by the reaction of the Grignard reagent from 0.70 mole of 1-bromo-*trans*-3-pentene and 0.94 mole of ethylene oxide. The procedure used was similar to that described by Huston and D'Arcy.[29] The alcohol was obtained in a 49% yield and had the following properties: b.p. 77° at 11 mm., n_D^{20} 1.4437, density 0.8536 g./ml. at 20°, m.p. of α-naphthylurethan, 79–80°.

Anal. Calcd. for $C_{18}H_{21}O_2N$: N, 4.95. Found: N, 4.98.

1-Bromo-*trans*-5-heptene was prepared in a 56% yield using 36.5 g. (0.32 mole) of *trans*-5-hepten-1-ol, 0.12 mole of pyridine, and 0.15 mole of phosphorus tribromide in 66 ml. of carbon tetrachloride. The bromide had a b.p. of 85° at 34 mm. and n_D^{20} 1.4691.

trans-6-Octenoic acid was prepared in a 52% yield by the carbonation of the Grignard reagent obtained from 30.1 g. (0.17 mole) of 1-bromo-*trans*-5-heptene.

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(28) L. Crombie and S. H. Harper, *J. Chem. Soc.*, 873 (1950).

(29) R. C. Huston and H. M. D'Arcy, *J. Org. Chem.*, 18, 16 (1953).

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF DELAWARE]

β-Cyano-α-hydroxycinnamates from the Xylenes

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This paper describes the synthesis, separation, and characterization of β-cyano-α-hydroxycinnamates from the xylenes. The separated isomers from *o*-xylene and *m*-xylene have been used to obtain pure hydrolytic cleavage products.

It has been shown in previous reports[1] that isomeric monoalkylphenylacetonitriles could be separated through the intermediate β-cyano-α-hydroxycinnamates. We have accordingly applied this process to the nitriles from the xylenes and have also characterized the products.

The mixture of monochloromethylation products from *o*-xylene led to a mixture of ethyl β-cyanodimethyl-α-hydroxycinnamates. The lower melting isomer I was best separated from the mixture by crystallization from ethyl acetate. The less abundant higher melting isomer II could then be obtained from the non-volatile residue of the filtrate by crystallization from toluene. The relative amounts of I and II that have been isolated are in the ratio 9:4.

Mild alkaline hydrolysis[1] of I gave the pure nitrile which was further hydrolyzed to 3,4-dimethylphenylacetic acid and a small amount of the amide. 3,4-Dimethylacetophenone[2a,b] synthesized from *o*-xylene was converted successively to 3,4-dimethylbenzoic acid, the acid chloride, the diazoketone and the identical 3,4-dimethylphenylacetic acid, thus establishing that I is ethyl β-cyano-3,4-dimethyl-α-hydroxycinnamate, and that the methyl groups in this series are in positions 3 and 4.

The nitrile from II was found to be a solid which by similar refluxing with alkali gave almost entirely the corresponding amide. This was converted to the acid by saponification in diethylene glycol. The structure of the acid was established by oxidation[3] to hemimellitic acid. This was converted to trimethyl hemimellitate which was identical with an authentic sample.[4] These facts show that in this series the methyl groups are in the 2,3-positions and that II is ethyl β-cyano-2,3-dimethyl-α-hydroxycinnamate.

Likewise the ethyl β-cyanodimethyl-α-hydroxycinnamates expected from the chloromethylation products of *m*-xylene (III,IV) and *p*-xylene (V) have been isolated. The separation of the esters derived from *m*-xylene was tedious due to the small amount of IV. Some simplification was attained by the fact that the sodium salt of III crystallized well from the alcohol medium and IV could be obtained from the filtrate. The mild alkaline hydrolysis of III gave the nitrile. More vigorous hydrolysis of III gave the amide and the acid. This acid was oxidized to trimellitic acid which shows that the methyl groups in III and its degradation products are in positions 2 and 4. Similarly the structure of the 2,6-isomer (IV) was shown by hydrolysis to the amide and acid followed by oxidation of the acid to hemimellitic acid. The identity of the single

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(2) (a) K. v. Auwers, *Ber.*, 45, 2780 (1912); (b) O. Grummit and E. N. Case, *J. Am. Chem. Soc.*, 64, 880 (1942).

(3) W. P. Campbell and D. Todd, *J. Am. Chem. Soc.*, 62, 1287 (1940).

(4) We are indebted to Professor Lee Irvin Smith, University of Minnesota, for this sample.

TABLE I

Dimethyl-β-cyano-α-hydroxy-cinnamates				Dimethylphenyl-acetonitriles		Dimethylphenyl-acetamides		Dimethylphenylacetic Acids		
No.	Di-methyl	M.P.	N% Found[a]	B.P. (mm.)	N% Found[b]	M.P.	N% Found[c]	M.P.	C% Found	H% Found[d]
I	3,4-	89–90	5.87	63–65 (0.5)	9.54	174–175	8.54	93.5–94.5	73.15	7.66
II	2,3-	126–127	5.76	52–53[e]	9.59	166–167	8.56	116–117	73.08	7.59
III	2,4-	95–96	5.64	133 (9)	9.60	183–184	[f]	105–106	[f]	
IV	2,6-	113–114	5.72			180–181	8.61			
V	2,5-	118	5.67	113–115 (4)	[g]	154	[h]	128	[h]	

[a] Calcd. 5.72. [b] Calcd. 9.65. [c] Calcd. 8.59. [d] Calcd. C, 73.14; H, 7.37. [e] M.p. [f] P. Barbier and V. Grignard, *Compt. rend.*, 148, 646 (1909). [g] W. Herz, *J. Am. Chem. Soc.*, 75, 73 (1953). [h] M. Guerbet, *Compt. rend.*, 125, 36 (1897).

ester from *p*-xylene was established by hydrolysis to the known nitrile, amide and acid (See Table I).

EXPERIMENTAL

Chloromethyl and cyanomethyl derivatives. The monochloromethylation of *o*-xylene (213 g., 2.02 moles) was effected by passing hydrogen chloride through a stirred mixture with 67 g. (0.82 mole) of formalin and 537 g. (5.47 moles) of hydrochloric acid (sp. gr. 1.19) for 6 hr. at 50°. The mixture of chloromethylxylenes (71.7 g.; 47%) had b.p. 46–49° (0.05 mm.). Similarly *m*-xylene (2.02 moles) in 3.75 hr. gave 111 g. (87%) of monochloromethyl derivatives, b.p. 87–90.5 (3–2 mm.). Similar monochloromethylation of *p*-xylene for 8 hr. gave 163.7 g. (72.5%), b.p. 79–85° (6.6 mm.). These products were converted to the nitriles as previously described.[1] The mixture of nitriles from *o*-xylene (70% yield) had b.p. 72–82° (0.27 mm.) and the mixture from *m*-xylene (82% yield) had b.p. 121–123° (3 mm.). The one product 2,5-dimethylphenylacetonitrile was obtained in 77% yield from *p*-xylene.

Preparation and separation of ethyl β-cyano-3,4-dimethyl-α-hydroxycinnamate (I) *and ethyl β-cyano-2,3-dimethyl-α-hydroxycinnamate* (II). A solution of sodium ethoxide from 13.6 g. (0.59 mole) of sodium and 215 cc. of alcohol was cooled to room temperature and quickly mixed with 87 g. (0.59 mole) of ethyl oxalate and 83.8 g. (0.58 mole) of the mixture of nitriles from *o*-xylene. After standing overnight the excess alcohol was removed under diminished pressure. The residue was shaken vigorously with a mixture of 300 g. of ice and water, 75 cc. of hydrochloric acid (sp. gr. 1.19) and 100 cc. of petroleum ether until all of the lumps were disintegrated. The ice cold product was filtered, washed with petroleum ether and iced water, and dried, yield 135 g. (95%), m.p. 74–79°.

Seven recrystallizations from toluene gave very small amounts of two isomers melting at 89–90° and 126–127°. Upon changing the solvent to ethyl acetate a relatively facile separation was obtained. From this solvent the lower melting isomer came out first and when the mother liquor was substantially free of it the solid residue from the removal of the ethyl acetate was crystallized from toluene to give the higher melting isomer.

Yield: I, m.p. 89–90°, 43.1 g. (29.6%). II, m.p. 126–127°, 18.4 g. (13.0%).

Preparation and separation of III *and* IV. The mixture of nitriles (186.7 g., 1.29 moles) from *m*-xylene was similarly added at once to the well stirred mixture of 203 g. (1.39 moles) ethyl oxalate with alcoholic sodium ethoxide prepared from 30.6 g. (1.33 moles) of sodium and 440 cc. of alcohol. Within a few minutes well formed crystals appeared and the mixture rapidly set to a semisolid mass. After 24 hr. the salt was filtered with the aid of a rubber dam and washed three times with alcohol. The salt was decomposed to the ester by stirring with a mixture of hydrochloric acid, ice, water, and petroleum ether. The collected air-dried product weighed 180 g., m.p. 85–89°. III had m.p. 95–96° when recrystallized from ethyl acetate.

The filtrate from the above salt was evaporated under diminished pressure. The glassy residue by treatment with hydrochloric acid, ice, and petroleum ether gave 59 g. more of product m.p. 85–93°. This was also crystallized from 60 cc. of ethyl acetate to give 29.5 g., m.p. 94–96°. The filtrate after concentration on the steam bath and allowing to stand overnight partly crystallized. The solid product was filtered and washed with petroleum ether, 12.5 g., m.p. 108–110°. Two crystallizations from toluene gave 5.8 g. of pure IV, m.p. 113–114°.

Alternate synthesis of 3,4-dimethylphenylacetic acid. A mixture of 3,4-dimethylbenzoic acid[5] (m.p. 166–167°, 3.00 g., 0.020 mole), thionyl chloride (2.40 g., 0.021 mole), 50 cc. of methylene chloride and 5 drops of pyridine was refluxed for 24 hr. The excess thionyl chloride was removed by evacuation for 5 hr. The solution of the residual oil in 200 cc. of ether was added slowly to a solution of 0.125 mole of diazomethane in 500 cc. of ether at 0°. After standing overnight at 0° the diazoketone was obtained as a viscous yellow oil by cautious distillation of diazomethane and ether. A solution of the oil in 50 cc. of dioxane was added dropwise to a mixture of 1.0 g. freshly prepared silver oxide, 2.5 g. sodium carbonate, 1.5 g. sodium thiosulfate and 100 cc. of water at 50–60°. The temperature was raised to 90° and heating and stirring were continued for 2 hr. The mixture was cooled, diluted with 100 cc. of water, filtered, and extracted with ether to remove oily material. The aqueous layer was acidified with nitric acid and extracted with ether. Evaporation of this extract gave 1.9 g. of yellow oil which slowly crystallized. The extraction of this residue with hot water and cooling of the aqueous solution gave 1.3 g. of white needles, m.p. 89–90°. Another crystallization from hot water raised the m.p. to 91–92°. The melting point was not depressed when admixed with the dimethylphenylacetic acid from I. The x-ray diffraction patterns were also superimposable.

Characterization of II. The hydrolysis of II in steps to the nitrile, amide, and acid proceeded less easily than in the case of I. A 2.00 g. (0.012 mole) sample of the amide (m.p. 166–167°) was suspended in 40 cc. of diethylene glycol containing 2 cc. of water and 1.50 g. (0.038 mole) of sodium hydroxide. The mixture was refluxed for 3 hr. The clear solution from dilution with 125 cc. of water was acidified with hydrochloric acid to give 1.75 g. (87%) of the acid, m.p. 116–117°.

This acid (500 mg.), 1 cc. of nitric acid (sp. gr. 1.42) and 2 cc. of water were heated[3] in a Carius tube (1″ × 36″) for 18 hr. by means of a salt bath at 195–205°. The tube was cooled carefully and gradually in a dry ice–acetone bath before opening. The contents were removed and the residue from evaporation was triturated with 1 cc. of nitric acid (sp. gr. 1.51), yield of crystals 38 mg. This material was esterified with diazomethane and the ester was crystallized from methyl alcohol, m.p. 99–100°. Mixed with an authentic

(5) J. Cologne and L. Pechot, *Bull. soc. chim. France*, [5], 16, 180 (1949).

sample of trimethyl hemimellitate the melting point was 99–100.5°.

Characterization of III. A suspension of 28.4 g. (0.116 mole) of III in a solution of 5.2 g. (0.13 mole) of sodium hydroxide in 200 cc. of water was slowly heated until dissolved (at 65°) and the nitrile began to separate (at 72°). The nitrile was extracted with petroleum ether. To the water layer was added 1.3 g. of sodium hydroxide and the heating process was repeated twice until no more nitrile separated. Yield 10 g. (61%). This nitrile (5.5 g.) was refluxed 10 hr. with a mixture of 2.25 g. of potassium hydroxide, 3.5 cc. of water and 25 cc. of alcohol to give 3 g. of the known 2,4-dimethylphenylacetamide and 3.1 g. of the known 2,4-dimethylphenylacetic acid (see *f* in Table). The acid was smoothly oxidized by alkaline permanganate to trimellitic acid, m.p. 226–227°, lit.[6] 228°.

III was further characterized by acidification of the ice-cold aqueous layer from the nitrile to yield 8.8 g. of shiny crystals. This product was dissolved in the minimum amount of hot 5% sodium hydroxide solution and reprecipitated by hydrochloric acid to give 6.5 g., m.p. 163–165°. It was necessary to dry the product in vacuo as the crystals underwent slow decomposition in the air.

Anal. Calcd. for $C_{11}H_{12}O_3$: Neut. equiv., 192; C, 68.71; H, 6.29. Found: Neut. equiv., 194; C, 68.50; H, 6.38.

The acid reacted readily with Tollen's reagent to produce a silver mirror. It also gave a 2,4-dinitrophenylhydrazone, m.p. 201–202°. One attempt to oxidize the substance with permanganate to another crystalline acid gave only a viscous oil. The acid by-product was not further investigated.

Anal. Calcd. for $C_{17}H_{16}O_6N_4$: N, 15.05. Found: N, 15.06.

Characterization of IV. A mixture of 2.7 g. (0.11 mole) of IV, 6.0 g. (0.11 mole) of potassium hydroxide, 30 cc. of water and 45 cc. of alcohol was refluxed for 48 hr. The alcohol was distilled and water was added to precipitate the amide which was crystallized from hot alcohol. The aqueous filtrate was acidified to give 1 g. of crude acid. This sample of acid was oxidized with an excess of aqueous permanganate with stirring under reflux for 12 hr. The excess permanganate was destroyed by addition of a few drops of methanol. The hot aqueous filtrate was concentrated to a small volume, filtered, acidified, and extracted with ether to give 0.2 g. hemimellitic acid, m.p. 186–188°, lit.[6] m.p. 190°.

NEWARK, DEL.

(6) Huntress and Mulliken, *Identification of Pure Organic Compounds I*, 116, 120 (1941). John Wiley and Sons, New York.

[CONTRIBUTION FROM THE HORMEL INSTITUTE, UNIVERSITY OF MINNESOTA]

Syntheses of Unsaturated Fatty Aldehydes[1]

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Oleyl-, linoleyl- and linolenyl-aldehydes were prepared by a modified Grundmann synthesis. The procedure can be used for the preparation of radioactive aldehydes on a milligram scale.

Most methods reported[2] for the synthesis of aldehydes are not applicable to the preparation of aliphatic aldehydes having methylene-interrupted systems of double bonds. In the present investigation, the procedures described by Brown and McFarlin,[3] Weygand,[4] and Grundmann[5] were selected as the most promising, and were compared by applying them to the synthesis of oleyl aldehyde. A modified Grundmann synthesis gave the purest product and satisfactory yields and therefore it is described in detail.

Grundmann treated the acid chloride with diazomethane to obtain a diazo ketone, which was converted with acetic acid into a ketol acetate. The latter, after reduction with aluminum isopropylate and subsequent saponification, yielded a diol which was split with lead tetraacetate to give the aldehyde of the same chain length as the initial acid.

In the case of highly unsaturated compounds, the use of aluminum isopropylate results in the formation of polymers and the yields of diols are very low. The present author used lithium aluminum hydride for the reduction of ketol acetates[2] to avoid excessive condensations. It is not necessary to purify the ketol acetates since lithium aluminum hydride reduces the expected contaminants such as acid, acid chloride, ester, and chloroketone to mono alcohols which can be separated from the glycol by distillation or by column chromatography. Prolonged treatment of the diol with lead tetraacetate in the final reaction produces a small amount of contaminating acid, which can be extracted easily with dilute sodium carbonate solution. Neutral compounds, which appear as

(1) This research was supported by grants given to Dr. H. Schlenk by the United States Air Force through the Air Force Office of Scientific Research of the Air Research and Development Command, under Contract No. 18(603)18, by the U. S. Atomic Energy Commission (AT(11-1)-236), and by The Hormel Foundation.

(2) E. Mosettig, "The Synthesis of Aldehydes from Carboxylic Acids," in *Organic Reactions*, John Wiley & Sons, Inc., New York, 1954, Vol. VIII, Chapter 5, p. 218; O. Bayer, "Methoden zur Darstellung und Umwandlung von Aldehyden," in *Methoden der Organischen Chemie*, Thieme-Verlag, Stuttgart, 1954, Vol. 7, 1, p. 1.

The use of lithium aluminum hydride as reducing agent in the Grundmann synthesis was already suggested by Mosettig.

(3) H. C. Brown and R. F. McFarlin, *J. Am. Chem. Soc.*, **78**, 252 (1956).

(4) F. Weygand, *Angew. Chem.*, **65**, 525 (1953); S. S. Nigam and B. C. L. Weedon, *J. Chem. Soc.*, 3320 (1957).

(5) Chr. Grundmann, *Ann.*, **524**, 31 (1936).

contaminants in syntheses where a reduction is the final step, are very difficult to remove.

Radioactive oleyl aldehyde for metabolic studies was prepared from randomly-labeled oleic acid,[6] all steps being carried out in a single test tube. The yield and purity of radioactive aldehyde were equal to those of "cold" preparations, despite its preparation on a micro scale. Each reaction product and purification procedure was checked by paper chromatography.[7] By this means, formation of side products, yields, and purities could be determined without analytical difficulty or significant loss of material.

Infrared and ultraviolet spectra of the polyunsaturated aldehydes indicated that no steric changes of the system of double bonds occurred in the course of their synthesis.

EXPERIMENTAL

Oleic, linoleic, and linolenic acids were obtained from The Hormel Foundation.

All procedures were carried out under purified nitrogen, using oxygen-free water and anhydrous solvents free from peroxides. In all cases, the fatty acid chlorides were prepared from the acids by boiling for 2 hr. under reflux with a threefold excess of oxalyl chloride.[8] This excess was removed at 80–90° under vacuum, and the residual fatty acid chlorides were used without further purification.

Fatty aldehydes via *diazo ketones.* The preparation of oleyl aldehyde will be given here. All other syntheses were performed under the same conditions.

(*a*) *Preparation of glycols.* Thirty grams (0.1 mole) of oleoyl chloride, dissolved in 100 ml. of ether, was added during a period of 10 min. to a stirred solution of 0.25 mole diazomethane in 500 ml. of ether kept at 0–5°. After warming to room temperature and standing for 2–4 hr., the excess diazomethane and most of the solvent were removed by a stream of nitrogen. The remaining yellow oil was added slowly to 50 ml. of acetic acid at 50–60°. After 2 hr. at this temperature the decomposition of the diazo ketone was completed by refluxing for 10 min.

The slightly yellow solution was poured into water and the ketol acetate was extracted with ether. The product was washed with water to neutrality and then dried over sodium sulfate. The ether was removed, first by evaporation and finally by heating the residual oil to 50° under high vacuum. The crude ketol acetate contained about 10% of chloroketone. Paper chromatography showed that the addition of potassium acetate, as suggested by Grundmann, does not improve the purity of the ketol acetate.

The crude ketol acetate in 200 ml. of ether was treated with an unfiltered solution of 4.0 g. (0.1 mole) of lithium aluminum hydride in 350 ml. of the same solvent. The sequence in which the reactants were added did not affect the quality and yield of the product. The mixture was refluxed for 1 hr. and, after addition of a little ethyl acetate, it was poured over 200 g. of crushed ice. The milky suspension was acidified with dilute sulfuric acid and extracted several times with ether. The product can be checked for complete reduction by warming a few milligrams with several drops of 50% aqueous potassium hydroxide in a water bath.[9] Residual ketol is indicated by a yellow or brown color. Paper chromatography indicated that these crude preparations contained about 10–15% of primary C_{18} alcohol and about 5% of secondary C_{19} alcohol and/or free acid. The mono alcohols and the glycols have boiling points of approximately 170° and 190–195° at 2 mm., respectively, and their separation by distillation is possible. A pear-shaped Claisen flask with a modified Pyros-Glover type receiver was used for this purpose. To keep the length of exposure to heat at a minimum, the products were distilled in portions of 0.1 mole or smaller from a bath preheated to 180°. Additional amounts of pure glycol were obtained by chromatographing the intermediate distilled fractions [6.5 g. in 15 ml. of petroleum ether (35–60°)] on alumina (40 g., activated, Harshaw) in a tube 2 × 30 cm. The chromatogram was developed successively with 100 ml. of methylene chloride, 100 ml. of ether, and 200 ml. of ethanol, a sequence of solvents which had been used by Trappe[10] for similar fractionations. A total of 24 15-ml. fractions was collected, and each was spot-tested on paper.[6] The first peak of the column chromatogram represented primary and secondary alcohols, which were not separated from each other, and about 1.5–2 g. of pure glycol was recovered from the second peak.

cis-*Nonadecene-10-diol-1,2,* m.p. 33.5–35.0°,[11] n_D^{40} 1.4583, was obtained in yields never below 15 g. (55%) in several experiments.

Anal. Calcd. for $C_{19}H_{38}O_2$: O, 10.75. Found: O, 10.4. Periodate titration: 100.5% glycol.

All-cis-*nonadecadiene-10,13-diol-1,2,* m.p. 17.5–19.0°, n_D^{40} 1.4720, was obtained in yields of about 45%, i.e., 12.5 g., from 28 g. of linoleic acid in several experiments.

Anal. Calcd. for $C_{19}H_{36}O_2$: O, 10.8. Found: O, 11.2. Periodate titration: 98.3% glycol.

All-cis-*nonadecatriene-10,13,16-diol-1,2,* m.p. 6.0–7.5°, n_D^{40} 1.4800, was obtained in yields of 10–12 g. (35–45%) when 28 g. of linolenic acid was used as starting material.

Anal. Calcd. for $C_{19}H_{34}O_2$: O, 10.9. Found: O, 11.2. Periodate titration: 98.4% glycol.

(*b*) *Preparation of aldehydes.* About 40–45 g. (0.1 mole) of lead tetraacetate and 0.5 ml. of acetic acid were added to a solution of 15 g. (0.05 mole) of nonadecene-10-diol-1,2 in 100 ml. of benzene and kept at 60° for 3 hr. Excess reagent was destroyed by addition of ethylene glycol. The solution was cooled to room temperature, poured into 500 ml. of 20% acetic acid in water, and extracted several times with benzene. The combined extracts were washed first with dilute acetic acid to remove the lead salts and finally with water to neutrality. Such preparations contain small amounts of free acids, which are removed by extracting the benzene solutions with 1% aqueous sodium carbonate. The aldehydes obtained in this manner are chromatographically pure. They are colorless and remain liquid at −20°. They may be distilled at 150–160°, 2 mm., and the analyses and yields reported refer to distilled products. The 2,4-dinitrophenylhydrazones were prepared in ethanol and sulfuric acid.[12]

Oleyl aldehyde, n_D^{20} 1.4538, was obtained in an amount of 9.0 g. (33% over-all yield) in the preparation described above.

Anal. Calcd. for $C_{18}H_{34}O$: C, 81.14; H, 12.86; O, 6.00. Found: C, 81.29; H, 12.40; O, 6.3.

2,4-Dinitrophenylhydrazone, yellow crystals from ethanol, m.p. 65.5–66.5° (reported m.p. 67–68°[5]).

(6) H. K. Mangold and H. Schlenk, *J. Biol. Chem.*, **229**, 731 (1957).

(7) H. K. Mangold, B. G. Lamp, and H. Schlenk, *J. Am. Chem. Soc.*, **77**, 6070 (1955); H. Schlenk, J. L. Gellerman, J. A. Tillotson, and H. K. Mangold, *J. Am. Oil Chemists' Soc.*, **34**, 377 (1957).

(8) T. R. Wood, F. L. Jackson, A. R. Baldwin, and H. E. Longenecker, *J. Am. Chem. Soc.*, **66**, 287 (1944).

(9) H. Schlenk, B. G. Lamp, and B. W. de Haas, *J. Am. Chem. Soc.*, **74**, 2550 (1952).

(10) W. Trappe, *Biochem. Z.*, **306**, 316 (1940); **307**, 97 (1941); *Hoppe-Seyler's Z. physiol. Chem.*, **273**, 177 (1942).

(11) All melting points are uncorrected.

(12) *Organic Reagents for Organic Analysis,* 2nd Edition, Hopkin & Williams, Ltd., Chadwell Heath, Essex, England, 1950, p. 68.

Linoleyl aldehyde, n_D^{20} 1.4632, was obtained in an amount of 7.5 g. (27%) using 28 g. of acid as starting material.

Anal. Calcd. for $C_{18}H_{32}O$: C, 81.76; H, 12.20; O, 6.05. Found: C, 81.45; H, 12.02; O, 6.6.

2,4-Dinitrophenylhydrazone, light orange crystals from ethanol, m.p. 42.5–43°.

Linolenyl aldehyde, n_D^{20} 1.4761, was obtained in several preparations in amounts of 6–6.5 g. (20–25%), using 28 g. of acid as starting material.

Anal. Calcd. for $C_{18}H_{30}O$: C, 82.39; H, 11.52; O, 6.1. Found: C, 82.11; H, 11.45; O, 7.19.

2,4-Dinitrophenylhydrazone, light orange crystals from ethanol, which decompose with darkening within 1 day at room temperature, m.p. 40–40.5°.

Paper chromatography. The paper chromatographic methods used to evaluate the synthetic procedures were essentially the same as described previously for other lipides.[7] A system of 75% acetic acid in water with siliconized Whatman No. 1 paper at 30° was generally applied in the chromatography of starting materials and intermediates. The R_f values of oleyl, linoleyl, and linolenyl aldehydes were 0.15, 0.26, and 0.48, respectively. The diols were chromatographed with 60% aqueous tetrahydrofuran. Iodine vapors were used to locate the spots of unsaturated compounds on the paper.

Spectral analyses. According to their infrared spectra, oleic and linoleic acids were pure *cis* compounds, but linolenic acid, prepared by the bromination-debromination method, contained 5–10% of its unsaturation in *trans* form. The same amount of *trans* unsaturation was found in the triene-diol and in linolenyl aldehyde.

Absorption curves of the diols were obtained using carbon tetrachloride solutions in the near-infrared region (0.9–3μ)[13] and with carbon disulfide and tetrachloroethylene solutions between and 2 and 15μ. Only the bands characteristic of saturated and unsaturated hydrocarbon chains and of bounded O—H— groups were present. The aldehydes in the solvents mentioned also showed only bands characteristic of C—H— bonds, *cis* double bonds, and aldehyde groups in the same regions. It was found that spectra of synthetic mixtures of a long-chain aldehyde with the corresponding acid do not reveal less than about 10% of the latter, under the conditions of measurement used. Considerably smaller percentages of acid can be detected by paper chromatography. No trimer[14] was found in any of the aldehyde preparations by either infrared spectroscopy or paper chromatography, but they were detected in commercial samples of saturated aldehydes.

No conjugation was detected in any of the aldehydes by ultraviolet spectroscopy. When isomerized with alkali,[15] maxima appeared at 232 mμ with linoleyl aldehyde or alcohol and at 232 and 268 mμ with the linolenyl analogs. The intensities of these absorptions were of the same magnitude as those obtained from linoleic and linolenic acids. The presence of such unsaponifiables, therefore, would give erroneous results when assaying the polyunsaturated fatty acids of biological materials by the alkali isomerization method.

After this paper was submitted for publication, the author became aware that the synthesis of unsaturated aldehydes by a Grundmann method was outlined, without experimental details, by H. P. Kaufmann.[16]

Acknowledgment. The author is greatly indebted to Dr. H. Schlenk for advice in this investigation. Infrared analyses were made by Dr. J. R. Chipault and Mr. G. Mizuno. Near-infrared analyses were made by Dr. R. T. Holman and Mr. P. R. Edmondson. The cooperation and help received is gratefully appreciated.

AUSTIN, MINN.

(13) R. T. Holman and P. R. Edmondson, *Anal. Chem.*, **28**, 1533 (1956).

(14) H. P. Kaufmann and H. Kirschnek, *Fette, Seifen, Anstrichmittel*, **55**, 847 (1953).

(15) R. T. Holman, in *Methods of Biochemical Analysis*, Interscience Publishers, Inc., New York, 1957, Vol. IV, pp. 99, 126.

(16) Meeting of the International Society of Industrial Chemists, Comunicaciones de las Secciones 13 A 23, Madrid, Oct. 22–31, 1955. Vol. II, p. 1085.

Notes

A department for short papers of immediate interest.

Flavonoids of Various *Prunus* Species. VIII. The Flavonoids in the Wood of *Prunus mume*

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The pattern of the flavonoid compounds obtained from the wood of *Prunus mume* Siebold et Zuccarini, called "mume" in Japanese and belonging to section *Prunophora*, differs from the other species of section *Cerasus* reported before.[1] The specific constituent kaempferid-7-glucoside (3,5-dihydroxy-7-glucosidoxy-4′-methoxyflavone) was obtained instead of genkwanin and chrysin which had been found to be characteristic of the latter section.

Kaempferid-7-glucoside was hydrolyzed by acid into one mole each of kaempferid and glucose. The glycoside produced an olive green coloration with ferric chloride. The absorption maximum at 367 mμ showed the presence of a free hydroxyl group at the 3 position. The maximum absorption of the glycoside was identical with that of its aglycone, kaempferid, and this fact indicated that the hydroxyl group in the 3 position of the glycoside was free from sugar.[2] (The solvent used was redistilled methanol.) The hydrolysis product from the methylated glucoside gave no coloration with ferric chloride. From these facts, it was evident that the hydroxyl group at position 7 was the one involved in glycoside formation. Since this compound has not previously been reported as a natural product, the name "mumenin" is proposed for it.

In addition to mumenin, the compounds naringenin (5,7,4′-trihydroxyflavanone), prunin (the 7-glucoside of naringenin), (+)-catechin, (−)-epicatechin, leucoanthocyanidin, and a new flavanone glycoside have also been obtained. Details on the last two compounds will be reported in a later paper. The yield of the new flavanone glycoside was poor and purification of the leucoanthocyanin has thus far been unsuccessful.

EXPERIMENTAL

Wood chips (500 g.) of *Prunus mume* (cut down in February), prepared from a stem of 8-cm. diameter, were extracted twice with 4 l. methanol for 3 hr. each. A total of 2.1 kg. wood chips was extracted. After filtration and subsequent distillation of the methanol, the residual 200 ml. of sirup was extracted 6 times with 400-ml. portions of ether. The ether-insoluble residue was then extracted 10 times with 400-ml. portions of ethyl acetate.

Ether-soluble portion. After distillation of the ether, the remaining 26 g. of sirup was extracted with 300 ml. hot benzene for 30 min. The residue was extracted with hot water (150 ml.), and finally dissolved in 20 ml. methanol.

After concentration of the benzene solution to 50 ml., white crystals of naringenin were gradually deposited.

The hot water-soluble portion, red brown in color, was extracted by ether with Soxhlet liquid percolator for 1 hr. After evaporation of the ether, the residue was dissolved in 100 ml. water. This water-soluble portion was extracted twice with 100 ml. ether to give a pale yellow solution. After evaporation of the ether, the residue was recrystallized from 20 ml. water. Crystals of (+)-catechin deposited, and, after two recrystallizations, the yield of (+)-catechin was 30 mg.

The mother liquor of the water-soluble portion was repeatedly extracted with ethyl acetate. After evaporation of the ethyl acetate, the residue was dissolved in 50 ml. acetone and an equal volume of benzene was added. The pale yellow supernatant solution was evaporated to dryness. The whitish yellow residue was dissolved in 10 ml. of ethyl acetate and after a week (−)-epicatechin precipitated; yield 1.0 g.

From the methanol-soluble portion, no crystalline substance was obtained, but naringenin and eriodictyol were found in this fraction by paper chromatography.[3]

Ethyl acetate-soluble portion. The combined ethyl acetate solution was evaporated to 200 ml., then 200 ml. of water was added. On standing for 2 days in an ice box, an oily blackish brown mass was precipitated on the bottom of the flask. After decanting, the residue was mixed with 20 ml. of methanol and allowed to stand for a week at room temperature. Yellow crystals of mumenin gradually appeared; yield, 2.4 g. The mother liquor was evaporated on a water bath to one third its volume; yellow crystals of mumenin deposited on standing, yield 3.0 g.

After evaporation of the remainder of solvent from the ethyl acetate fraction, the residue was dissolved in 150 ml. of benzene. A red resinous substance precipitated. The supernatant yellow solution was then evaporated to dryness, leaving a yellow substance. The red resinous precipitate was repeatedly treated with this acetone-benzene procedure to give a total of 32 g. of yellow substance. This yellow substance was extracted in a Soxhlet with ether for 20 hr. The residual substance (23 g.) was dissolved in 130 ml. warm water, and after cooling, 100 ml. ethyl acetate was added. After a month in an ice box, a crystalline mass (a mixture of a new flavanone glycoside and prunin) gradually appeared on the interface of the two liquids and was collected by filtration with a yield of 1.8 g. on recrystallization from 30 ml. ethyl acetate. Prunin was obtained as colorless needles. After three recrystallizations from methanol, the melting point of prunin rose to 224°[4]; yield 0.3 g. After evaporation of ethyl acetate, the residue was recrystallized twice from dilute methanol to produce colorless long needles of a new flavanone glycoside, m.p. 141°; yield 0.2 g.

The ethyl acetate-soluble portion was evaporated, and the residue was treated by the acetone-benzene method described above. From this portion, a substance containing

(1) M. Hasegawa and T. Shirato, *J. Am. Chem. Soc.*, **74**, 6114 (1952); **76**, 5559, 5560 (1954); **77**, 3557 (1955); **79**, 450 (1957); and M. Hasegawa, *J. Am. Chem. Soc.*, **79**, 1738 (1957).

(2) S. Hattori, *Acta Phytochim. (Japan)*, **6**, 131 (1932).

(3) M. Hasegawa, *J. Japan. Forestry Soc.*, **38**, 107 (1956).

(4) All melting points are uncorrected.

leucoanthocyanin was obtained as a yellowish powder; yield, 7.8 g.

The reddish brown precipitate obtained by the acetone-benzene method was dissolved in 20 ml. methanol, and, after 2 weeks, 1.7 g. of mumenin was obtained as yellow crystals.

Thus, from 2.1 kg. wood chips of *Prunus mume*, 30 mg. (+)-catechin, 1.0 g. (−)-epicatechin, 32 mg. naringenin, 0.3 g. prunin, 0.2 g. of a new flavanone glycoside, 7.1 g. mumenin, and 7.8 g. leucoanthocyanin were obtained.

(+)-Catechin. The melting point of (+)-catechin (97°) as well as of its anhydrous substance did not alter when mixed with authentic specimens obtained from *Prunus yedoensis*.[1]

(−)-Epicatechin. After recrystallization from water, it was obtained as plates of m.p. 236°. It gave a green coloration with ferric chloride. The chromatographic data (R_f 0.18 in *m*-cresol:acetic acid:water 25:1:24, R_f 0.52 in isopropyl alcohol:water 22.78) agreed with that of an authentic specimen which was kindly supplied by Prof. Tsujimura.[5] The melting point was not depressed by admixture with the authentic specimen (m.p. 236°). Acetate: m.p. 150°.

Naringenin. After 3 recrystallizations from dilute methanol, naringenin melted at 246°, yield: 32 mg. The mixed melting point with an authentic specimen (m.p. 248°) obtained from *Prunus yedoensis*[1] was the same.

Prunin. This glycoside proved to be identical with authentic prunin (m.p. 224°) on chromatographic comparison and by mixed melting point determination. On hydrolysis with 2% hydrochloric acid, it produced naringenin of m.p. 246° and glucose (ascertained by paper chromatography).

Mumenin. This glycoside showed a greenish brown coloration with ferric chloride and an orange one with magnesium powder and hydrochloric acid in methanol solution. Mumenin crystals are difficultly soluble in most organic solvents except pyridine and dioxane. It was recrystallized from pyridine-water and gave microscopic yellow prisms of m.p. 278°. R_f: 0.95 (*m*-cresol:acetic acid:water 25:1:24), and 0.10 (isopropyl alcohol:water 22:78). Absorption: λ_{max} 260 mμ, 320 mμ, 367 mμ; λ_{min} 239 mμ, 285 mμ, 329 mμ.

Anal. Calcd. for $C_{22}H_{22}O_{11}.{}^1/_2H_2O$: C, 56.05; H, 4.88; OCH_3, 6.58. Found: C, 56.00; H, 4.85; OCH_3, 6.52.

Mumenin pentaacetate. This acetate was prepared by the usual method using acetic anhydride and one drop of conc. sulfuric acid. It was obtained in colorless long prisms of m.p. 210–212°.

Anal. Calcd. for $C_{34}H_{34}O_{17}$: C, 57.14; H, 4.76. Found: C, 56.76; H, 4.92.

Hydrolysis of mumenin. The glycoside (0.1095 g.), 55 ml. water, and 16 ml. conc. sulfuric acid were heated for 8 hr. under refluxing. After cooling, the precipitated aglycone was collected, washed, and dried; yield, 0.0719 g. After the aglycone was filtered, the filtrate was neutralized with barium hydroxide and then barium carbonate. The neutralized solution was dried over potassium hydroxide granules in a vacuum desiccator, and examined chromatographically. Glucose was the only sugar found.

The aglycone (kaempferid) was recrystallized from dilute methanol 3 times and obtained as yellow prisms of m.p. 228°.[6] Absorption: λ_{max} 266 mμ, 367 mμ; λ_{min} 240 mμ, 280 mμ.

Anal. Calcd. for $C_{16}H_{12}O_6$: C, 64.00; H, 4.03. Found: C, 63.88; H, 4.02.

Kaempferid triacetate, m.p. 197°.

Kaempferid trimethyl ether (kaempferol tetramethyl ether). This derivative was obtained as faint yellow needles of m.p. 158° by heating an acetone solution of kaempferid with dimethyl sulfate and potassium carbonate. The mixed melting point of kaempferid trimethyl ether with the authentic specimen of kaempferol tetramethyl ether was not depressed.

Anal. Calcd. for $C_{19}H_{18}O_6$: OCH_3, 36.25. Found: OCH_3, 36.51.

Mumenin dimethyl ether. Mumenin (0.4 g.) was suspended in 200 ml. acetone. Then 10 g. potassium carbonate and 2 ml. dimethyl sulfate were added and the whole was heated for 16 hr. When the reaction was over, the liquid was evaporated after removal of mineral salts; the residue was mixed with water; and the solidified mass was washed with water and recrystallized from methanol to produce faint yellow prisms of m.p. 248–250°; yield, 0.2 g. Absorption: λ_{max} 260 mμ, 310 mμ (inflection), 344 mμ; λ_{min} 247 mμ, 283 mμ.

Anal. Calcd. for $C_{22}H_{20}O_9(OCH_3)_2$: OCH_3, 18.97. Found: OCH_3, 19.05.

Hydrolysis of mumenin dimethyl ether. A mixture of mumenin dimethyl ether (125 mg.) and 50 ml. of 4% sulfuric acid was heated over a flame for 40 min. After cooling, the precipitate was filtered and recrystallized from methanol to give yellow needles of m.p. 282°.[7] The yield was 64.5 mg. It gave no coloration with ferric chloride.

Anal. Calcd. for $C_{18}H_{16}O_6$: OCH_3, 28.38. Found: OCH_3, 28.40.

Acknowledgment. I wish to thank Professor Shizuo Hattori, the University of Tokyo, for his advice given during this investigation. I am also indebted to Professor Michiyo Tsujimura, Ochanomizu University, who has given me the sample of (−)-epicatechin, and to Miss Nobue Furusawa of the Government Forest Experiment Station for making elementary analyses. I appreciate very much the collaboration of Mr. T. Shirato in this work.

Finally I thank Dr. Simon H. Wender, the University of Oklahoma, for his kindness in reading my manuscript.

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(5) M. Tsujimura, *J. Agr. Chem. Soc. Japan*, 29, 407 (1955).

(6) C. Ciamician and P. Silber, *Ber.*, 32, 861 (1899).

(7) H. Nakamura and G. Hukuti, *J. Pharm. Soc. Japan* 60, 179 (1940).

An Improved Procedure for Preparing Glycerol Ethers[1]

S. C. GUPTA[2] AND F. A. KUMMEROW

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Batyl alcohol, a natural occurring glycerol ether found in the liver of various Elasmobranchii (shark, rays, etc.) was found to be identical with 1-stearyl glycerol ether.[3–5] The 1- and 2-stearyl

(1) This investigation was supported by research grant No. A-1671 from the National Institute of Arthritis and Metabolic Diseases, U. S. Public Health Service.

(2) Portion of a thesis presented by S. C. Gupta as partial fulfillment of the requirements for the degree of Doctor of Philosophy in Food Technology.

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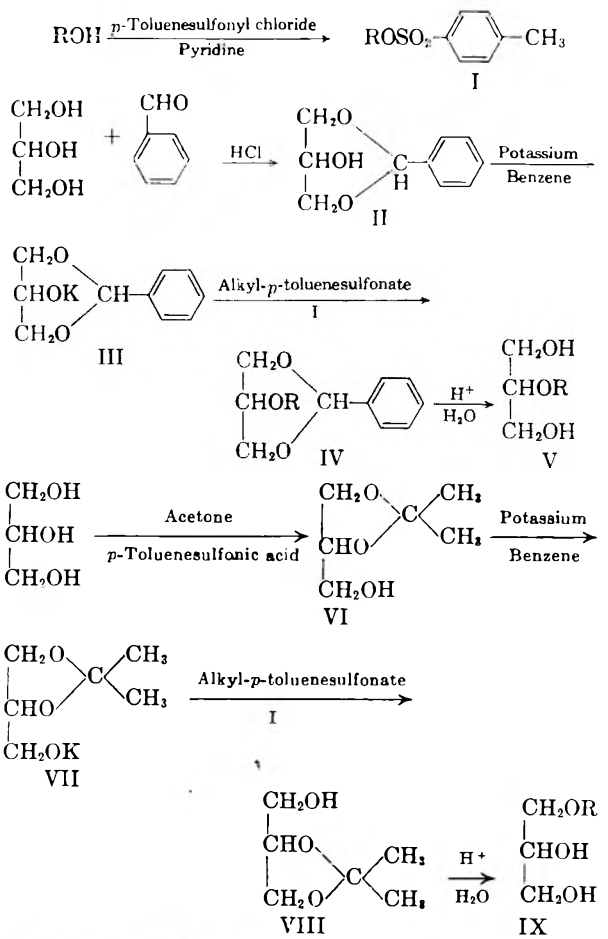
glycerol ethers have been prepared by condensing an excess amount of stearyl iodide with the potassium salt of 1,3-benzylideneglycerol or of 1,2-isopropylideneglycerol in benzene, followed by hydrolysis with acetic acid.[5] The excess stearyl iodide was removed by distillation under vacuum. The unsaturated glycerol ether–selachyl alcohol (1-oleyl glycerol ether) has been prepared in both (+) and (−) forms by condensing oleyl *p*-toluenesulfonate with the sodium salts of (+) and (−)-1,2-isopropylideneglycerol in glycol dimethyl ether.[6] The sodium salts of (+)- and (−)-1,2-isopropylideneglycerol were obtained by using sodium naphthalene as an intermediate compound. Later it was found by the same authors[7] that elaidinization had occurred during synthesis, and they therefore modified their procedure by condensing (+)- and (−)-1,2-isopropylidene-3-(*p*-toluenesulfonoyl) glycerol with sodium oleoxide. The latter was prepared by the use of sodium naphthalene as an intermediate. Baer *et al.*[6] had found that traces of naphthalene were difficult to remove, the products had to be distilled in a molecular still several times before they could be obtained in pure form.

In the present method for the preparation of glycerol ethers, the procedures of Davis *et al.*[5] and that of Baer and Fischer[6] were combined. The stearyl *p*-toluenesulfonate[6] (I) was condensed with the potassium salt of 1,3-benzylideneglycerol (III) or of 1,2-isopropylideneglycerol (VII) in benzene.[5] By this modified procedure, the crude glycerol ethers from stearyl alcohol were obtained in 90–96% yield on the basis of stearyl *p*-toluenesulfonate (I). The intermediate products, 1,3-benzylideneglycerol 2-stearyl ether (IV) as well as 1,2-isopropylideneglycerol 3-stearyl ether (VIII) were isolated in the crude state. It was found from the saponification value of these crude intermediate products that the *p*-toluenesulfonyl group in stearyl *p*-toluenesulfonate (I) was displaced completely. These intermediate products were purified by crystallization from petroleum ether (40–60°), m.p., 59–60°; 60–61°, respectively. On hydrolysis of 1,3-benzylideneglycerol 2-stearyl ether (IV) with dilute hydrochloric acid, 2-stearyl glycerol ether (V) was obtained, m.p. 69–70°. It has been reported to melt at 62–63° by Davis *et al.*[5] The possibility of this compound being 1-stearyl glycerol ether (IX) was eliminated because it could not be oxidized by periodic acid.[8] Moreover, when 2-stearyl glycerol ether (IV) was mixed with an equal quantity of 1-stearyl glycerol ether (IX), the mixture melted at 60–64°.

The syntheses of 2-oleyl and 2-linoleyl glycerol ethers have been attempted by this modified



procedure. Analysis of samples by means of infrared spectrophotometer indicated that these glycerol ethers were not elaidinized during their preparation. Due to difficulties encountered in purification, they have not been obtained in pure enough form for accurate carbon hydrogen values.

EXPERIMENTAL

1,3-Benzylideneglycerol (II). The method of Carter *et al.*[9] was used to prepare this compound from glycerol (C.P.) and benzaldehyde. It was obtained in 20% yield, m.p. 81–82°.

1,2-Isopropylideneglycerol (VI). The method described in organic syntheses[10] was used to prepare this compound from glycerol (C.P.) and acetone (C.P.). It was obtained in 87.4% yield, n_D^{25} 1.4388.

Stearyl alcohol. This alcohol was obtained from a sample of commercial alcohol[11] by repeated crystallization from ethyl acetate, m.p. 56°.

Stearyl p-toluenesulfonate (I). The stearyl *p*-toluenesulfonate (I) was prepared by condensing stearyl alcohol with *p*-toluenesulfonyl chloride in the presence of pyridine.[6] It was purified by crystallization from petroleum ether, yield 84.2%, saponification value 131.9 (calcd. 132), and m.p. 56°.

2-Stearyl glycerol ether (V). This ether was prepared in two stages; in the first stage, 1,3-benzylideneglycerol 2-stearyl

(6) E. Baer, I. L. Rubin, and H. O. L. Fischer, *J. Biol. Chem.*, **155**, 447 (1944).

(7) E. Baer and H. O. L. Fischer, *J. Biol. Chem.*, **170**, 337 (1947).

(8) W. D. Pohle, V. C. Mehlenleacher, and J. C. Cook, *Oil & Soap*, **22**, 115 (1945).

(9) H. Hilbart and N. M. Carter, *J. Am. Chem. Soc.*, **51**, 1601 (1929).

(10) M. Renoll and M. S. Newman, *Org. Syntheses*, Coll. Vol. III, 502 (1955).

(11) The stearyl alcohol was supplied through the courtesy of Archer-Daniels-Midland Co.

ether (IV) was obtained by condensing the stearyl *p*-toluenesulfonate (I) with the potassium salt of 1,3-benzylideneglycerol (III) in benzene; in the second stage, 1,3-benzylideneglycerol 2-stearyl ether (IV) was hydrolyzed with dilute hydrochloric acid.

Five hundred ml. of dry benzene and 6.8 g. (0.17 mole) of freshly cut (0.5 cm.) pieces of potassium were placed in a dry 1-liter three-necked round bottom flask fitted with a sealed mechanical stirrer and a reflux condenser. A calcium chloride tube was connected to the reflux condenser to protect the reaction from moisture. The third neck was closed by a glass stopper. The flask was heated carefully to allow the benzene to reflux, until the potassium melted (1–1.5 hr.) and then stirring was started slowly. The potassium was first distributed in fine particles. A part of it on continuous refluxing and stirring disappeared, forming a light blue solution, leaving the remaining in suspension. To this solution, 31.5 g. (0.17 mole) of 1,3-benzylideneglycerol (II) was added very slowly. The stirring and refluxing was continued for 2–3 hr. until a clear light brown solution was obtained, then 70.1 g. (0.16 mole) of stearyl *p*-toluenesulfonate (I) in 250 ml. of benzene was added slowly through a dropping funnel. The solution in the flask was heated to allow it to reflux and was stirred during the addition of stearyl *p*-toluenesulfonate (I). The stirring and heating was continued for another 12–16 hr. to complete the reaction, a brownish precipitate, potassium *p*-toluenesulfonate, appeared. Approximately 400 ml. of benzene was removed from the condensation product by distillation and traces of potassium in the neck of the flask decomposed cautiously with moist ether. The residue in the flask was extracted with ether, the extract was washed with water and dried over anhydrous potassium carbonate. The ether was removed by distillation and the last traces of solvent removed under vacuum. The 1,3-benzylideneglycerol 2-stearyl ether (IV) was obtained in 100.2% yield, saponification value 0.00. It was recrystallized from petroleum ether (40–60°), yield 98.7%, m.p. 59–60°.

Anal. Calcd. for $C_{28}H_{48}O_3$: C, 77.72; H, 11.18. Found: C, 77.57; H, 11.24.

Hydrolysis of 1,3-benzylideneglycerol 2-stearyl ether (IV). Fifty and one-tenth g. of 1,3-benzylideneglycerol 2-stearyl ether (IV) was placed in a 250-ml. round bottom flask. About 20 ml. of 0.5*N* hydrochloric acid was added and the flask was heated on a steam bath for 1 hr. The resultant product was cooled, filtered, and washed with cold water. The crude 2-stearyl glycerol ether (V) was dried under vacuum, yield 98.3%. It was recrystallized from petroleum ether (40–60°), yield 86.6%; acetyl value 261.6 (calcd. 261.7) and m.p. 70–71°.

Anal. Calcd. for $C_{21}H_{42}O_3$: C, 73.25; H, 12.79. Found: C, 73.27; H, 13.19.

1-Stearyl glycerol ether (IX). This ether was prepared under conditions similar to those described for 2-stearyl glycerol ether (V). Approximately 4.5 g. (0.11 mole) of potassium was used in 500 ml. of benzene and 15.8 g. (0.12 mole) of 1,2-isopropylideneglycerol (VI) was substituted for 1,3-1,3-benzylideneglycerol (III). Forty-seven and five-tenths g. (0.11 mole) of stearyl *p*-toluenesulfonate (I) was added. The crude 1,2-isopropylideneglycerol 3-stearyl ether (VIII) was obtained in 100.1% yield, saponification value 0.00. It was recrystallized from petroleum ether, yield 97.2% m.p. 60–61°.

Anal. Calcd. for $C_{24}H_{48}O_3$: C, 74.94; H, 12.48. Found: C, 75.2; H, 12.56.

Crude 1-stearyl glycerol ether (IX) was obtained on the hydrolysis of 35.5 g. of 1,2-isopropylideneglycerol 3-stearyl ether (VIII) with 15 ml. of 0.5*N* hydrochloric acid, yield 92.4%. It was recrystallized from petroleum ether, yield 90.0%, acetyl value 261.4 (calcd. 261.7); m.p. 69–70°.

Anal. Calcd. for $C_{21}H_{44}O_3$: C, 73.25; H, 12.79. Found: C, 72.89; H, 12.91.

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Isolation of Cycloeucalenol from West Indian Mahogany Wood[1]

LUIS AMORÓS-MARÍN, WANDA I. TORRES, AND CONRADO F. ASENJO

Received July 7, 1958

We wish to report the isolation of cycloeucalenol from the unsaponifiable fraction of the oil from West Indian mahogany wood (*Swietenia mahagoni* Jacq.).

EXPERIMENTAL

Finely shredded mahogany hardwood was extracted exhaustively with petroleum ether (b.p. 35–60°). The petroleum ether was removed by distillation. The remaining viscous reddish oil (0.75% of wood), on standing at ice box temperature, deposited a waxy white precipitate, insoluble in petroleum ether. This waxy material was removed. Its composition and properties have been studied and reported elsewhere.[2] The supernatant oil was filtered and 100 g. saponified with 150 ml. of 5*N* alcoholic KOH. Extraction of the alkaline saponified solution with petroleum ether removed 18 g. of a white crystalline material, which after several recrystallizations from the above solvent, yielded a product with a constant melting point. The crystals thus obtained (compound I) had the following properties: m.p. 135–136°,[3] $[\alpha]_D^{26°}$ +42° (in chloroform). The purified crystals gave a positive digitonin and a reversed Salkowski test. The conventional Tortelli-Jaffe and Lieberman-Burchard tests were negative. With the latter test, however, compound I gave a brown solution with a green fluorescence.

Anal. Calcd. for $C_{30}H_{50}O$: C, 84.4; H, 11.8. Found: C, 84.4; H, 11.7.[4]

A mixed melting point with authentic cycloeucalenol[5–8] (4-β-demethyl-24-methylenecycloartanol), did not show any depression.

Several derivatives were prepared. Their melting points, analysis, and other characteristics are compared in Table I, with those reported for cycloeucalenol by Cox *et al.*[6]

In Fig. 1 are shown the superimposed infrared spectra curves[9] of compound I from West Indian mahogany and

(1) Aided by a grant from the Agricultural Experiment Station of the University of Puerto Rico.

(2) C. F. Asenjo, L. Amorós-Marín, W. Torres, and A. del Campillo, *J. Agric. Univ. of Puerto Rico*, 42, 185 (1958).

(3) All melting points are uncorrected.

(4) Elemental analysis done by Geller Laboratories, West Englewood, N. J.

(5) We are indebted to Dr. Roland E. Kremers and collaborators, Institute of Paper Chemistry, Appleton, Wis. for suggesting to one of us (C.F.A.) the possible identity of our compound with cycloeucalenol.

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(8) We wish to thank Prof. T. J. King, Nottingham University, England, for the gift of some cycloeucalenol for our comparison.

(9) We are indebted to Mr. J. S. Ard, Eastern Utilization Research and Development Division (EURDD), Philadelphia, Pa., for the infrared spectra of compound I and the cycloeucalenol supplied to us by Professor T. J. King. Our thanks to Dr. C. F. Krewson, Head, Biochemical Investigations, Plant Products Laboratory (EURDD), for making this cooperation possible.

TABLE I

DERIVATIVES PREPARED FROM CYCLOEUCALENOL, ISOLATED FROM WEST INDIAN MAHOGANY AND EUCALYPTUS, RESPECTIVELY

Derivative	*Swietenia mahagoni* Jack	*Eucalyptus microcorys*	Calculated for Derivatives of $C_{20}H_{50}O$
Cycloeucalenol 3,5-dinitrobenzoate			
M.P.	204–205°	205°	
Analyses	C = 71.6% H = 8.5% N = 4.4%	C = 71.9% H = 8.3% N = 4.5%	C = 71.6% H = 8.4% N = 4.5%
Cycloeucalenol benzoate			
M.p.	127–128°	130°	
Analyses	C = 83.9% H = 10.3%	C = 83.7% H = 10.5%	C = 83.7% H = 10.3%
Cycloeucalenyl acetate			
M.p.	105–106°	110°	
$[\alpha]_D^{26°}$	+63.0°	+63.0°	
Analyses	C = 81.8% H = 11.2%	C = 81.9% H = 11.5%	C = 82.0% H = 11.2%
Hydrogenated cycloeucalenol (cycloeucalanol)			
M.p.	144–145°	149–150°	
$[\alpha]_D^{26°}$	+46.4°	+52.0°	
Analyses	C = 83.9% H = 12.1%	C = 84.2% H = 12.1%	C = 84.0% H = 12.2%
Hydrogenated cycloeucalenol acetate (cycloeucalanyl acetate)			
M.p.	105–106°	112–113°	
$[\alpha]_D^{26°}$	+61.3°	+62.0°	
Analyses	C = 81.9% H = 11.5%	C = 82.0% H = 11.9%	C = 81.6% H = 11.6%
Oxidized cycloeucalenol (cycloeucalenone)			
M.p.	82–83°	84°	
2,4-Dinitrophenylhydrazone of cycloeucalenone			
M.p.	236°	246°	
Light absorption in $CHCl_3$	λ_{max} at 368–370 mμ	λ_{max} at 368 mμ	
ϵ	23,700	24,000	
Analyses	C = 70.2% H = 8.3% N = 9.6%	C = 71.9% H = 8.7% N = 9.4%	C = 71.5% H = 8.7% N = 9.3%
Cycloeucalenol *p*-nitrobenzoate[a]			
M.p.	178°	—	
Analyses	C = 77.0% H = 9.3% N = 2.3%	—	C = 77.2% H = 9.3% N = 2.4%
Cycloeucalenol dibromo acetate[a]			
M.p.	159–160°	—	
Analyses	C = 61.4% H = 8.3% Br = 25.0%	—	C = 61.1% H = 8.3% Br = 25.4%

[a] These derivatives have not been reported before, as far as we know.

cycloeucalenol from Eucalyptus. The spectral lines of each coincide within instrumental error limits, except for negligible impurity effects in compound I just detectable at 1713 and 855 cm.$^{-1}$ Otherwise these two curves are identical.

The occurrence of this 4-monomethylated sterol in West Indian mahogany wood furnishes additional evidence of its wide distribution in nature, since it has been isolated before from the woods of the *Eucalyptus microcorys*[6] and *Erythrophloeum guineense*.[6]

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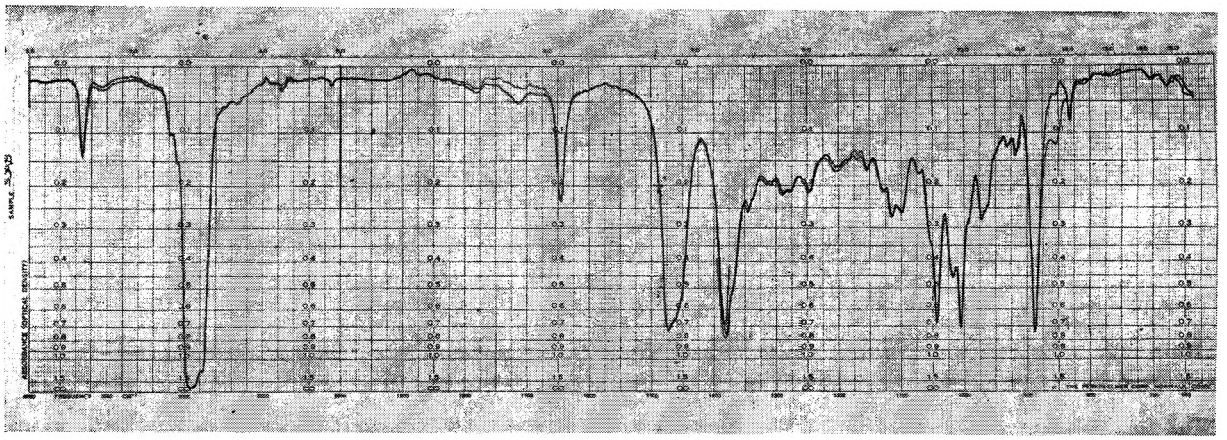


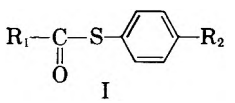
Fig. 1. Translucent picture made by superimposing the infrared spectra curves of compound 1 from West Indian mahogany and cycloeucalenol from Eucalyptus. In the few places where there is no perfect congruency of the two curves the lower line is that of compound 1

Ultraviolet Absorption Spectra of Some Ortho-Anisyl Esters and Thiolesters

G. CILENTO

Received August 12, 1958

In previous papers[1] evidence was presented that in the photoexcited state of the 240 mμ transition shown by *p*-anisyl thiolesters (I: R_1 = CH_3, C_6H_5, *p*-CH_3O—C_6H_4, *p*-NO_2—C_6H_4; R_2 = OCH_3) sulfur utilizes a *d* orbital; that is, there is some mi-



I

gration of negative charge outside the anisyl ring.

Bordwell and Boutan[2] have criticized this view on the ground that the bathochromic shift of the first primary band[3] on passing from *p*-hydroxyphenyl thiolacetate (I:R_1 = $-CH_3$; R_2 = $-OH$) to the corresponding anion is of the same magnitude as that occurring on passing from phenol itself to the phenolate anion and that therefore sulfur should not be concerned in this transition of para substituted phenyl thiolacetates. In answer to this objection, it should be noted that the expansion effect appears to be weak, the energy for "raising" an electron from the *p* level to the *d* level in sulfur being only slightly overbalanced by the increased delocalization of the π-electron system of the ring. Parallel examples are found in such cases where one of the two groups is capable of only a weak resonance effect. Thus on passing from *p*-chlorobenzonitrile (λ_{max} = 237.5 mμ)[4] to *p*-chloronitrobenzene (λ_{max} = 280 mμ)[4] the shift (42.5 mμ) is almost identical to that (44.5 mμ) resulting on passing from benzonitrile (λ_{max} = 224 mμ)[4] to nitrobenzene (λ_{max} = 268.5 mμ).[4,5]

Spectroscopic indication of the enlargement of the *M*-shell of a sulfur atom flanked by a carbonyl group has now also been presented by Knott.[6a] However, Knott,[6b] in commenting on the ultraviolet absorption spectra of aryl thiolesters, points out that since such molecules are not planar, contributions involving a sulfur decet are hindered or excluded. This objection is answered in a simplified way, schematically represented in Fig. 1 where R is either an alkyl or aryl group.

The expansion effect being weak, it should disappear when the groups are ortho to each other, as

(1) (a) G. Cilento, *Experientia*, **8**, 421 (1952); (b) *J. Am. Chem. Soc.*, **75**, 3748 (1953); (c) G. Cilento and W. F. Walter, *J. Am. Chem. Soc.*, **76**, 4469 (1954).

(2) F. G. Bordwell and P. J. Boutan, *J. Am. Chem. Soc.*, **78**, 854 (1956).

(3) The nomenclature of the bands, used here is that of Doub and Vandenbelt, ref. 4.

(4) L. Doub and J. M. Vandenbelt, *J. Am. Chem. Soc.*, 69, 2714 (1947).

(5) The objections of Bordwell and Boutan based on the comparative spectral study of thiocyanates can be rebutted on the ground that while in an excited state of the transition in phenyl thiocyanate the sulfur atom would be expected to act as a moderate donor incorporating the nonbonding 3 pπ electrons in the aromatic 2 pπ shell, in the excited state of *p*-hydroxyphenyl thiocyanate another energetically equivalent conjugation is feasible in which the donor properties of the HO-group and the acceptor properties of the sulfur atom are used.

Several arguments can be advanced against their suggestion that the effect of the *p*-CH_3O group in aryl thiolesters is merely to resolve the absorption. The strongest one is to note that on passing from *p*-CH_3O—C_6H_4—COS—C_6H_5 to *p*-CH_3O—C_6H_4—COS—C_6H_4—OCH_3-*p* the same band obtained on passing from phenyl thiolacetate to *p*-anisyl thiolacetate arises in a region where formerly there was only a broad, rather shallow minimum[1b] being thus meaningless to speak of resolution in such a case.

However their objection to our statement[1b] that in aryl thiolesters sulfur acts equally well as donor and acceptor is sound. The adjective "well" in that statement is misleading being in contrast with what was clearly stated in a preceding paragraph.

(6) (a) E. B. Knott, *J. Chem. Soc.*, 937 (1955); (b) *J. Chem. Soc.*, 949 (1955).

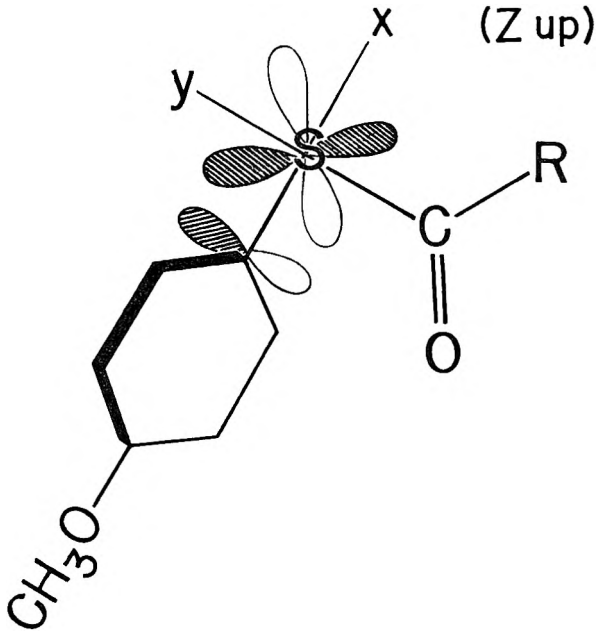
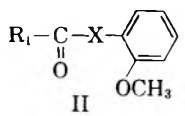


Fig. 1. Schematic representation of the possibility of conjugation between the 2 pπ shell of a twisted anisyl group (xz plane) and the sulfur d_{x+y} orbital. (Only the p_y orbital on the nearest aromatic carbon atom is shown.)

conjugative effects are usually smaller for ortho than for para substituents.[7,8] This has indeed been confirmed by studying the absorption spectra of *o*-anisyl esters and thiolesters (II: R_1 = CH_3—, C_6H_5—; X = O,S).



II

The spectra of *o*-anisyl acetate and of *o*-anisyl thiolacetate are represented in Fig. 2, where for comparative purpose the spectra of the corresponding nonsubstituted compounds[1c] have also been included. In the spectrum of the anisyl ester the peak at 217 mμ is certainly the primary aromatic absorption; the system of bands at longer wavelengths is the secondary absorption. In the corresponding thiolester the absorption at shorter wave lengths is presumably due to the overlapping of the thiolester band and of the primary band of the ring. The absorption toward the red is the secondary aromatic band.

The spectra of *o*-anisyl benzoate, of *o*-anisyl thiolbenzoate, and for comparative purpose of the unsubstituted parent compounds,[1b] are shown in Fig. 3. The peaks at 224 mμ and 232 mμ in the spectrum of *o*-anisyl benzoate are to be ascribed to the primary anisyl band and to the primary benzoyl absorption, respectively. The absorption above 260 mμ is the overlap of both secondary bands.

(7) L. Doub and J. M. Vandenbelt, *J. Am. Chem. Soc.*, **71**, 2414 (1949).

(8) *Cf.* C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, G. Bell and Sons Ltd., London 1953, p. 267.

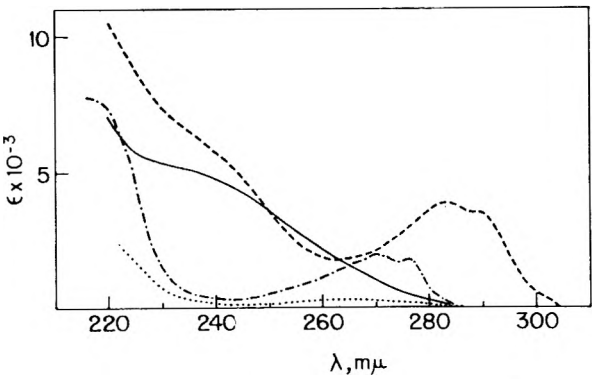


Fig. 2. Absorption spectra in C_2H_5OH of: $H_3C—\overset{\overset{O}{\|}}{C}—O—C_6H_5$.....; $H_3C—\overset{\overset{O}{\|}}{C}—S—C_6H_5$ ———; $H_3C—\overset{\overset{O}{\|}}{C}—O—C_6H_4—OCH_3(o)$ - . - . - .; $H_3C—\overset{\overset{O}{\|}}{C}—S—C_6H_4—OCH_3(o)$ - - - -

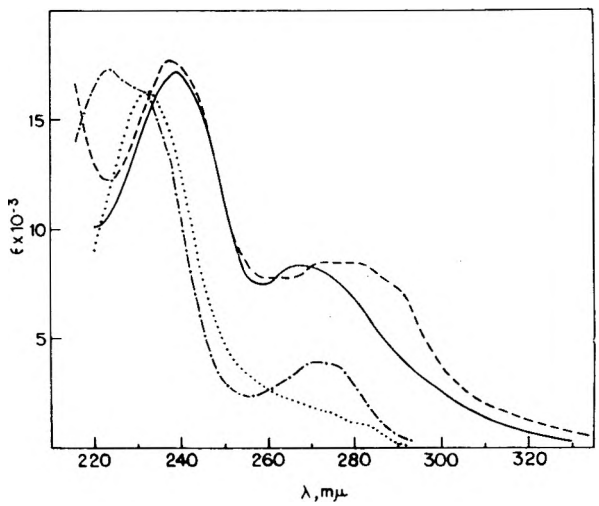


Fig. 3. Absorption spectra in C_2H_5OH of: $C_6H_5—\overset{\overset{O}{\|}}{C}—O—C_6H_5$.....; $C_6H_5—\overset{\overset{O}{\|}}{C}—S—C_6H_5$ ———; $C_6H_5—\overset{\overset{O}{\|}}{C}—O—C_6H_4—OCH_3(o)$ - . - . - .; $C_6H_5—\overset{\overset{O}{\|}}{C}—S—C_6H_4—OCH_3(o)$

In the spectrum of the anisyl thiolester the maximum at 238 mμ is certainly the primary benzoyl absorption, whereas the primary anisyl absorption in the region 260–285 mμ is presumably the overlap of the thiolester band and of both secondary ring absorptions.

In conclusion, it is seen that there is no evidence of an absorption band due to conjugation of the anisyl ring with sulfur in the ortho derivatives.

EXPERIMENTAL

Guaiacol acetate was prepared from acetic anhydride and guaiacol.[9]

(9) H. O. Mottern, *J. Am. Chem. Soc.*, **56**, 2107 (1934).

Guaiacol thiolacetate. Thioguaiacol was prepared from the diazonium salt of *o*-anisidine and potassium ethyl xanthogenate according to Mauthner.[10] The mercaptan (7.3 g.) was allowed to react with acetyl chloride (3.8 ml.). A large excess of pyridine (15 ml.) was added and the mixture added to water and ice. Carbonate was added, the oil was collected, washed several times with water, dissolved in ethyl ether, the ethereal solution was dried, and the ether distilled off. The oily residue was twice distilled, b.p. (0.1 mm.) 101°. The compound is a liquid, colorless when pure; it gives a positive reaction of Raschig-Feigl.

Anal. Calcd. for $C_9H_{10}O_2S$: C, 58.21; H, 5.53; S, 17.58. Found: C, 58.40; H, 5.77; S, 17.77.

When the present work was in progress this thiolester was described by Charonnat and Lazelari[11] who report b.p. (15 mm.) 145°. However their sample was reported as being yellowish and, therefore, probably was not very pure.

Guaiacol benzoate was prepared by condensation of benzoyl chloride and guaiacol in the presence of pyridine. The mixture was treated with water, the product collected, and washed with alkali, acid, and water. The ester was twice recrystallized from methanol, m.p. 58–59°. Reported m.p. 57–58°.[12]

Guaiacol thiolbenzoate was prepared in a way similar to that used for guaiacol benzoate. This new compound is a colorless solid, which melts at 105.5–106.5°.

Anal. Calcd. for $C_{14}H_{12}O_2S$: C, 68.82; H, 4.95; S, 13.12. Found: C, 68.71; H, 4.99; S, 12.70.

Absorption measurements were carried out as in an earlier paper.[1c]

Acknowledgment. We wish to thank the Rockefeller Foundation and the (Brazilian) "Conselho Nacional de Pesquisas" Rio de Janeiro, for material help.

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(10) F. H. Mauthner, *Ber.*, **39**, 1347 (1906).

(11) R. Charonnat and I. Lazelari, *Compt. rend.*, **238**, 119 (1954).

(12) Lange's Handbook of Chemistry, 5th ed., Handbook Publishers, Inc., Sandusky, Ohio, 1944.

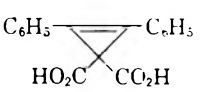
On Darling's Cyclopropene Derivative and Its Rearrangement[1]

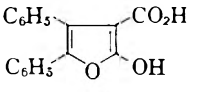
RONALD BRESLOW, RUDOLPH WINTER, AND MERLE BATTISTE

Received July 28, 1958

Few authentic cyclopropene derivatives are known, and the erroneous attribution of cyclopropene structures to some substances, such as Feist's acid,[2] seems to have led to a general distrust of all cyclopropene assignments in the earlier literature. We wish to report that the 1,2-diphenylcyclopropene-3,3-dicarboxylic acid structure (I) assigned by Darling[3] to a compound obtained by him from vigorous alkaline treatment of a nitrocyclopropane compound is indeed correct, and that the substance is a member of a group of rather stable derivatives of the strained cyclopropene molecule.

We have prepared Darling's compound by an alternate route, utilizing the reaction of diphenylacetylene with diazomalonic ester. After hydrolysis, an acid was obtained which melted at 205° (dec.) [Darling reports[3] "about 190° (dec.)"]. As confirmation of the identity of the two substances we have prepared the dimethyl ester, m.p. 143–143.5° (reported[3] 140–142°), and its dibromide, m.p. 197–198° (reported[3] 194–195°). In addition, we find that the lactone from thermal decomposition of the acid has m.p. 149–151° (reported[3] 149–151°).


(I)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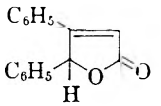
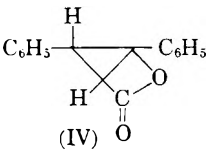

(III)


(IV)

One of the key bits of evidence offered by Darling for the cyclopropene structure was the formation of dibenzoylmethane on oxidation, which we have confirmed. Although this would seem to leave no room for doubt, more or less reasonable arguments, which will not be detailed here, can be made for the possibility of structure II. This, apparently the only alternative to Darling's structure, is however in poor agreement with some of the experimental facts and is completely ruled out by our finding that the corresponding Δ^1-1,2-diphenylcyclopropene monocarboxylic acid, m.p. 209.5–211.5° (dec.), prepared from reaction of diazoacetic ester and diphenylacetylene, followed by alkaline hydrolysis, has an ultraviolet spectrum which is virtually identical with that of the dicarboxylic acid; the two compounds thus have similar structures. On the alternative basis its structure would have to be that of III or a tautomer, which is of course a neutral lactone.

We have prepared[4] III and find that it is in fact identical with the neutral lactone, m.p. 149–151°, which results from pyrolysis of the cyclopropene diacid. Darling had rejected this structure in favor of IV on the basis that the hydrolysis product was not an olefin, but it is known[5] that in base III is hydrolyzed to desylacetic acid.

The diphenylcrotonolactone III is also formed on pyrolysis of the cyclopropene monocarboxylic acid; these rearrangements are readily formulated

(1) Part of this work was first presented at the 132nd Meeting of the American Chemical Society, New York, September 1957.

(2) See, for instance, A. S. Kende, *Chem. & Ind. (London)*, 544 (1956).

(3) S. F. Darling and E. W. Spanagel, *J. Am. Chem. Soc.*, **53**, 1117 (1931).

(4) J. Thiele and F. Straus, *Ann.*, **319**, 155 (1901).

(5) J. Thiele, *Ann.*, **306**, 194 (1899).

on a mechanistic basis, and presumably derive part of their driving force from the relief of ring strain. It is interesting, however, that under many other conditions the cyclopropene system in these compounds is remarkably stable. Thus, refluxing an ester of the monoacid with potassium *t*-butoxide in *t*-butyl alcohol for 60 hr. leaves the cyclopropene system intact,[6] and even in acid, to which it is more sensitive, the compound is unaffected by 40% sulfuric acid in methanol at room temperature or by refluxing *N* methanolic sulfuric acid, although more vigorous conditions cause rearrangement to III. The stability of these compounds, which results from the heavy conjugating substitution, suggests that related cyclopropene derivatives should also be readily preparable.[7]

EXPERIMENTAL

Diphenylcyclopropenedicarboxylic acid (I). A mixture of 17 g. of diphenylacetylene with 1 g. of electrolytic copper dust was heated at 125° with stirring. Diazomalonic ester[8] (9.3 g.) was added over 1.5 hrs. and the reaction was continued until N_2 evolution had ceased. After solution in ether and filtering, the solvent was removed and the mixture directly hydrolyzed by refluxing for 90 min. with 30 g. KOH in 200 ml. of methanol. After dilution and recovery of the diphenylacetylene by extraction the solution was acidified and the product collected with chloroform. Percolation of the extract through Florex and removal of the solvent yielded 1.5 g. of the acid after crystallization from ether/petroleum ether; m.p. 205° (dec.).

Anal. Calcd. for $C_{17}H_{12}O_4$: C, 72.85; H, 4.32. Found: C, 73.32; H, 4.37.

In the infrared the compound showed carbonyl absorption at 5.98 μ. In the ultraviolet spectrum it showed maxima at 306, 315, and 225 mμ (log ϵ 4.48, 4.38, and 4.30, respectively).

The dimethyl ester of (I) was prepared with diazomethane. Crystallized from ether/petroleum ether it had m.p. 143–143.5°.

Anal. Calcd. for $C_{19}H_{16}O_4$: C, 74.04; H, 5.23; mol. wt., 308. Found: C, 74.26; H, 5.30; mol. wt. (Rast, camphor), 297, 290.

In the infrared the compound absorbs at 5.90 and 5.98 μ. The ultraviolet spectrum shows maxima at 306, 322, 225, and 230 mμ (log ϵ 4.48, 4.40, 4.11, and 4.08 respectively).

The diester dibromide was prepared from the above compound by Darling's procedure,[3] m.p. 197–198°.

Anal. Calcd. for $C_{19}H_{16}O_4Br_2$: Br, 34.2. Found: Br, 34.19.

The compound showed absorption in the ultraviolet at 220 mμ, (log ϵ_{max} 3.9). The dibromide was not affected by treatment with potassium permanganate solution in acetone at room temperature.

The neutral lactone (III). This compound, prepared by melting (I) according to Darling,[3] had m.p. 149–151°; in the infrared it had a strong band at 5.77 μ, and in the ultraviolet it absorbed at 272 mμ (log ϵ 4.26), and had strong end absorption.

α,β-Diphenylcrotonolactone was prepared by the method of Thiele.[4] The m.p. of 150–152° (reported 152°) was undepressed on mixture with the above lactone, and their infrared and ultraviolet spectra were identical in all respects.

1,2-Diphenylcyclopropene-3-carboxylic acid was prepared in a similar manner to that of the dicarboxylic acid, but the ethyl diazoacetate was added dropwise to the diphenylacetylene at 135–140° over 2.5 hr. The product, crystallized from acetone, had m.p. 209–211° (dec.) (23% yield).

Anal. Calcd. for $C_{16}H_{12}O_2$: C, 81.33; H, 5.12. Found: C, 81.29, H, 5.27.

The ultraviolet spectrum of the compound had maxima at 306, 323, 225, and 232 mμ (log ϵ 4.52, 4.42, 4.34, and 4.28 respectively). On heating at 220–230°, the acid was converted to (III), m.p. 149–152° (20% yield), as evidenced by identity of spectra.

The *methyl ester*, m.p. 83–85°, had maxima in the ultraviolet at 306, 323, 224, and 232 mμ (log ϵ 4.53, 4.42, 4.34, and 4.29 respectively). This spectrum was unaffected by refluxing with 1 *N* sulfuric acid in methanol for 24 hr. or by standing with 40% methanolic sulfuric acid for 12 hr., although on refluxing of this latter solution for 19 hr the compound was converted into (III), m.p. 152–154°, in 40% yield. Both the monoacid and its methyl ester show the expected carbonyl absorption in the infrared.

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(6) R. Breslow and M. Battiste, *Chem. & Ind. (London)*, 1143(1958).

(7) For one example, *cf.* R. Breslow, *J. Am. Chem. Soc.*, **79**, 5318 (1957).

(8) H. Lindemann, A. Wolter, and R. Groger, *Ber.*, **63**, 702 (1930).

Influence of Metallic Cation on Substitution *versus* Elimination Reactions of Alkyl Halides with Alkali Bases[1]

W. H. PUTERBAUGH[2] AND CHARLES R. HAUSER

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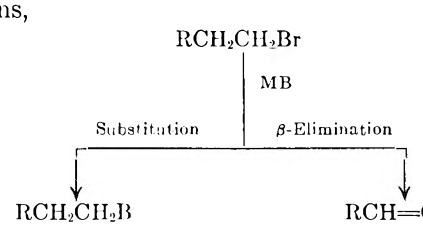
An alkyl halide may undergo with an alkali base (MB) the substitution and β-elimination reactions,



Although variations in the basic strength of the anion B^- are known to influence the relative extents of these two courses of reaction,[3] variations in the metallic cation associated with the basic anion in alcohol appears to have no appreciable effect on the two courses. Thus, no significant difference in the ratio of the substitution and elimination products was observed by Newman and Evans[4] on treatment of 2-ethylhexyl bromide with lithium, sodium, and potassium ethoxides in ethanol solution.

However, differences in the ratio of the two types of products have been observed on varying the alkali cation associated with certain stronger

(1) Supported by a grand from the Duke University Research Council.

(2) Present address, Department of Chemistry, Thiel College, Greenville, Pa.

(3) See C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, Cornell University Press, Ithaca, N. Y., 1953, pp. 451–452; E. E. Royals, *Advanced Organic Chemistry*, Prentice-Hall, Inc., New York, N. Y., 1954, p. 299.

(4) M. S. Newman and F. J. Evans, Jr., *J. Am. Chem. Soc.*, **76**, 4187 (1954).

TABLE I

TERTIARY AMINES AND OLEFINS FROM ALKYL BROMIDES WITH EQUIVALENTS OF ALKALI DIETHYLAMIDES

Alkyl Bromide	Alkali Diethyl-amide	Solvent at 35–40°C.	Time, Hours	Amine Yield, %	Olefin Yield, %	Recovered Alkyl Bromide, %	Residue, Grams
n-Octyl	Lithium	Ether	2.5	47	0	42	6[a]
n-Octyl	Lithium[b]	Ether	17.0	89	Trace[c]	0	2
n-Octyl	Sodium	Benzene	7.0	30	5[d]	4	9
n-Octyl	Sodium	Benzene	6.5	22	19[e]	29	13
2-Ethylhexyl	Lithium	Ether	5.0	45	Trace[c]	45	5[a]
2-Ethylhexyl	Sodium	Benzene	6.5	24	16[f]	2	14

[a] This residue is presumably diphenyl incurred in the preparation of the lithiumphenyl. [b] In this experiment two equivalents of the base were treated with one equivalent of the alkyl bromide. [c] A small amount of material giving a positive test for unsaturation with potassium permanganate was found in the neutral fraction. [d] Estimated by titration with bromine in carbon tetrachloride of an aliquot of neutral material, b.p. 95–116° (760 mm.), consisting of a mixture of recovered heptane (dispersant for sodium) and olefin. [e] Estimated by refractive index of neutral material, b.p. 109–122° (760 mm.), consisting of a mixture of recovered toluene (dispersant for sodium) and olefin. [f] Estimated by titration with bromine in carbon tetrachloride of an aliquot of neutral material, b.p. 107–116° (760), consisting of a mixture of recovered toluene and olefin.

bases in less dissociating solvents. Shreve and Rothenberger[5] obtained relatively less olefin from certain alkyl halides with sodium amide in liquid ammonia than with potassium amide.[6] Newman and co-workers[7] realized better yields of the substitution product from 1-bromo-3-chloropropane with the lithium derivative of 1-hexyne than with the sodium or potassium derivative.

We have found that *n*-octyl and 2-ethylhexyl bromides undergo relatively more of the substitution reaction and relatively less β-elimination with lithium diethylamide in refluxing ether than with sodium diethylamide in benzene at about the same temperature (Table I). For example, *n*-octyl bromide underwent largely the substitution reaction with the lithium reagent to form tertiary amine I, whereas this halide evidently exhibited mainly β-elimination with the sodium reagent.

$$n\text{-}C_8H_{17}Br \xrightarrow[\text{ether}]{LiN(C_2H_5)_2} \underset{\text{I}}{n\text{-}C_8H_{17}N(C_2H_5)_2}$$

It can be seen from Table I that the yield of tertiary amine I was 89% with two equivalents of the lithium reagent. A lower yield (47%) of this amine was realized with an equivalent of this reagent, but much of the halide was recovered and none of the olefin was detected. A similar result was obtained with 2-ethylhexyl bromide and the lithium reagent. On the other hand, the sodium reagent not only produced lower yields of the tertiary amine, but it also gave considerable amounts of the olefin or residue that may be assumed to have arisen from the olefin. In a blank experiment with octene-1 and sodium diethylamide, similar residuous material was obtained and only about half of the olefin was recovered.[8]

It should be pointed out that the sodium diethylamide employed in the two experiments with *n*-octyl bromide was prepared with sodium phenyl that had been obtained from sodium dispersions in *n*-heptane and toluene respectively (see notes *d* and *e*, Table I). Nevertheless, the yield of the tertiary amine I based on the halide used minus that recovered was about 31% in both experiments. The differences in the yields of the olefin may be attributable to the use of different detection methods and to different degrees of polymerization.

Similarly, lithiumphenyl reacted with *n*-octyl bromide to give a better yield of *n*-octylbenzene (II) than sodiumphenyl. The yields of this substitution product based on the halide that reacted were 78% and 51% respectively. Moreover, much less residue was obtained with the lithium reagent.

$$n\text{-}C_8H_{17}Br \xrightarrow{LiC_6H_5} \underset{\text{II}}{n\text{-}C_8H_{17}C_6H_5}$$

The use of ether with the lithium reagent and benzene with the sodium reagent in these experiments may have had some effect on the two courses of reaction.

These results (as well as the earlier ones)[7] indicate that when a substitution type of reaction is desired with a nitrogen or carbon base, the lithium reagent would, in general, be chosen over the sodium reagent.

(5) R. N. Shreve and L. W. Rothenberger, *Ind. Eng. Chem.*, **29**, 1361 (1937).

(6) We have observed that, in contrast to sodium or potassium amide in liquid ammonia, lithium amide failed to react appreciably with *n*-octyl bromide in liquid ammonia during 2 hr., and 89% of the unchanged bromide was recovered. Similarly, 73% of this halide was recovered after refluxing with lithium amide in triethylamine for 7 hr.

(7) M. S. Newman, M. W. Renoll, and I. Auerbach, *J. Am. Chem. Soc.*, **70**, 1023 (1948).

(8) This experiment was performed by A. Theodore Stewart in this laboratory. Since the sodium diethylamide was prepared from sodium and chlorobenzene, the polymerization of the olefin might possibly have been effected by unused metal as well as by the sodium diethylamide.

EXPERIMENTAL[9]

Lithiumphenyl solutions (1*M*) were prepared and standardized according to the method described by Jones and Gilman.[10]

Sodiumphenyl. In a flame-dried flask under a nitrogen atmosphere was placed 0.5 mole of sodium as a 45% dispersion in toluene[11] or a 50% dispersion in *n*-heptane.[11] The dispersion was immediately covered with dry benzene, and about 5 ml. of a solution of 28.7 g. (0.255 mole) of chlorobenzene in 25 ml of benzene was added. As soon as formation of the sodiumphenyl commenced, as evidenced by a rise in temperature and the formation of black granular particles in the grey mixture, the stirrer was started and the flask immersed in a Dry Ice–methanol bath. The remainder of the chlorobenzene solution was then added during 30 min. to 1 hr., while maintaining the temperature of the reaction between 25–40° by proper adjustment of the cooling bath. After conclusion of the addition, the reaction mixture was stirred an additional 30 min. at room temperature to insure completion of the reaction. At the end of this time, the reaction mixture consisted of a black suspension of sodiumphenyl granules. This material was used immediately for further reaction (see below) without storage.

Reaction of alkyl halides with metallo diethylamides. (*Table* I). (*A*) *With lithium diethylamide.* To 200 ml. (0.2 mole) of a *M* lithiumphenyl solution was added dropwise with stirring over 20 min. 16.1 g. (0.22 mole) of diethylamine in 25 ml. of dry ether. After stirring for an additional 10–20 min., a solution of an equivalent of the alkyl halide in an equal volume of ether was added during 0.5 hr., and the reaction completed by refluxing for the time indicated. The reaction mixture was cooled and decomposed by the addition of 50 ml. of water, and the ether layer, to which was added an ether extract of the aqueous layer, was extracted with several portions of 5*N* hydrochloric acid solution, washed with water and dried over $CaCl_2$. The acidic extracts were combined, made strongly basic with 5*N* sodium hydroxide solution, salted out with sodium chloride, and extracted with several portions of ether. The ether layer containing the basic fraction was then dried over potassium hydroxide. The solvents were removed from both fractions and the residues distilled to yield recovered halide and amine. Material from the neutral fraction boiling in the range 80–103° (760 mm.) was tested with potassium permanganate solution to determine the presence of olefin. Only traces of material giving a positive test for unsaturation were obtained.

(*B*) *With sodium diethylamide.* To 0.25 mole of sodiumphenyl, prepared as described above, was added during 30 min., 20.5 g. (0.28 mole) of diethylamine in 25 ml. of benzene and the black, sirupy mixture stirred an additional 30–60 min. to insure formation of the sodium diethylamide. To the stirred liquid was added during 30 min. an equivalent of the alkali halide in an equal volume of benzene, and the reaction then completed as indicated in Table I. The reaction mixture was cooled, and 20 ml. of ethanol added cautiously to decompose any unreacted sodium followed by water. The reaction mixture was then worked up as described above for lithium diethylamide. Since the olefins formed in these reactions boil close to that of the toluene or heptane used as dispersant for the sodium, the neutral material was carefully fractionated and the various fractions tested with potassium permanganate solution to determine the presence of olefin. If olefin was indicated present in the fraction, the amount present was estimated by the methods indicated in Table I.

The following new amines were prepared by these methods. From *n*-octyl bromide there was obtained *N,N*-diethyl-*n*-octylamine, b.p. 221–224° (760 mm.), 93–95° (10 mm.).

Anal. Calcd. for $C_{12}H_{27}N$: C, 77.75; H, 14.69. Found: C, 77.70; H, 14.67.

From 2-ethylhexyl bromide there was obtained *N,N*-diethyl-2-ethylhexylamine, b.p. 205–208° (760 mm.).

Anal. Calcd. for $C_{12}H_{27}N$: C, 77.75; H, 14.69; N, 7.56. Found: C, 77.75; H, 14.34; N, 7.56.

Reaction of n-octyl bromide with metallo phenyls. (*A*) *With lithiumphenyl.* To 250 ml. (0.25 mole) of a *M* solution of lithiumphenyl in ether was added dropwise during 2.5 hours, 48.3 g. (0.25 mole) of *n*-octyl bromide in 50 ml. of ether. The reaction mixture was stirred for 30 min. at room temperature, then stirred and refluxed for 1.5 hr., cooled and decomposed with water. The ether layer was washed with dilute hydrochloric acid, saturated sodium bicarbonate solution and water, and, after combining with an ether extract of the aqueous layers, dried over calcium chloride. The solvent was removed and the residue distilled *in vacuo* to give 5.7 g. (12%) of recovered *n*-octyl bromide, b.p. 77–81° (10 mm.), 32.8 g. (69%) of *n*-octyl benzene, b.p. 125–127° (10 mm.) (reported[12] b.p. 264–265° (760 mm.), and 2.8 g. of gummy residue. A small low-boiling forerun gave a negative test with potassium permanganate solution.

(*B*) *With sodiumphenyl.* To 0.25 mole of sodiumphenyl was added during 45 min., 48.3 g. (0.25 mole) of *n*-octyl bromide in 50 ml. of benzene. The reaction mixture was stirred at room temperature for 1 hr., then stirred and refluxed for 1 hr. After cooling and decomposing with methanol followed by water, the benzene layer was worked up as described above for lithium phenyl. There was obtained 15.3 g. (32%) of recovered *n*-octyl bromide, b.p. 79–82° (10 mm.), 16.3 g. (35%) of *n*-octyl benzene, b.p. 129–134° (12 mm.), and 14.9 g. of high boiling residue. A small low-boiling forerun gave only a weak positive test with potassium permanganate solution.

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(9) Analyses by Clark Microanalytical Laboratories, Urbana, Ill. Melting points and boiling points are uncorrected. Distillations described herein were performed on a 30 cm. Vigreux column.

(10) R. G. Jones and H. Gilman, *Org. Reactions*, Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 353.

(11) Generous samples of these materials were obtained from the National Distillers Corporation through the courtesy of Dr. V. L. Hansley.

(12) F. Eisenlohr and L. Schulz, *Ber.*, **57**, 1815 (1924).

Microbiological Synthesis of 2-Hydroxyandrosta-1,4-diene-3,17-dione[1]

C. GUAL, S. R. STITCH,[2] M. GUT, AND R. I. DORFMAN

Received August 25, 1958

The recent publication on the synthesis of 2-hydroxy-$\Delta^{1,4}$-3-keto steroids by Baran[3] prompts us to report, as part of a study on possible precursors to the aromatic ring A, the microbiological conversion of 2α-hydroxytestosterone to 2-hydroxy-

(1) Supported in part by Research Grants No. C-2207 and CRTY-5001, Division of Research Grants, National Institutes of Health, U. S. Public Health Service.

(2) Present address: Radiobiological Research Unit, A.E.R.E., Harwell, Didcot, Berkshire, England.

(3) J. S. Baran, *J. Am. Chem. Soc.*, **80**, 1687 (1958).

androsta-1,4-diene-3,17-dione by means of *Bacillus sphericus*.[4]

EXPERIMENTAL[9]

2α-Hydroxytestosterone (I) (100 mg.) was incubated with a two-day culture of *Bacillus sphericus* (A.T.C.C. No. 7055), in 250 ml. of nutrient broth in a Fernback Flask at 30°. The nutrient broth was prepared as follows: yeast extract 3 g., N-Z-Case (peptone) 5 g., and water 1000 ml. The steroid dissolved in 2 ml. ethanol was added aseptically and the incubation mixture rotated on a shaker for 48 hr. After incubation the broth was extracted with 3 × 100 ml. of redistilled ethyl acetate. The extracts were washed 2 × 50 ml. with $NaHCO_3$ and twice with distilled water. The ethyl acetate extracts were dried over anhydrous Na_2SO_4 and evaporated at 60° under vacuum. The residue was chromatographed on a silica gel adsorption column and the eluates from a 14:1 and 9:1 mixture of benzene–ethyl acetate were pooled. The dried residue was applied to No. 1 Whatman paper and run for 48 hr. in the ligroin propyleneglycol system of Savard.[10] A compound with a running rate of androsta-1,4-diene-3,17-dione was detected with the Zimmermann, Turnbull's blue (ferric chloride and potassium ferricyanide) and blue tetrazolium reagents. After eluting this zone, the dried material was crystallized twice from ether-hexane, giving 13 mg. of III, m.p. 148–150°, $[\alpha]_D^{22}$ +67° ($CHCl_3$). The ultraviolet spectrum in methanol showed λ_{max}^{MeOH} 253 mμ with a small shoulder at 284 mμ. The infrared spectra indicated maxima at 3425, 1740, 1675, 1620, and 1218 cm.$^{-1}$ The identity of III was established by comparison of its physical constants, including infrared spectra, with an authentic sample of 2-hydroxyandrosta-1,4-diene-3,17-dione[11] and its acetate. The acetate of III was prepared with acetic anhydride in pyridine and crystallized from ethyl acetate to give IV, m.p. 225–228°, λ_{max}^{MeOH} 246 mμ, ν_{max} 1768, 1730, 1670, 1645, 1610, and 1208 cm.$^{-1}$ In the 3:1 benzene–ethyl acetate eluate from the silica gel column, a minute amount of a compound more polar than III, was found. This product (II?) gave a negative test with potassium ferricyanide and ferric chloride, absorbed ultraviolet light at 238 mμ, and by infrared analysis was found to contain a pentacyclic ketone, a hexacyclic α,β-unsaturated ketone, and an absorption band indicating free hydroxy group.

The possibility of III being an artifact (since ketols can be oxidized with very mild oxidative agents) has been eliminated by incubating I with a denatured culture of *Bacillus sphericus*. After extraction and purification no enol could be detected with Turnbull's reagent and the recovery of the starting material was nearly quantitative.

Oxidation of 2-hydroxy-Δ[4]-3-keto steroids to their Δ[1]-analogs could be brought about either by removal of the two hydrogens at carbon 1 and 2, or by oxidation of the alcoholic function at carbon 2 to the ketone, which would then enolize.[12] Axial hydroxyl functions are oxidized with greater ease, but little is known about similar oxidations in biological systems.[13]

Recently Kuslinsky[14] suggested a 1- or 2-hydroxy intermediary in the 1,2-dehydrogenation. Since it is known that dehydration of hydroxy compounds proceeds most readily between an axial hydroxy function and an adjacent axial hydrogen, it is quite likely that a 1α-hydroxy derivative would be the intermediary in this reaction. The finding that the 2α-OH group of I, located in the equatorial position, does not interfere with the 1,2-dehydrogenation, is consistent with this mechanism. Steroids hydroxylated at position C_1 are being used to test this hypothesis although evidence by Levy and Talalay[15] suggests that the 1,2-dehydrogenation involves direct removal of hydrogen by an hydrogen acceptor.

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(4) A number of microorganisms[5–8] are able to produce dehydrogenation of steroids at the 1,2 position.

(5) E. Vischer, C. Meystre, and A. Wettstein, *Helv. Chim. Acta*, **38**, 835 (1955).

(6) E. Vischer, C. Meystre, and A. Wettstein, *Helv. Chim. Acta*, **38**, 1502 (1955).

(7) A. Nobile, N. Charney, P. L. Perlman, H. L. Herzog, C. C. Payne, N. E. Tully, M. A. Jernik, and E. B. Hershberg, *J. Am. Chem. Soc.*, **77**, 4184 (1955).

(8) T. H. Stoudt, W. J. McAleer, J. M. Chemerda, M. A. Kozlowski, R. F. Hirschmann, V. Marlott, and R. Miller, *Arch. Biochem.*, **59**, 304 (1955).

(9) The melting points were taken on a Fisher-Johns block and are uncorrected; the infrared spectra were recorded on a Perkin-Elmer Model 12C, all samples dispersed in potassium bromide.

(10) K. Savard, *Recent Progress in Hormone Research*, **9**, 185 (1954).

(11) We wish to express our thanks to Dr. J. S. Baran for sending us a sample of 2-hydroxyandrosta-1,4-diene-3,17-dione.

(12) Compare E. T. Stiller and O. Rosenheim, *J. Chem. Soc.*, 353 (1938); Ch. Meystre, H. Frey, W. Voser, and A. Wettstein, *Helv. Chim. Acta*, **39**, 734 (1956).

(13) Compare the oxidation of quinic acid to 5-dehydroquinic acid by mutants of *Escheria coli* and others: D. B. Davis, *J. Bact.*, **64**, 729 (1952).

(14) S. Kushinsky, *J. Biol. Chem.*, **230**, 31 (1958).

(15) H. R. Levy and P. Talalay, *J. Am. Chem. Soc.*, **79**, 2658 (1957).

Reactions of δ-Valerolactone with *ortho*- and *peri*-Naphthylenediamines

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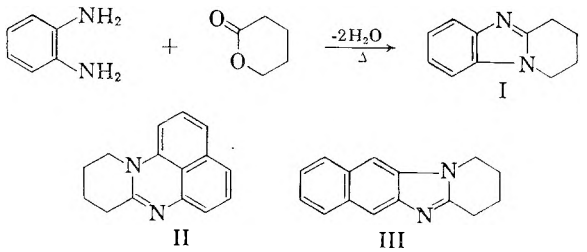
Although butyrolactone[1] and γ-valerolactone[2] have been condensed with *o*-phenylenediamine[1,2] and with 1,2-naphthylenediamine,[2] the use of δ-valerolactone in such reactions has not been reported. Insomuch as 1,2-, 2,3-, and 1,8-naphthylenediamines, as well as δ-valerolactone, are all available commercially, these reactions appeared of interest.

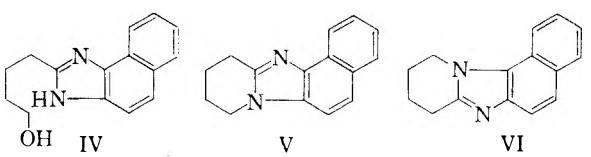
To evaluate the reaction, the known[3,4] 1,2,3,4-tetrahydropyrido[*a*]benzimidazole (I) was prepared. Although the yield was only 15%, the nature of the product was unquestionable, and the authenticity of the reaction was demonstrated. Further, despite the rather low yield, this is easily the most convenient preparation of I yet reported, and the yield could possibly be improved by minor modifications.

(1) A. Bistrzycki and W. Schmutz, *Ann.*, **415**, 1 (1917).
(2) W. Reppe *et al.*, *Ann.*, **596**, 209 (1955).
(3) R. Huisgen and R. Rist, *Ann.*, **594**, 159 (1955).
(4) K. H. Saunders, *J. Chem. Soc.*, 3275 (1955).

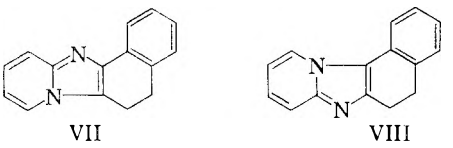


The reaction was then extended to 1,8- and 2,3-naphthylene diamines, which produced II and III in about 70 and 80% yields, respectively. The structures of these new products were supported by microanalyses and by ultraviolet and infrared spectra. Efforts to aromatize III by heating with palladium-charcoal or rhodium-charcoal at 195–200° in trichlorobenzene or in ethylene glycol, or by treatment with sulfur, chloranil, or lead tetraacetate, were unsuccessful. This is in accord with the difficulty reported[4] in the aromatization of I. Oxidation of III in acetic acid with chromic acid readily gave the 6,11-quinone, again without dehydrogenating the pyridine ring.

When 1,2-naphthylenediamine was condensed with δ-valerolactone, two products were isolated, each in rather low yield. The less soluble of the two is probably IV, a structure supported by the microanalyses and by infrared and ultraviolet spectra. The second product was shown by analysis to have the formula $C_{15}H_{14}N_2$, and could be either V or VI. Compound V has been prepared previously,[5,6] and comparison of the infrared spectrum of an authentic sample[6] with that of the $C_{15}H_{14}N_2$ product demonstrated their identity. No evidence was found for the formation of VI under the conditions studied, and efforts to convert IV into either V or VI by the action of heat alone, left it unaffected.



The structure of a homolog of compound V also was examined. Reitmann[7] condensed 2-aminopyridine with 2-bromo-1-tetralone, and assigned the product structure VII, although the possibility of structure VIII was not disproven. We have repeated the preparation of Reitmann's product, and oxidized it with chromic acid to the known[6] 5,6-dihydrobenzo[*e*]pyrido[*a*]benzimidazole-5,6-dione. The accuracy of structure VII is, therefore, confirmed.



EXPERIMENTAL[8]

1,2,3,4-Tetrahydropyrido[a]benzimidazole (I). A mixture of 5.00 g. of polymeric δ-valerolactone and 5.40 g. of *o*-phenylenediamine was heated for 16 hr. in an oil bath at 230°. The cooled melt was boiled several times with water (discarding the aqueous extracts) then extracted several times with (a total of 200 ml. of) hot benzene. The benzene solution was passed through a column of alumina and stripped of solvent *in vacuo*. The resulting pale yellow solid (2.40 g.), upon crystallization from cyclohexane, afforded 1.30 g. (15.1% yield) of white prisms, m.p. 100–102.5° (lit.[3,4] 100–101°; 101–102°); λ_{max} 248.5–251,* 254, 276.5, and 283 mμ. (ε 5770, 5970, 5560, and 6425.)

8,9,10,11-Pyrido[a]perimidine (II). A mixture of 5.00 g. of polymeric δ-valerolactone, 7.90 g. of 1,8-diaminonaphthalene, and 5 ml. of chlorobenzene was heated for 3 hr. at 230–250°, allowing the solvent and water to distill out. The residual oil was dissolved in hot acetic acid and drowned into 300 ml. of water. Ammonium hydroxide was added until a slight permanent precipitate was produced, and the mixture was clarified with charcoal and filtered. Basification of the filtrate with ammonium hydroxide yielded an oil which crystallized when triturated with benzene and ligroin (yield: 7.85 g., 70.6%, m.p. 133–136.4°). Two recrystallizations from methyl cyclohexane gave yellow prisms, m.p. 147.8–149.5°, λ_{max} 235 and 330 mμ. (ε 34,500 and 16,630.)

Anal. Calcd. for $C_{15}H_{14}N_2$: C, 81.08; H, 6.31; N, 12.61. Found: C, 80.85; H, 6.45; N, 12.84.

The *picrate* formed yellow felted needles from methanol, m.p. 234.3–235.0° dec.

Anal. Calcd. for $C_{21}H_{17}N_5O_7$: C, 55.87; H, 3.77; N, 15.52; O, 24.83. Found: C, 56.14; H, 3.45; N, 15.30; O, 24.65.

1,2,3,4-Tetrahydronaphtho[2,3-d]pyrido[a]imidazole (III). The product was obtained crude (m.p. 180–184°) in 80.5% yield from 2,3-naphthalenediamine by the same technique used to prepare II. Crystallization from benzene or nitromethane gave yellow needles, m.p. 191–193°, λ_{max} 241, 259,* 310,* 320, 323, and 338.5 mμ. (ε 37,700, 3035, 6990, 9030, 9100, and 6910.)

Anal. Calcd. for $C_{15}H_{14}N_2$: C, 81.08; H, 6.31; N, 12.61. Found: C, 80.88; H, 6.20; N, 12 81.

The *picrate* was prepared in methanol and crystallized from methyl Cellosolve; m.p. 271.5–272.0°.

Anal. Calcd. for $C_{21}H_{17}N_5O_7$: C, 55.87; H, 3.77; N, 15.52; O, 24.83. Found: C, 55.53; H, 3.67; N, 15.79; O, 25.08.

Oxidation of III with chromic acid in acetic acid gave the *6,11-quinone* in good yield. Crystallization from acetonitrile gave fine yellow needles, m.p. 250–251°; λ_{max} 225,* 248, 275.5,* 282, and 332 mμ. (ε = 9310, 41,750, 14,750, 15,300, and 3400.)

Anal. Calcd. for $C_{15}H_{12}N_2O_2$: C, 71.43; H, 4.76; N, 11.10. Found: C, 71.25; H, 4.71; N, 11.23.

2-(4-Hydroxybutyl)-naphth[1,2]imidazole (IV). The reaction of 1,2-diaminonaphthalene with δ-valerolactone was run on 0.05 molar scale and worked up in the same manner used for the preparation of II and III. The oily product was

(5) G. Morgan and J. Stewart, *J. Chem. Soc.*, 1057 (1939).

(6) W. L. Mosby and R. J. Boyle, *J. Org. Chem.*, in press.

(7) J. Reitmann, U. S. Patent **2,057,978**, Oct. 20, 1936.

(8) All melting points were taken in Pyrex capillaries in a Hershberg melting-point apparatus using Anschütz thermometers. The ultraviolet spectra were all measured in ethanol solution using a Cary recording spectrophotometer, and points of inflection are indicated by asterisks. The infrared spectra were determined upon a Perkin-Elmer Model 321 recording spectrophotometer. The polymeric δ-valerolactone was obtained from the Union Carbide Chemicals Co. and the naphthylenediamines from the Aldrich Chemical Co.

extracted with hot benzene, leaving 2.05 g. (16.7% yield) of insoluble white solid, m.p. 170.8–173.6°. Recrystallization from acetonitrile improved the melting point only slightly (m.p. 172–174°); λ_{max} 222–227,* 243, 248.5, 274–277,* 283, 315, 321–325, and 328 mμ. (ϵ = 32,300, 48,600, 52,600, 4,600, 4,790, 4,175, 3,640, and 5,150.) The infrared spectrum in acetonitrile solution shows absorption at 2.85μ and 3.05μ attributed, respectively, to the OH and NH functions.

Anal. Calcd. for $C_{15}H_{16}N_2O$: C, 75.00; H, 6.66; N, 11.66; O, 6.66. Found: C, 74.46; H, 6.51; N, 11.94; O, 6.99.

The *picrate* was prepared in methanol and crystallized from methyl Cellosolve, m.p. 233.5–235.2°.

Anal. Calcd. for $C_{21}H_{19}N_5O_8$: C, 53.73; H, 4.05; N, 14.91; O, 27.31. Found: C, 53.93; H, 4.18; N, 15.15; O, 27.21.

8,9,10,11-Tetrahydrobenzo[e]pyrido[a]benzimidazole (V). Evaporation of the benzene extracts of the crude product IV and crystallization of the solid from benzene gave 0.98 g. (8.8% yield of white clusters, m.p. 160.2–162.2°. Recrystallization from benzene gave pure V, m.p. 161.5–162.5°.

5,6-Dihydrobenzo[e]pyrido[a]benzimidazole (VII), was prepared by Reitmann's method.[7] Crystallization from methylcyclohexane gave short, white needles, m.p. 159.4–160.6° (lit.[7] 157°); λ_{max} 253, 283–288, 298, 327–333, 341, and 356 mμ. (ϵ = 34,200, 5210, 4560, 10,980, 12,800, and 8290.)

Solution in hydrochloric acid gave the hydrochloride, which was purified by crystallization from methanol–ethyl acetate or from butanol. The fluffy white crystals had an *instantaneous* melting point of 307–308°.

Anal. Calcd. for $C_{15}H_{12}N_2 \cdot HCl$: C, 70.15; H, 5.06; N, 13.85; O, 10.91. Found: C, 69.96; H, 5.08; N, 13.97; O, 10.54.

The *picrate* was prepared in methanol and crystallized from methyl Cellosolve, m.p. 249–250°.

Anal. Calcd. for $C_{21}H_{15}N_5O_7$: C, 56.12; H, 3.34; N, 15.59; O, 24.94. Found: C, 56.05; H, 3.03; N, 15.31; O, 25.04.

Acknowledgments. The author wishes to thank Dr. Jessie Gove for the infrared spectra, Mr. F. C. Dexter for the ultraviolet spectra, Mr. O. E. Sundberg and his associates for the microanalyses, and Mrs. Regina Moynihan for technical assistance.

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Some 9,10-Disubstituted Phenanthrenes

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For the synthesis of some new vat dye systems, a quantity of 9-bromo-10-nitrophenanthrene was required. The best procedure for the nitration of 9-bromophenanthrene to produce the 9-bromo-10-nitro compound, was described by Callow and Gulland.[1] Although the yield of pure material is only about 15%, this compound is potentially interesting as the starting point for a number of syntheses.

In an effort to prepare 10,10′-dinitro-9,9′-biphenanthryl, treatment of 9-bromo-10-nitrophenanthrene with copper powder in refluxing triethylbenzene gave no reaction, whereas the use of nitrobenzene as a solvent produced a black tar. The bromine atom also appeared surprisingly inert to nucleophilic displacement by several reagents. The bromonitro compound was recovered unchanged from treatment with boiling methanolic sodium methoxide or *p*-toluenesulfonamide in methyl Cellosolve, although boiling with piperidine readily gave 9-nitro-10-piperidinophenanthrene.

Several attempts were made to replace the halogen by cyanide before the proper conditions were found. Refluxing the bromonitro compound in pyridine with cuprous and potassium cyanides and a little acetonitrile afforded a fairly good yield of 10-nitro-9-phenanthrenecarbonitrile. However, the use of neither potassium cyanide in ethanol, nor cuprous cyanide in pyridine or in benzyl cyanide gave the desired reaction. When the nitrobromo compound was treated with cuprous and potassium cyanides in dimethyl sulfoxide, the sole product isolated (in 7% yield) was 9,10-phenanthrenedicarbonitrile. Presumably hydroxyphenanthrenes constituted the major products in this experiment.

Attempts to hydrolyze the nitronitrile by the action of 85% phosphoric or 96% sulfuric acids in boiling acetic acid, or by the action of hot polyphosphoric acid, left it unaffected. Under alkaline conditions, hydrolysis of the nitro group occurred, and 10-hydroxy-9-phenanthrenecarbonitrile was formed. Catalytic reduction of the nitronitrile produced 10-amino-9-phenanthrenecarbonitrile.

Reduction[2,3] of 9-bromo-10-nitrophenanthrene with stannous chloride, zinc and acid or ammonium sulfide, was known to be accompanied by debromination to yield 9-aminophenanthrene. This is, in fact, the major evidence for the constitution of the nitrobromo compound. Reduction by means of hydrazine and a palladium catalyst[4,5] also was accompanied by debromination. The lability of the halogen is not a specific characteristic of the 9,10-bromonitro compound, however, since an isomeric bromonitrophenanthrene (*v.i.*) and even 9-bromophenanthrene itself suffer hydrogenolysis of the bromine when treated with hydrogen in the presence of palladium. By employing a "neutral iron reduction" it was possible to isolate 10-bromo-9-phenanthrylamine in 35% yield.

Nitration of 9-acetamidophenanthrene[6] gave, in very low yield, an acetamidonitrophenanthrene, almost certainly the 9,10-isomer.

During one run of the nitration of 9-bromophenanthrene a product isomeric with the 9,10-bromo-

(1) R. K. Callow and J. M. Gulland, *J. Chem. Soc.*, 2424 (1929).

(2) J. Schmidt and G. Ladner, *Ber.*, **37**, 3573 (1904).

(3) P. C. Austin, *J. Chem. Soc.*, 1760 (1908).

(4) P. M. G. Bavin, *Can. J. Chem.*, **36**, 238 (1958).

(5) M. J. S. Dewar and T. Mole, *J. Chem. Soc.*, 2556 (1956).

(6) G. H. Keyes and L. G. S. Brooker, *J. Am. Chem. Soc.*, 59, 74 (1937).

nitro compound was isolated from the mother liquors. This 9-bromo-x-nitrophenanthrene (m.p. 190.0–198.8°) was converted by the von Braun reaction into the 9-cyano-x-nitro homolog (m.p. 265.0–267.5°). Despite the proximity of these melting points to those of the 9,10-isomers, mixture melting points showed in each case a significant depression, and the infrared spectra of the two sets of isomers were clearly different. Reduction by means of hydrazine and palladium-charcoal readily gave a phenanthrylamine identified as the 3-isomer. This evidence establishes the nitrobromo compound as the 3,9- or 3,10-derivative. A choice between these structures cannot be made with certainty from the evidence at hand, although, insomuch as acetylation of 9-bromophenanthrene has been shown[7] to yield the 3-acetyl-9-bromo compound, it seems probable that our product is 9-bromo-3-nitrophenanthrene.

EXPERIMENTAL[8]

9-Bromo-10-nitrophenanthrene was prepared by Callow and Gulland's procedure.[1] Crystallization of the crude reaction product three times from benzene gave yellow needles of pure material, m.p. 209.5–211.0° (lit. m.p. 207–208°[9] or 195–203°[1]) in 12–15% yield.

10-Nitro-9-piperidinophenanthrene. A mixture of 3.02 g. of nitrobromophenanthrene, 6.0 ml. of piperidine, and a trace of cuprous chloride was boiled under reflux for an hour, then diluted with water. The resulting oil solidified when triturated with water, and the solid was crystallized three times from methanol giving 1.40 g. (46% yield) of golden yellow platelets, m.p. 136.4–137.2°.

Anal. Calcd. for $C_{19}H_{18}N_2O_2$: C, 74.51; H, 5.88; N, 9.15. Found: C, 74.40; H, 5.94; N, 9.21.

10-Nitro-9-phenanthrenecarbonitrile. A mixture of 3.00 g. of bromonitrophenanthrene, 2.00 g. of potassium cyanide, 2.00 g. of cuprous cyanide, 2.0 ml. of acetonitrile, and 10.0 ml. of dry pyridine was stirred and boiled under reflux for 16.5 hr. The dark reaction mixture was poured into water and the solid was filtered, washed with water, and dried. Extraction with boiling toluene, and concentration of the extracts yielded yellow crystals, m.p. 259–265°. Recrystallization from benzene gave 1.30 g. of yellow needles, m.p. 265.0–267.7°.

Anal. Calcd. for $C_{15}H_8N_2O_2$: C, 72.62; H, 3.23; N, 11.29. Found: C, 72.60; H, 3.19; N, 11.00.

9,10-Phenanthrenedicarbonitrile. The preceding experiment was duplicated with the exception that the 10 ml. of pyridine was replaced by 20 ml. of dimethyl sulfoxide. A dull yellow solid (0.32 g., m.p. 283–287°) was the sole product isolated. Two crystallizations from chlorobenzene (charcoal) afforded 0.20 g. of yellow needles, m.p. 290–292°. The infrared spectrum was extremely simple and showed a nitrile absorption at 4.50μ.

Anal. Calcd. for $C_{16}H_8N_2$: C, 84.21; H, 3.51; N, 12.28. Found: C, 84.40; H, 3.75; N, 12.10.

9-Amino-10-phenanthrenecarbonitrile. Hydrogenation of 2.48 g. of 9-nitro-10-phenanthrenecarbonitrile and 0.70 g. of 10% palladium-charcoal in 50 ml. of ethanol, followed by crystallization of the product from ethanol, gave a pale yellow solid m.p. 173.6–178.0°. Two recrystallizations from benzene removed an insoluble fraction and afforded 0.85 g. of nearly white, felted needles having an instantaneous melting point of 176–177°. If put into the bath below 175°, the compound decomposes over a range.

Anal. Calcd. for $C_{15}H_{10}N_2$: C, 82.57; H, 4.59; N, 12.84. Found: C, 82.50; H, 4.58; N, 13.20.

9-Hydroxy-10-phenanthrenecarbonitrile. A solution of 2.48 g. of 9-nitro-10-phenanthrenecarbonitrile and 2.50 g. of potassium hydroxide in 2 ml. of water and 12 ml. of methyl Cellosolve was boiled under reflux for 0.5 hr., then diluted with 125 ml. of water. Acetic acid was added to bring the *p*H to near neutrality, and the milky solution was treated with charcoal and filtered. Acidification of the filtrate yielded 1.83 g. (83.5%) of pale greenish solid. Crystallization from acetic acid (charcoal) gave 1.00 g. of yellow solid, m.p. 242–244°. Two recrystallizations from toluene and one from glycol diacetate afforded 0.40 g. of pale yellow needles, m.p. 247–249°. The infrared spectrum showed the expected bands at 3.15 and 4.50μ arising from the OH and CN functions.

Anal. Calcd. for $C_{15}H_9NO$: C, 82.19; H, 4.10; N, 6.40; O, 7.30. Found: C, 82.22; H, 3.83; N, 6.22; O, 7.38.

The *benzoate* ester, after three crystallizations from toluene, formed white prisms, which, when immersed in the heating bath at 195°, sweat and partially melt at 202–204°, then resolidify and melt at 209.0–209.5°.

Anal. Calcd. for $C_{21}H_{15}NO_2$: C, 80.51; H, 4.79; N, 4.47. Found: C, 80.50; H, 4.50; N, 4.65.

10-Bromo-9-phenanthrylamine. A mixture of 5.0 g. of fine iron filings, 10 ml. of water, and 1 ml. of acetic acid was stirred and boiled under reflux for 20 min. Then 3.02 g. of bromonitrophenanthrene and 10 ml. of ethanol were added, and the boiling was continued overnight. The thick reaction mixture was extracted three times with 40-ml. portions of boiling benzene. The combined, dried benzene extracts were treated with hydrogen chloride and the precipitated amine hydrochloride (3.15 g.) was filtered, washed with benzene, and dried. The salt was dissolved in pyridine and poured into water, and the free amine was filtered and dried (wt. 2.38 g.). Two crystallizations from cyclohexane gave very fine white needles, m.p. 131.0–131.7° (dec.).

Anal. Calcd. for $C_{14}H_{10}BrN$: C, 61.76; H, 3.68; Br, 29.40; N, 5.15. Found: C, 62.13; H, 3.81; Br, 29.12; N, 5.20.

9-Acetamido-10-nitrophenanthrene. To a solution of 0.50 g. of 9-acetamidophenanthrene in 40 ml. of acetic acid, was added 1.30 ml. of a 10% solution of nitric acid (d. 1.4) in acetic acid. The solution was warmed on a steam bath for 2 hr., then was diluted with water and filtered. The resulting brown solid (0.45 g.) was crystallized twice from ethyl acetate, giving 50 mg. of light yellow product, m.p. 267.5–269.0°.

Anal. Calcd. for $C_{16}H_{12}N_2O_3$: C, 68.57; H, 4.29; N, 10.00. Found: C, 68.30; H, 4.83; N, 9.90.

9-Bromo-3(or 6?)-nitrophenanthrene. Concentration of the mother liquors from one run of the preparation of 9-bromo-10-nitrophenanthrene yielded a small crop of crystalline solid, which upon recrystallization from benzene, gave yellow needles, m.p. 190.0–191.8°.

Anal. Calcd. for $C_{14}H_8BrNO_2$: C, 55.62; H, 2.65; Br, 26.5; N, 4.64; O, 10.60. Found: C, 55.70; H, 2.81; Br, 26.3; N, 4.31; O, 10.00.

3(or 6?)-Nitro-9-phenanthrenecarbonitrile. In the same manner employed for the 9,10-isomer, 1.00 g. of 9-bromo-3-nitrophenanthrene was subjected to the von Braun reaction. Four crystallizations from acetic acid yielded 0.20 g. of pale yellow microneedles, m.p. 268–269°.

Anal. Calcd. for $C_{15}H_8N_2O_2$: C, 72.62; H, 3.23; N, 11.29; O, 12.90. Found: C, 72.39; H, 3.03; N, 11.47; O, 13.07.

3-Phenanthrylamine. A slurry of 50 mg. of 9-bromo-3-nitrophenanthrene, 20 mg. of 10% palladium charcoal, 0.50 ml. of 85% hydrazine hydrate, and 5 ml. of ethanol was stirred and boiled for 5 min. The catalyst was filtered off and the filtrate was evaporated. The solid was washed with water and crystallized from methyl cyclohexane, giving 28

(7) J. Schultz, M. A. Goldberg, E. P. Ordas, and G. Carsch, *J. Org. Chem.*, 11, 307 (1946).

(8) All melting points were taken in Pyrex capillaries using a Hershberg melting point apparatus and Anschütz thermometers.

(9) J. Schmidt and A. Kämpf, *Ber.*, 35, 3117 (1902).

mg. (87.5% yield) of white leaves, m.p. 83.5–86.0° (lit.[5] 86–87°). Treatment with acetic anhydride and pyridine gave 3-acetamidophenanthrene, m.p. 202.5–203.5° (lit.[10] 200–201°).

9-Phenanthrylamine was obtained from 9-bromo-10-nitrophenanthrene (in 91% yield) in a manner analogous to the preparation of the 3-isomer. It crystallized in white felted needles, m.p. 136.8–137.8° (lit.[11] 136–137.5°). The acetyl derivative formed white needles, m.p. 214.5–215.0° (lit.[6] 213–215°).

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(10) A. Werner, *Ann.*, **321**, 248 (1902).
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Preparation and Molecular Complexes of Tetrahalophthalate Esters

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The molecular complexing properties of tetrahalophthalic anhydrides have been the subject of several studies,[1–5] but the molecular complexing properties of the tetrahalophthalate esters have not been investigated, although the yellowish green color of a dimethyl tetrachlorophthalate-dimethylaniline mixture has been reported.[2] This report on some of the complexing properties and synthesis of several tetrahalophthalates, two of which have not previously been characterized, resulted from finding that these materials were useful gas chromatographic liquid phases for aromatic materials.[6] Separation and retention on gas chromatographic columns containing the tetrahalophthalates is a function of the electron donor characteristics of the aromatic hydrocarbons. Details will be reported elsewhere.

(1) P. Pfeiffer and T. Böttler, *Ber.*, **51**, 1819 (1918).
(2) P. Pfeiffer and E. Flater, *Ber.*, **55**, 413 (1922); P. Pfeiffer, *Organische Molekülverbindungen*, 2nd ed., Ferdinand Ecke, Stuttgart, Germany (1927).
(3) D. S. Pratt and G. A. Perkins, *J. Am. Chem. Soc.*, **40**, 198 (1918).
(4) N. P. Buu-Hoï and P. Jaquignon, *Compt. rend.*, **234**, 1056 (1952); *Bull. soc. chim. France*, **7**, 488 (1957); *Bull. soc. chim. France*, **7**, 1272 (1957); *Experientia*, **9**, 375 (1957).
(5) H. V. Hess and G. B. Arnold, U. S. Patent **2,652,435** (Sept. 15, 1953); U. S. Patent **2,652,436** (Sept. 15, 1953).
(6) S. H. Langer, C. Zahn, and G. Pantazoplos, *Chem. and Ind. (London)*, 1145 (1958).

The molecular complexing behavior of the tetrahalophthalates reported here and their low melting points suggest that they may be useful reagents for separation and/or purification of the polyalkylaromatic fractions from coal tar and petroleum. Conversely, interaction with an aromatic hydrocarbon could be used for purifying and separating the tetrahalophthalate esters themselves.

Data on the tetrahalophthalate esters that were prepared are listed in Table I. Where possible, we prefer a modification of the azeotropic distillation procedure of Nordlander and Cass[7] for preparation of the symmetrical diesters. The reaction of the potassium salt of the monoalkyl ester and the alkyl halide[8] was used for preparation of the mixed ester.

Solid hexamethylbenzene 1:1 complexes of di-*n*-propyl tetrachlorophthalate, di-*n*-butyl tetrachlorophthalate, and di-*n*-propyl tetrabromophthalate were isolated from solution. All were white crystalline solids. The intensity of yellow color on initial mixing of the chlorophthalates with hexamethylbenzene was in the order di-*n*-butyl>di-*n*-propyl. Methyl propyl tetrachlorophthalate did not give a solid complex with hexamethylbenzene by our procedure; mixtures of these two materials gave only a faint yellow color even in concentrated solution.

The light yellow colors observed on mixing the tetrachlorophthalates with durene, isodurene, and hemimellitene probably indicate complex formation. Evidently interaction with mesitylene (no color) is weaker; this may be due to a steric factor.[9]

The interactions of the tetrahalophthalates with dimethylaniline are also of interest. The colors of the solutions obtained undoubtedly indicate complex formation and suggest the possible use of tetrahalophthalates as liquid substrates for aromatic amines in gas chromatography.

EXPERIMENTAL

A. Di-n-propyl tetrachlorophthalate. A mixture of 288 grams (1.01 mole) of tetrachlorophthalic anhydride, 360 grams (6 moles) of propyl alcohol, 4 grams (0.021 mole) of *p*-toluenesulfonic acid monohydrate, and 35 ml. of benzene was refluxed continuously for 16 days in a flask, fitted with a 6-in. Vigreux column connected to a Dean-Stark trap and condenser. With slow reflux, a total of 25.5 ml. of aqueous phase separated in the trap. At intervals, additional *p*-toluenesulfonic acid (3 × 1 g.) and small aliquots of benzene were added.

Volatile material was distilled from the flask up to a pot temperature of 168°. The cooled residue was extracted with 6% aqueous sodium bicarbonate which was then extracted with benzene.

(7) B. W. Nordlander and W. E. Cass, *J. Am. Chem. Soc.*, **69**, 2679 (1947).
(8) H. R. Gamrath and W. E. Weesner, U. S. Patent **2,588,512** (March 11, 1952).
(9) M. Tamres, D. R. Virzi, and S. Searles, *J. Am. Chem. Soc.*, **75**, 4358 (1953); L. J. Andrews and R. M. Keefer, *J. Am. Chem. Soc.*, **71**, 3644 (1949); **72**, 5034 (1950); R. S. Mulliken, *J. Am. Chem. Soc.*, **74**, 811 (1952).

TABLE I

DIALKYL TETRAHALOPHTHALATES

	B.P., °C./(mm.)	n_D^{25}	Sapon. Equiv. Calcd.	Sapon. Equiv. Found	Literature
Methyl propyl tetrachlorophthalate	176/1.3 M.p. 37.6–39.2	1.5491	180	180	
Di-*n*-propyl tetrachlorophthalate	191/2, 174/1 M.p. 26°	1.5365 d_4^{20} 1.37	194	193	B.p. 170–175°/1, n_D^{25} 1.5348[a] B.p. 159–184°/1, m.p. 26°[b]
Di-*n*-butyl tetrachlorophthalate	194–195/1 178/0.5	1.5288 d_4^{20} 1.31	208	209	B.p. 180–185°/1, n_D^{25} 1.5292[a] B.p. 207–214°/3[b]
Di-*n*-propyl tetrabromophthalate	206/0.7 M.p. 64–65.2		283	283	

[a] Reference 7. [b] Reference 10.

The sodium salt of the monoalkyl ester or diacid (formed during extraction of unreacted acid) tends to solvate or emulsify the diester (as well as solvents such as chloroform and carbon tetrachloride) in water; to minimize formation of these salts, reaction should be carried as near to completion as practical. During product recovery, aqueous solutions are easier to handle if all unreacted acid is not extracted initially. That is, sufficient sodium bicarbonate need be used to assure only removal of the *p*-toluenesulfonic acid catalyst in the first extraction with sodium bicarbonate.

The organic layers were combined, diluted with additional benzene, and extracted again with an excess of sodium bicarbonate solution. The benzene solution was washed, dried with magnesium sulfate, and filtered.

After removal of solvent and two distillations at reduced pressure, 235 g. (60.5% yield) of product, n_D^{25} 1.5367–69, was recovered. Recrystallization at room temperature (<26°[10]) gave pure propyl tetrachlorophthalate n_D^{25} 1.5365. Additional pure product was recovered after bicarbonate extraction of mother liquor and redistillation.

Anal. Calcd. for $C_{14}H_{14}O_4Cl_4$: C, 43.32; H, 3.64; Cl, 36.55. Found: C, 43.49; H, 3.71; Cl, 36.86.

B. Di-n-butyl tetrachlorophthalate. Procedure was similar to *A*. Initial *p*-toluenesulfonic acid concentration was doubled. Toluene was added to help remove water azeotropically. Yield was 62.8% after 2 successive vacuum distillations.

C. Di-n-propyl tetrabromophthalate. A mixture of 347.8 g. (0.75 mole) of tetrabromophthalic anhydride (Michigan Chemical Co., St. Louis, Mich.), 270 g. (4.5 moles) propyl alcohol, 6 g. (0.032 mole) of *p*-toluenesulfonic acid monohydrate and 40 ml. of benzene was reacted as in *A* continuously for 21 days. An additional 5 g. of *p*-toluenesulfonic acid monohydrate and benzene were added at intervals during reaction. Aqueous phase removed totaled 25.4 ml. The product was extracted and recovered as in *A*. During the second extraction with sodium bicarbonate, a copious precipitate, apparently a sodium salt of tetrabromophthalic acid or the monopropyl ester, formed, and was removed by filtration with suction through a Buchner funnel.

After solvent removal, product was distilled twice at reduced pressure to give a total of 119.8 g. (28.3% yield) of crude product, b.p. 206–213°/0.7 mm., which solidified on cooling. Several recrystallizations of heart-cut material from ethyl alcohol gave pure product with m.p. 64–65.2°.

Anal. Calcd. for $C_{14}H_{14}O_4Br_4$: C, 29.71; H, 2.49; O, 11.31. Found: C, 29.76 H, 2.67; O, 11.20.

D. Reaction of potassium monoalkyl tetrachlorophthalate with propyl bromide. Methyl propyl tetrachlorophthalate. After 1 mole of tetrachlorophthalic anhydride had been refluxed with 6 moles of methyl alcohol for 6 hr. and cooled, 76 g. (0.55 mole) of pulverized potassium carbonate was added, with stirring and gentle heating. After 1.5 hr., 148 g. (1.2 moles) of propyl bromide was added, followed by addition of 1.5 ml. of triethylamine. The mixture was refluxed 10.5 hr. and volatile material removed by distillation. One l. of water and 300 ml. of benzene were added. The organic layer was washed and dried with magnesium sulfate before removal of solvent. Two distillations at reduced pressure gave 17.6% yield of liquid product, n_D^{25} 1.5491, which solidified on standing.

Anal. Calcd. for $C_{12}H_{10}O_4Cl_4$: C, 40.03; H, 2.80; Cl, 39.39. Found: C, 40.07; H, 2.90; Cl, 39.10.

Molecular complexes. E. Hexamethylbenzene/di-n-propyl tetrachlorophthalate complex. This procedure was typical of those used for isolating the hexamethylbenzene complexes. To 1.030 g. (2.65×10^{-3} mole) di-*n*-propyl tetrachlorophthalate in 1 ml. absolute ethanol was added 0.426 g. (2.63×10^{-3} mole) hexamethylbenzene (recrystallized, m.p. 165.4–166°); a yellow color appeared on mixing. After addition of 5 ml. of ethanol and warming to complete solution, the yellow color disappeared. The mixture was allowed to stand overnight, filtered, and the precipitate washed with 1/2 ml. of methanol and dried *in vacuo* at 10 mm. for 15 min. Product, 1.21 g. of white needles, had decomposition temperature 80.6°.

Anal. Calcd. for $C_{12}H_{18}.C_{14}H_{14}O_4Cl_4$: C, 56.74; H, 5.86; Cl, 25.77; sapon. equiv., 275. Found: C, 56.45; H, 5.94; Cl, 25.88; sapon. equiv., 273.

F. Hexamethylbenzene/di-n-butyl tetrachlorophthalate complex. Procedure as in E; bright yellow color on mixing. Twenty % excess of the ester was used. White crystals, dec. 49.6°.

Anal. Calcd. for $C_{12}H_{18}.C_{18}H_{18}O_4Cl_4$: C, 58.14; H, 6.27; Cl, 24.52. Found: C, 58.64; H, 6.49; Cl, 24.14.

G. Hexamethylbenzene/di-n-propyl tetrabromophthalate. As in *E*, m.p. 94.6–95.5°.

Anal. Calcd. for $C_{12}H_{18}.C_{14}H_{14}O_4Br_4$: C, 42.88; H, 4.43; O, 8.79. Found: C, 42.29; H, 4.36; O, 8.79.

H. Hexamethylbenzene/methyl propyl tetrachlorophthalate complex. Procedure as in *E* resulted in recovery of hexamethylbenzene. No color was observed on mixing methyl propyl tetrachlorophthalate with hexamethylbenzene. In carbon tetrachloride where the other tetrachlorophthalates gave clear yellow solutions with hexamethylbenzene, methyl propyl tetrachlorophthalate gave only the faintest yellow color.

I. Qualitative tests. Color tests were made by mixing approximately equal parts of tetrahalophthalate and hydrocarbon and warming to solution where necessary.

1. The tetrahalophthalates of Table I were tested by examining solutions of these materials with 1,2,4,5-tetramethylbenzene (durene), 1,2,3,5-tetramethylbenzene (isodurene), 1,2,3-trimethylbenzene (hemimellitene), and mesitylene. Methyl propyl tetrachlorophthalate gave no color with these hydrocarbons, and mesitylene gave no color with any of the tetrahalophthalates. The two symmetrical dialkyl tetrachlorophthalates gave light yellow solutions in the approximate order of intensity (shortly after mixing) durene > isodurene > hemimellitene. The only polymethyl-

(10) J. K. Stevenson, L. E. Cheyney, and M. M. Baldwin, *Ind. and Eng. Chem.*, 42, 2170 (1950).

benzene which gave a yellow color (faint) with propyl tetrabromophthalate was hemimellitene.

2. Dimethylaniline. On mixing with dimethylaniline, dibutyl and dipropyl tetrachlorophthalates were orange-red and brown-red respectively, while the bromophthalate and methyl propyl tetrachlorophthalate were yellow-green and yellow, respectively.

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Preparation of 1-Alkylated 2-Haloethers by the Grignard Method. 2-Bromo-1,1-dimethylethyl Ethyl Ether[1]

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In the course of an investigation of the properties of 2-haloethers the authors have had occasion to prepare 2-bromo-1,1-dimethylethyl ethyl ether, which has not previously been reported. This compound is of special interest because it cannot lose hydrogen bromide in a simple way or rearrange to a 1-haloether, two possibilities in the thermal decomposition[3] of 2-bromoethers, without the breaking of a carbon-carbon bond.

The desired 2-bromoether was synthesized following the general procedure of Sherrill and Walter[3c] for a similar 2-bromo-1,1-dialkylated ether, modified to employ ethyl vinyl ether as a starting material,[4] from which 1,2-dibromoethyl ethyl ether was made. The over-all yield (25%, based on starting vinyl ether) was considerably better than those previously given[5,3c] for such compounds.

During the work reported here it was found that 2-chloro-1-methylethyl ethyl ether could not be made from 1,2-dichloroethyl ethyl ether and the Grignard reagent prepared from methyl iodide. Reaction was violent and by either mode of addition, Grignard reagent to halogenated ether or halogenated ether to Grignard reagent only tars and small quantities of impure products resulted.[6] This compound could, however, be synthesized in good yield (48%, based on the dichloro ether)[7] when methyl chloride was used instead of methyl iodide.

EXPERIMENTAL[8]

2-Bromo-1-methylethyl ethyl ether (I). To 144 g. (2.00 moles) of redistilled (fraction boiling at 34.4°) ethyl vinyl ether (General Aniline and Film Corp.) and 700 ml. of sodium-dried diethyl ether in a 3-necked, 2-liter flask fitted with a dropping funnel, mercury-sealed stirrer, and reflux condenser, immersed in a Dry Ice–acetone bath at −70°, bromine was added at the rate of one drop per second. All openings to the system were fitted with drying tubes. The bromine color was lost rapidly after the addition of each drop. Addition was stopped when the bromine color persisted (320 g., 2.00 moles, of bromine), and a few drops of the vinyl ether were added to decolorize the solution. This solution of 1,2-dibromoethyl ethyl ether was then removed from the bath and added at 0°, in an assembly like that just described, to a Grignard solution, in excess, made from methyl bromide (65.2 g., 2.68 g.-atoms, magnesium and 840 ml. ether, with about 10% excess methyl bromide). Addition required about 5 hr. whereupon the mixture was refluxed with stirring for 8 hr. Then the product was poured onto ice and dilute hydrochloric acid, the ether layer separated, washed with 10% sodium bicarbonate and then with water until the washings were neutral. After drying over calcium chloride, the bulk of the solvent ether was removed by fractionation at atmospheric pressure. The remaining 2-bromoether was distilled (Vigreux column) at reduced pressure over a few sodium hydroxide pellets. The main fraction boiled at 39°/18 mm. and weighed 275 g. (82%). Redistillation gave 252 g. (75%) of a product of constant boiling point and refractive index, b.p. 36.5°/16.5 mm., n_D^{25} 1.4396, d_4^{25} 1.2689.

Ethyl isopropenyl ether (II). Dehydrohalogenation was effected with solid potassium hydroxide in a copper flask, according to the procedure of Sherrill and Walter.[3c] Careful control of the temperature was necessary to moderate the vigorous reaction that ensued. From 208 g. (1.24 moles) of I, 81.2 g. (76%) of II was obtained upon redistillation, b.p. 59.2–61.2/733 mm., n_D^{27} 1.3882.

2-Bromo-1,1-dimethylethyl ethyl ether (III). Bromine was added to 74.5 g. (0.865 mole) of II in 435 ml. of diethyl ether as in the preparation of I except that the temperature of the bath was kept at −30°, since the bromination was slower and at lower temperatures an increasing amount of frozen bromine collected at the bottom of the flask. An almost theoretical amount of bromine (138.5 g., 0.867 mole) was used, with the solution pale yellow at the end of the addition. This solution was then added dropwise with stirring to the Grignard reagent (made from 30.2 g., 1.24 g.-atoms, magnesium, 390 ml. ether and a slight excess of

(1) Based in part on the honors thesis of C.D.C., B.A., Williams College, 1954.

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(3) (a) F. B. Tutwiler and R. L. McKee, *J. Am. Chem. Soc.*, **76**, 6342 (1954); (b) M. H. Palomaa and A. Kenetti, *Ber.*, **64B**, 797 (1931); (c) M. L. Sherrill and G. F. Walter, *J. Am. Chem. Soc.*, **58**, 742 (1936).

(4) D. C. Rowlands, K. W. Greenlee, J. M. Derfer, and C. E. Boord, *J. Org. Chem.*, **17**, 807 (1952). See also D. Gagnaire, *Compt. rend.*, **245**, 1732 (1957).

(5) C. G. Schmitt and C. E. Boord, *J. Am. Chem. Soc.*, **54**, 751 (1932).

(6) See V. S. Abramov and A. P. Pakhomova, *Zhur. Obshchei Khim.*, **24**, 1198 (1954), for a similar observation in the reaction of methyl magnesium iodide with 1,2-dibromoethyl ethyl ether.

(7) The authors are indebted to Mr. W. A. Dickens of this laboratory for help in this preparation. The physical constants of the product obtained, which was distilled to constant boiling point and refractive index, differ from those previously recorded and give a better value for the molar refraction; b.p. 30.3°/25 mm., n_D^{25} 1.4103, d_4^{25} 0.9582, M_R Calcd. 31.80 (Ref. 10), M_R found 31.72. See L. C. Swallen and C. E. Boord, *J. Am. Chem. Soc.*, **52**, 651 (1930); A. Dewael, *Bull. soc. chim. Belg.*, **39**, 395 (1930); V. A. Sklyarov, *J. Gen. Chem. U.S.S.R.*, **9**, 2121 (1939); A. K. Seleznev and A. Balakirev, *Zhur. Priklad Khim.*, **27**, 650 (1954).

(8) Boiling points of pure compounds are corrected.

methyl bromide) held in an ice bath at 0°. After addition was complete the reaction mixture was stirred at room temperature for 10 hr. and then allowed to stand for 8 hr. The product was worked up as in the preparation of I except for the addition of a few pellets of sodium hydroxide (the solution was pale yellow before the solvent ether was removed). After distilling a forerun of about 4 ml. a main fraction of 90 g. (49%) of very slightly yellow product was obtained, b.p. 34.1–34.5°/8.0 mm. A small quantity of dark brown, lachrymatory residue was left. Careful refractionation[9] gave 80 g. (44%) of product of constant boiling point and refractive index, b.p. 37.5°/8.0 mm., n_D^{25} 1.4453, d_4^{25} 1.2315, M_R Calcd.[10] 39.32, M_R found 39.16.

Anal. Calcd. for $C_6H_{13}OBr$: C, 39.80; H, 7.24; Br, 44.13. Found:[11] C, 39.91; H, 7.10; Br, 43.96.

This compound, in contrast to I and those previously studied,[3a] was found neither to lose HBr nor to commence to fume in moist air at temperatures up to its normal boiling point (about 162°). It was found, however, to undergo peroxidation quite easily upon standing.

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(9) We continued to distill over sodium hydroxide pellets though they seemed not to be necessary.

(10) Using Eisenlohr's atomic refractions. See K. Fajans in A. Weissberger, *Physical Methods of Organic Chemistry*, 2nd ed., Part Two, Interscience Publishers, Inc., New York, New York, 1949, p. 1163.

(11) Analysis by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

Some Reactions of RX Compounds with Triphenylsilyllithium in Tetrahydrofuran

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Incidental to a study of some silyllithium compounds with epoxides, [1] a significant difference was noted in the behavior of epichlorohydrin and epibromohydrin toward triphenylsilyllithium in tetrahydrofuran. The particular difference that concerns us here involves the formation of hexaphenyldisilane. The yield of this product from the epibromohydrin reaction was 68.6%; and essentially none of it was obtained from the reaction with epichlorohydrin. The formation of this coupling product may be due, at least in part, to a halogen-metal interconversion reaction.[2]

This unusual secondary coupling reaction suggested an examination of other related types. Reactions are now reported of triphenylsilyllithium with *n*-butyl chloride, *n*-butyl bromide, *n*-dodecyl chloride, allyl chloride, cyclopentyl chloride, 1,3-dichloropropane, and 1,3-dibromopropane. The pronounced effect of the nature of the halogen is reflected in the reactions with *n*-butyl chloride and *n*-butyl bromide.

$$(C_6H_5)_3SiLi + n\text{-}C_4H_9Br \longrightarrow (C_6H_5)_3SiSi(C_6H_5)_3\ (60\%) + (C_6H_5)_3SiC_4H_9\text{-}n\ (10\%)$$

Under corresponding conditions, *n*-butyl chloride gave a 75% yield of the "primary" coupling product, *n*-butyltriphenylsilane. Related variations occur with mono and polyhalogenated aromatic compounds,[3] in which the secondary coupling product (hexaphenyldisilane) is formed in some cases in yields close to 90%.

EXPERIMENTAL

Reaction of triphenylsilyllithium with n-butyl chloride. A solution of triphenylsilyllithium (0.05 mole) in tetrahydrofuran was added dropwise to 4.63 g. (0.05 mole) of *n*-butyl chloride. The reaction was exothermic and Color Test I was negative immediately after the addition. Work-up of the reaction mixture gave a solid residue which was crystallized from methanol, yielding 11.8 g. (75%) of *n*-butyltriphenylsilane, m.p. 89–90°; identified by a mixed melting point determination with an authentic sample, and by comparison of infrared spectra.

Reaction of triphenylsilyllithium with n-butyl bromide. A solution of triphenylsilyllithium (0.025 mole) in tetrahydrofuran was added dropwise to 3.42 g. (0.025 mole) of *n*-butyl bromide. The reaction was exothermic and Color Test I was negative immediately after addition. Subsequent to hydrolysis by dilute sulfuric acid, 3.90 g. (60%) of hexaphenyldisilane was isolated, m.p. 349–350°. Work-up of the organic layer gave an oily residue which was chromatographed on alumina. Using petroleum ether (b.p. 60–70°) as an eluant, there was obtained 0.8 g. (10%) of *n*-butyltriphenylsilane, m.p. 90–91°, after recrystallization from methanol. A mixed melting point determination with the compound obtained from the reaction of triphenylsilyllithium with *n*-butyl chloride was not depressed, and their infrared spectra were superimposable.

Reaction of triphenylsilyllithium with n-dodecyl chloride. A solution of triphenylsilyllithium (0.026 mole) in tetrahydrofuran was added dropwise to 5.30 g. (0.026 mole) of *n*-dodecyl chloride. The reaction was exothermic and Color Test I was negative immediately after addition. Work-up gave a solid which was recrystallized twice from methanol to yield 3.20 g. (28.7%) of *n*-dodecyltriphenylsilane, m.p. 65–67°; identified by mixed melting point determination with an authentic sample and by infrared spectra.

Reaction of triphenylsilyllithium with allyl chloride. A solution of triphenylsilyllithium (0.025 mole) in tetrahydrofuran was added dropwise to 1.91 g. (0.025 mole) of allyl chloride. The reaction was exothermic and Color Test I was negative immediately after the addition. The work-up gave a solid residue which was chromatographed on alumina. Using petroleum ether (b.p. 60–70°) and carbon tetrachloride as the eluants there was isolated 4.20 g. (56%) of allyltriphenylsilane, m.p. 90–91°, after recrystallization from petroleum ether (b.p. 60–70°); identified by a mixed melting point determination with an authentic sample. In addi-

(1) H. Gilman, D. Aoki, and D. Wittenberg, *J. Am. Chem. Soc.*, in press.

(2) H. Gilman and D. H. Miles, *J. Am. Chem. Soc.*, **80**, 611 (1958); A. G. Brook, H. Gilman, and L. S. Miller, *J. Am. Chem. Soc.*, **75**, 4759 (1953); A. G. Brook and S. Wolfe, *J. Am. Chem. Soc.*, **79**, 1431 (1957); D. Seyferth, *J. Am. Chem. Soc.*, **79**, 2738 (1957); R. A. Benkeser and R. G. Severson, *J. Am. Chem. Soc.*, **73**, 1424 (1951); A. G. Brook and H. Gilman, *J. Am. Chem. Soc.*, **76**, 278 (1954); O. H. Johnson and D. M. Harris, *J. Am. Chem. Soc.*, **72**, 5566 (1950); and H. Gilman and C. W. Gerow, *J. Am. Chem. Soc.*, **78**, 5823 (1956).

(3) Studies by Glen Dappen. Details of reactions of silylmetallic compounds with a wide variety of halogenated compounds will be reported later.

tion, there was obtained 0.40 g. (6%) of triphenylsilanol; identified by infrared spectra.

Reaction of triphenylsilyllithium with cyclopentyl chloride. A solution of triphenylsilyllithium (0.05 mole) in tetrahydrofuran was added dropwise to 5.23 g. (0.05 mole) of cyclopentyl chloride. The reaction was exothermic, but to a lesser extent than with primary halides. Color Test I was positive after addition. The reaction mixture was stirred at refluxing temperature for 18 hr. after which Color Test I was negative. Subsequent to hydrolysis, 1.2 g. (9.3%) of hexaphenyldisilane, m.p. 356–357°, was isolated. Work-up of the organic layer gave a solid residue which was chromatographed on alumina. From petroleum ether (b.p. 60–70°) as an eluant there was obtained 6.50 g. (40%) of cyclopentyltriphenylsilane, m.p. 112–116°, after recrystallization from ethanol. The product was identified by a mixed melting point determination with an authentic sample, and infrared spectra.

Reaction of triphenylsilyllithium with 1,3-dichloropropane. A solution of triphenylsilyllithium (0.05 mole) in tetrahydrofuran was added dropwise to 2.83 g. (0.025 mole) of 1,3-dichloropropane. The reaction was exothermic, and Color Test I was negative immediately after addition. Work-up gave a solid residue, which was recrystallized from petroleum ether (b.p. 60–70°), yielding 10.25 g. (73%) of 1,3-bis(triphenylsilyl)propane, m.p. 132–133.5°. Recrystallization from the same solvent raised the melting point to 133–134°. Infrared spectrum supported the structure of the product.

Anal. Calcd. for $C_{39}H_{36}Si_2$: Si, 10.02. Found: Si, 10.00, 9.92.

Reaction of triphenylsilyllithium with 1,3-dibromopropane. A solution of triphenylsilyllithium (0.04 mole) in tetrahydrofuran was added dropwise to 4.04 g. (0.02 mole) of 1,3-dibromopropane. The reaction was exothermic, and Color Test I was negative immediately after addition. Subsequent to hydrolysis, 7.4 g. (71.5%) of hexaphenyldisilane, m.p. 355–357°, was isolated. A very small amount of the residue, which was obtained after work-up of the organic layer, has failed to give any pure product.

Acknowledgment. This research was supported in part by The United States Air Force under Contract AF 33(616)-3510 monitored by Materials Laboratory, Directorate of Laboratories, Wright Air Development Center, Wright-Patterson AFB, Ohio. Infrared analyses were obtained through the courtesy of the Institute for Atomic Research, Iowa State College.

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Cyanoethylation of Trichlorosilane

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The reaction of trichlorosilane and acrylonitrile in the presence of tertiary amines has been reported by Nozakura and Konotsune[1] and also by Prober and Cooper[2] to give 3-trichlorosilylpropionitrile (I). This product has also been reported[3] to have been prepared from the same reagents in the presence of triphenylphosphine.

While evaluating various catalysts for the reaction of acrylonitrile and trichlorosilane, several amides were found to promote the formation of I. The reactants were heated to reflux for 24 hr. or longer in the presence of two mole percent of the amide. The table lists the yields of I obtained with various amides. None of these amides promoted cyanoethylation of methyldichlorosilane. The product in each case had the same melting point as that reported by Nozakura and Konotsune,[1] who related the structure of their product to the known 3-trimethylsilylpropionamide.[4] The isomeric 2-trichlorosilylpropionitrile was not detected in any of the mixtures although its properties[5] should have made its detection very easy.

Treatment of I with ethanol and pyridine gave the known 3-triethoxysilylpropionitrile (II)[1] in good yields, and 3-methyldichlorosilylpropionitrile (III)[2] was prepared from I and methyl magnesium bromide. Hydrolysis of I and III gave polysiloxane resins and fluids.

The accepted mechanism for base-catalyzed cyanoethylation reactions[6] would lead one to expect trichlorosilane, polarized as $Cl_3Si^+H^-$,[7] to yield 2-trichlorosilylpropionitrile. Contrary to such expectations, certain catalysts bring about almost exclusive formation of 3-trichlorosilylpropionitrile. These catalysts are not the strong bases used in common cyanoethylations, but have been found among special classes of compounds which form relatively stable complexes with chlorosilanes.

Tertiary amines,[8,9] phosphines,[9] arsines,[9] and amides[10] form complexes involving the *d*-orbitals of silicon. These complexes are the probable reactive intermediates leading to 3-trichlorosilylpropionitrile.

To see if the amine hydrochlorides formed by decomposition of amide complexes[11] were catalyt-

(1) S. Nozakura and S. Konotsune, *Bull. Chem. Soc. Japan*, **29**, 322 (1956).

(2) M. Prober and C. D. Cooper, Fr. Patent 1,116,726 (1956).

(3) R. A. Pike and D. L. Bailey, Abstracts of the 134th meeting of the American Chemical Society, 49P, September 1958.

(4) L. H. Sommer and J. Rockett, *J. Am. Chem. Soc.*, **73**, 5130 (1951).

(5) S. Nozakura and S. Konotsune, *Bull. Chem. Soc. Japan*, **29**, 326 (1956).

(6) J. Hine, *Physical Organic Chemistry*, McGraw-Hill, New York, New York, 1956, p. 221.

(7) L. Pauling, *The Nature of the Chemical Bond*, 2nd ed., Cornell University Press, Ithica, 1940, pp. 58–69.

(8) A. B. Burg, *J. Am. Chem. Soc.*, **76**, 2674 (1954). V. Wannagot, R. Schwartz, H. Voss, and K. G. Knauff, *Z. anorg. u. allgem. Chem.*, **277**, 73 (1954).

(9) B. J. Aylett, H. J. Emeleus, and A. G. Maddock, *J. Inorg. & Nuclear Chem.*, **1**, 187 (1955).

(10) T. S. Piper and E. J. Rochow, *J. Am. Chem. Soc.*, **76**, 4318 (1954). Yu. Volnov, *Sbornik Statei Obshchei Khim., Akad. Nauk. S.S.S.R.*, **2**, 979 (1953).

(11) E. G. Rochow, *J. Am. Chem. Soc.*, **76**, 4852 (1954).

ically active species, diethylamine hydrochloride and aniline hydrochloride were tested, but they had no catalytic effect under these conditions.

EXPERIMENTAL

3-Trichlorosilylpropionitrile (I). A mixture of 106 g. (2 moles) of acrylonitrile, 271 g. (2 moles) of trichlorosilane, and 7.2 g. (0.1 mole) of dimethylformamide was refluxed for 24 hr. During this period the temperature increased from 37° to 83°.[12] Then an additional 135.5 g. of trichlorosilane was slowly added to the refluxing mixture over a period of 48 hr. The final reflux temperature was 105°. The lower boiling components were distilled from the mixture before the product was distilled at reduced pressure to give 272 g. (72%) of 3-trichlorosilylpropionitrile, m.p. 32–33°, b.p. 78–84° at 7–8 mm.

Anal. Calcd. for $C_3H_4NCl_3Si$: Si, 14.90; Neut. Equiv., 62.9. Found: Si, 15.3; neut. equiv., 62.6.

The amides listed in the table were evaluated as catalysts by refluxing equimolar amounts of trichlorosilane and acrylonitrile for 24 hr. in the presence of 2 mole % of the amide. The product was then distilled from the mixture in the yields shown.

CATALYSTS FOR THE CYANOETHYLATION OF TRICHLORISOLANE

Amide	% Yield in 24 Hr.
Dimethylformamide	42
N,N-Diethylbenzamide	38
N,N-Dibutylacetamide	38
N,N-Diethyldecanamide	42
p-Acetotoluide	43
Acetanilide	21
N,N-Dibutylbutyramide	35
N,N-Diethylpropionamide	34

3-Triethoxysilylpropionitrile (II).[1] A solution of 94 g. (0.5 mole) of I in 150 ml. of hexane was slowly added with stirring to a solution of 158 g. (2 moles) of pyridine, 92 g. of ethanol (2 moles), and 400 ml. of hexane. The mixture was cooled, filtered, and devolatilized. The residue was distilled at reduced pressure to give 86.7 g. (80%) of II, b.p. 108–110° at 10 mm., n_D^{22} 1.4121.

3-Methyldichlorosilylpropionitrile (III).[2] A solution of 0.5 mole of methyl magnesium bromide in 200 ml. of ether was added over a period of 1 hr. to a stirred solution of 94.2 g. (0.5 mole) of I in 200 ml. of ether. The stirring was continued for 0.5 hr., the solution was filtered, and the precipitate was washed with dry ether. The solvent was distilled from the combined filtrates, and the residue was distilled at 79–93° at 7–9 mm. to give 64 g. of crude product. Redistillation of the crude product gave 18.3 g. of pure III, b.p. 89° at 16 mm.; n_D^{22}, 1.4560; d_4^{25}, 1.206.

Anal. Calcd. for $SiC_4H_7NCl_2$: Neut. Equiv. 84.0. Found: 83.0.

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(12) An attempt to carry out this reaction in a sealed pressure bottle on a steam bath resulted in an explosion causing considerable damage to the surroundings.

Syntheses of *N*-Vinyl-secondary-amic Acids

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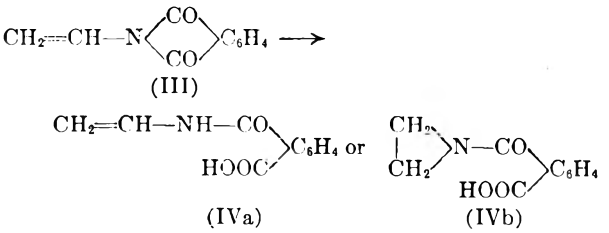
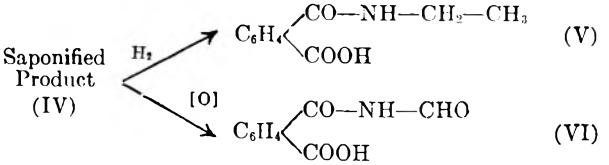
Since vinylamine (I) is unstable and is immediately isomerized into ethyleneimine (II) by the migration

$CH_2{=}CH{-}NH_2$ (I) $\qquad$ $CH_2{-}{-}CH_2$ (II) (CH_2–NH–CH_2)

of hydrogen from nitrogen to carbon, all reactions intended to form vinylamines yield ethyleneimine.[1] On the other hand *N*-vinylimides, that is, *N,N*-disubstituted vinylamines such as *N*-vinylphthalimide (III), are stable. It is a matter of much interest whether the partially saponified product of III is *N*-vinylphthalamic acid (IVα) (*N*-vinyl secondary amide type structure) or *N*-(*o*-carboxybenzoyl)ethyleneimine (IVb).



We attempted to saponify III with alkali under mild conditions, obtaining a product whose composition was found to be $C_{10}H_9NO_3$ by analysis. This is equivalent to IVa or IVb. Through the catalytic hydrogenation of the saponified product under ordinary pressure and at room temperature, *N*-ethylphthalamic acid (V) was obtained. By oxidizing the saponified product with dilute aqueous potassium permanganate at room temperature, *N*-(*o*-carboxybenzoyl)formamide (VI) was obtained. (The ethyleneimine ring is stable to potassium permanganate.[2]) In the infrared spectrum of the saponified product there are seen absorption bands at 3.02μ and 6.48μ which are considered to represent N—H of the secondary amide. If the saponified product were IVb, which is the tertiary imide and has no N—H group, these bands would not be expected. The absorptions at 6.02μ, 10.15μ, and 11.15μ, which are lacking in the infrared spectrum of the hydrogenated product (V), reveal the existence of a vinyl group, indi-

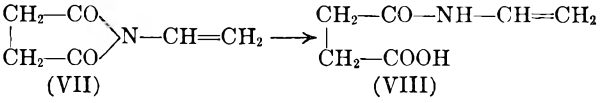


(1) C. C. Howerd and W. Markwald, *Ber.*, **32**, 2036 (1899).

(2) W. Markwald, *Ber.*, **33**, 765 (1900).

cating that the saponified product was IVa instead of IVb. In other words, a structure of the *N*-vinyl secondary amide type is stable.

By the similar saponification of *N*-vinylsuccinimide (VII), *N*-vinylsuccinamic acid (VIII), was obtained.



(VII) (VIII)

In the case of the saponification of *N*-vinylsaccharin, *o*-sulfamidobenzoic acid or saccharin was obtained.

EXPERIMENTAL

Materials. *N*-Vinylphthalimide,[3] *N*-vinylsuccinamide,[4] and *N*-vinylsaccharin were prepared by the pyrolysis of *N*-2-acetoxyethylphthalimide, *N*-2-acetoxyethylsuccinimide, and *N*-2-acetoxyethylsaccharin respectively. *N*-Vinylsaccharin is a new compound, m.p. 131–132° (from ethanol).

Anal. Calcd. for $C_9H_7NO_3S$: C, 51.67; H, 3.37; N, 6.70. Found: C, 51.61; H, 3.36; N, 6.64.

N-Vinylphthalamic acid (IVa). Five grams of *N*-vinylphthalimide (III) was added to 50 ml. of 10% aqueous potassium or sodium hydroxide while stirring at room temperature, after which most of III was neutralized with 5% sulfuric acid under ice-cooling. The precipitate which was filtered and washed with water, was extracted with ethanol and the solvent was concentrated under reduced pressure and at room temperature, and then IVa was obtained, m.p. 110–111.5° (dec.). IVa was also obtained by saponification with ethanolic potassium hydroxide.

Anal. Calcd. for $C_{10}H_9NO_3$: C, 62.82; H, 4.75; N, 7.32. Found: C, 62.72; H, 4.81; N, 7.25.

Hydrogenation of IVa. To 10 ml. of ethanol and 0.1 g. of Pd-black saturated with hydrogen in a hydrogenation vessel, 0.72 g. of IVa was added and hydrogenated with vigorous shaking under ordinary pressure and at room temperature. After hydrogenation was completed, the solution was filtered to remove the catalyst and the solvent was evaporated. Recrystallization of the residue from benzene gave 0.62 g. of *N*-ethylphthalamic acid (V), m.p. 133°. The mixed melting point of V with the authentic sample which was prepared by the saponification of *N*-ethylphthalimide was 132–133°.

Anal. Calcd. for $C_{10}H_{11}NO_3$: N, 7.25. Found: N, 7.13.

Oxidation of IVa *with potassium permanganate.* To the solution in which 1.7 g. of IVa was suspended by vigorous stirring in 30 ml. of water was added in 0.5 hr. another solution made by dissolving 0.86 g. of potassium permanganate in 60 ml. of water. Stirring was further continued for 20 min. after addition of potassium permanganate was completed. After addition of sodium hydrogen sulfide to the solution, the latter was extracted with 10 portions of 20 ml. of ethyl acetate. The extract was dried with anhydrous sodium sulfate and the solvent was evaporated. Recrystallization of the residue from ethanol gave 1.7 g. of VI, m.p. 150–151°.

Anal. Calcd. for $C_9H_7NO_4$: C, 55.96; H, 3.65; N, 7.25. Found: C, 55.77; H, 3.75; N, 6.98.

N-Vinylsuccinamic acid (VIII). Five grams of *N*-vinylsuccinimide (VII) was dissolved in 20 ml. of 10% aqueous sodium hydroxide. After the solution was filtered, the filtrate was neutralized with 5% sulfuric acid under ice-cooling. The solution was extracted with ether and the solvent was removed after the extract was dried with anhydrous calcium chloride. Recrystallization of the residue from ether gave VIII, m.p. 93–94°.

Anal. Calcd. for $C_6H_9NO_3$: N, 9.79. Found: N, 9.98. Hydrogenation of VIII gave *N*-ethylsuccinamic acid, m.p. 96–97°.

Saponification of N-vinylsaccharin. Two grams of *N*-vinylsaccharin was dissolved in a mixed solution of 10 ml. of ethanol and 10 ml. of aqueous potassium or sodium hydroxide, then the sclution was filtered and the filtrate was neutralized with 5% hydrochloric or sulfuric acid and extracted with ethyl acetate. After drying the extract with anhydrous calcium chloride, the solvent was distilled under reduced pressure. Recrystallization of the residue from ethanol gave saccharin, m.p. 224°. The mixed melting point with an authentic sample was 222–223°. The infrared spectra of the two coincided. The product obtained by saponification with 10% ethanolic potassium hydroxide in a similar method was also saccharin. The product of saponification with 10% aqueous sodium hydroxide was *o*-sulfamidobenzoic acid, m.p. 164–165°. The mixed melting point with the authentic sample[5] was 164–165°. The infrared spectra of the two perfectly coincided.

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(3) W. E. Hanford and H. B. Stevenson, U. S. Patent **2,276,840**; *Chem. Abstr.*, **36**, 4637 (1942).

(4) W. E. Hanford and H. B. Stevenson, U. S. Patent **2,231,905**; *Chem. Abstr.*, **35**, 3267 (1941).

(5) *Beilsteins Handbuch der Organischen Chemie*, 4te. Auflage, Julius Springer, Berlin, 1928, *Bd. XI*, 376. (Wilson, *Am. Chem. J.*, **30**, 354).

16-Hydroxylated Steroids. VIII.[1] 5β-Dihydrocortisone Approach to the Synthesis of Triamcinolone

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In 1956, this laboratory[2] announced the synthesis of triamcinolone (9α-fluoro-16α-hydroxy-prednisolone), a compound which has found considerable use in the treatment of rheumatoid arthritis and other disorders.[3] The importance of triamcinolone therefore merited further work on its preparation.[4]

One of the original syntheses of triamcinolone proceeded *via* 16α,21-diacetoxy-17α-hydroxy-4,9-

(1) Paper VII, S. Bernstein, M. Heller, R. Littell, S. M. Stolar, R. H. Lenhard, W. S. Allen, and I. Ringler, *J. Am. Chem. Soc.*, in press.

(2) S. Bernstein, R. H. Lenhard, W. S. Allen, M. Heller, R. Littell, S. M. Stolar, L. I. Feldman, and R. H. Blank, *J. Am. Chem. Soc.*, **78**, 5693 (1956). A detailed paper on this work has been submitted for publication to the *Journal of the American Chemical Society*.

(3) L. Hellman, B. Zumoff, M. K. Schwartz, T. F. Gallagher, C. A. Berntsen, Jr., and R. H. Freyberg, Paper presented before Am. Rheumatism Assoc. Meeting, Bethesda, Md., Nov. 30, 1956; R. H. Freyberg, C. A. Berntsen, Jr., and L. Hellman, *Arthritis and Rheumatism*, **1**, 215 (1958).

(4) A synthesis of triamcinolone based essentially on the introduction of the 16α-hydroxyl group by *Streptomyces roseochromogenus* has been announced by R. W. Thoma, J. Fried, S. Bonanno, and P. Grabowich, *J. Am. Chem. Soc.*, **79**, 4818 (1957).

(11)-pregnadiene-3,20-dione (VII).[2] A synthesis of the latter has now been established which utilizes 5β-dihydrocortisone (I)[5] as the starting material rather than Reichstein's substance S or cortisone.[2]

Ketalization of 5β-dihydrocortisone (I) with ethylene glycol in benzene[6] gave 3,20-bis-ethylenedioxy-17α,21-dihydroxy-pregnan-11-one (IIa) in 50% yield. Reduction with sodium borohydride[7] gave the 11β-hydroxy compound IIb in 84% yield. Acetylation of IIb provided a 77% yield of the 21-acetate IIc. Treatment of the latter with thionyl chloride in pyridine[8] gave 21-acetoxy-3,20-bis-ethylenedioxy-9(11),16-pregnadiene (III). The ketal protective groupings were then removed by treatment with dilute acetic acid,[8] and 21-acetoxy-9(11),16-pregnadiene-3,20-dione (IV) was obtained (in an over-all yield of 55% from IIc). Hydroxylation of IV with osmium tetroxide[9] followed by acetylation gave 16α,21-diacetoxy-17α-hydroxy-9(11)-pregnene-3,20-dione (Vb) in 52% yield. Bromination of Vb in dimethylformamide gave 16α,21-diacetoxy-4-bromo-17α-hydroxy-9(11)-pregnene-3,20-dione.[10] Dehydrobromination with anhydrous lithium chloride in dimethylformamide[11] afforded 16α,21-diacetoxy-17α-hydroxy-4,9(11)-pregnadiene-3,20-dione (VII). Thereby, an alternate pathway to triamcinolone was established.

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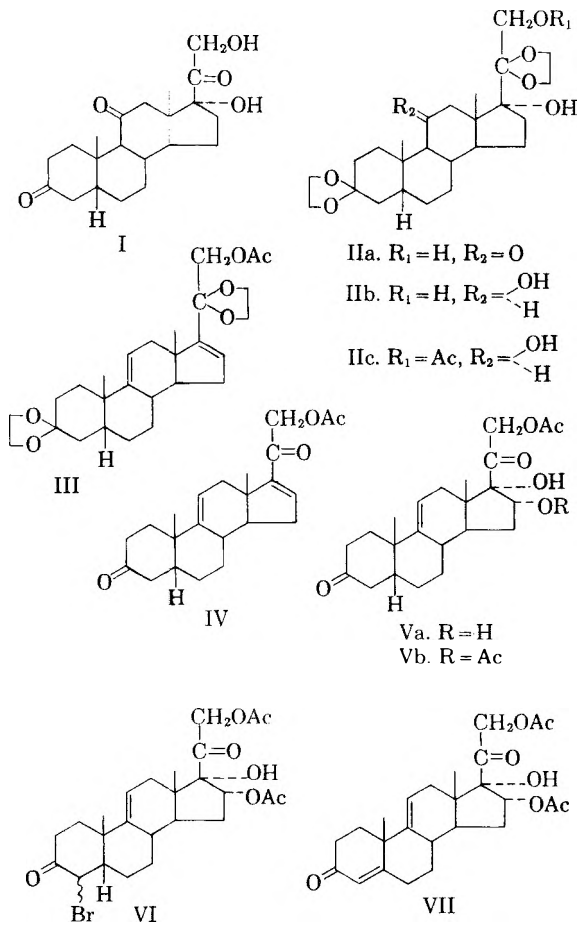

EXPERIMENTAL

3,20-Bisethylenedioxy-17α,21-dihydroxypregnan-11-one (IIa). A mixture of 5β-dihydrocortisone (17α,21-dihydroxypregnane-3,11,20-trione) (I, 1.60 g.), *p*-toluenesulfonic acid monohydrate (45 mg.), ethylene glycol (12 ml.), and benzene (100 ml.) was stirred and refluxed with continuous water removal for 5 hr. After the reaction mixture was neutralized with sodium bicarbonate, it was extracted with ethyl acetate. The solution was washed to neutrality with water, treated with magnesium sulfate and activated carbon, filtered through diatomaceous earth, and evaporated. Addition of ether gave 540 mg. of a white powder, m.p. 190–192°. A portion was crystallized twice from acetone-ether to give pure IIa, m.p. 190.5–191.5°; $[\alpha]_D^{25}$ +41° (*c*, 1.85 chloroform).

Anal. Calcd. for $C_{25}H_{38}O_7$ (450.55): C, 66.64; H, 8.50. Found: C, 66.75; H, 8.66.

In another run, 5.10 g. of I gave 3.15 g. (50%) of IIa, m.p. 186–188°.

3,20-Bisethylenedioxypregnane-11β,17α,21-triol (IIb). A mixture of 3,20-bisethylenedioxy-17α,21-dihydroxypregnan-11-one (IIa, 2.0 g.), tetrahydrofuran (100 ml.), 2.5% aqueous sodium hydroxide (15 ml.), and sodium borohydride (2.7 g.) was refluxed for 20 hr. The tetrahydrofuran was distilled under reduced pressure, and the resulting solution extracted with water to neutrality. Treatment with magnesium sulfate and activated carbon, filtration through diatomaceous earth, and evaporation gave a glass which, upon addition of petroleum ether, gave 1.52 g. of product, m.p. 170.5–171.5°. Crystallization of a 150-mg. portion from acetone–petroleum ether gave 100 mg. of pure IIb, m.p. 171–172°.

Anal. Calcd. for $C_{25}H_{40}O_7$ (452.57): C, 66.45; H, 8.91. Found: C, 66.58; H, 8.97.

In another run, with 3.10 g. of IIa there was obtained 2.6 g. (84%) of IIb, m.p. 162–168°.

21-Acetoxy-3,20-bisethylenedioxypregnane-11β,17α-diol (IIc). To a cooled solution of 3,20-bisethylenedioxypregnane-11α,17α,21-triol (IIb, 125 mg.) in pyridine (3 ml.) was added 1 ml. of acetic anhydride, and the solution was allowed to stand at room temperature overnight. Addition of methanol, and evaporation gave 90 mg. of a white powder, m.p. 166–168°. Two crystallizations from ether–petroleum ether gave 56 mg. of IIc, m.p. 166.5–167°; $[\alpha]_D^{25}$ +25° (*c*, 0.89, chloroform).

Anal. Calcd. for $C_{27}H_{42}O_8$ (494.61): C, 65.56; H, 8.56. Found: C, 65.51; H, 8.70.

In another run, a 77% yield of IIc, m.p. 166.5–167.5°, was obtained.

21-Acetoxy-9(11),16-pregnadiene-3,20-dione (IV). To a cooled (−5°) solution of 21-acetoxy-3,20-bisethylenedioxypregnane-11α,17α-diol (IIc, 5.6 g.) in 25 ml. of pyridine was added 3.0 ml. of thionyl chloride, and the solution was allowed to stand at −5° for 16 hr. The mixture was poured into ice water, and an oil was formed from which the water

(5) L. H. Sarett, *J. Am. Chem. Soc.*, **70**, 1454 (1948).

(6) R. Antonucci, S. Bernstein, R. Littell, K. J. Sax, and J. H. Williams, *J. Org. Chem.*, **17**, 1341 (1952).

(7) W. S. Allen, S. Bernstein, and R. Littell, *J. Am. Chem. Soc.*, **76**, 6116 (1954).

(8) W. S. Allen and S. Bernstein, *J. Am. Chem. Soc.*, **77**, 1028 (1955).

(9) W. S. Allen and S. Bernstein, *J. Am. Chem. Soc.*, **78**, 1909 (1956).

(10) R. P. Graber, A. C. Haven, Jr., and N. L. Wendler, *J. Am. Chem. Soc.*, **75**, 4722 (1953).

(11) R. P. Holysz, *J. Am. Chem. Soc.*, **75**, 4432 (1953).

was then decanted. The oil was dissolved in ethyl acetate, and the extract was washed four times with water, treated with magnesium sulfate and activated carbon, filtered through diatomaceous earth, and evaporated to afford 5.0 g. of glass (III) which would not crystallize.

The above glass dissolved in 70 ml. of 50% aqueous acetic acid was heated on a steam bath for 1 hr., water was added and the mixture was cooled. Crude IV which separated was collected and recrystallized from acetone–petroleum ether to give 2.3 g. (55%) of IV, m.p. 147–150°, which exhibited a positive Blue Tetrazolium test. A 300-mg. portion was crystallized three times from acetone–petroleum ether to give pure IV, m.p. 152.5–153.5°; $[\alpha]_D^{25}$ +125° (*c*, 1.21, chloroform); $\lambda_{max}^{abs.\ alc.}$ 238–239 mμ (ε 8,050).

Anal. Calcd. for $C_{23}H_{30}O_4$ (370.47): C, 74.56; H, 8.16. Found: C, 74.44; H, 8.34.

16α,21-Diacetoxy-17α-hydroxy-9(11)-pregnene-3,20-dione (Vb). To a solution of 21-acetoxy-9(11),16-pregnadiene-3,20-dione (IV) (2.22 g.) in benzene (30 ml.) and pyridine (1.0 ml.) was added 1.75 g. of osmic acid, and the solution was allowed to stand at room temperature for 20 hr. To this was added 100 ml. of water, 50 ml. of methanol, and 10.5 g. each of sodium sulfite and potassium bicarbonate. After the mixture was stirred vigorously for 5 hr., 100 ml. of chloroform was added and the mixture was filtered. The inorganic filter cake was washed with 200 ml. of hot chloroform. The organic layer was washed with water to neutral, treated with anhydrous sodium sulfate and activated carbon, filtered, and evaporated to afford a light brown glass. Crystallization from acetone–petroleum ether gave 1.03 g. of a light brown solid (Va), m.p. 171–177° (dec.).

The above material (1.03 g.) was dissolved in 10 ml. pyridine and 1.0 ml. acetic anhydride and the mixture was allowed to stand at room temperature for 64 hr. Evaporation of the solvents under reduced pressure gave a green oil which was dissolved in ethyl acetate, washed with dilute sulfuric acid, saturated sodium bicarbonate, and with water to neutral. Treatment with sodium sulfate and activated carbon, filtration, and evaporation gave 900 mg. of green oil which resisted attempts to crystallize. Chromatography on 45 g. of silica gel gave 700 mg. of glass by elution with 40% ether in benzene. Three crystallizations from acetone–petroleum ether gave 275 mg. of Vb, m.p. 175–190°; $[\alpha]_D^{25}$ ±0° (*c*, 1.09, chloroform).

Anal. Calcd. for $C_{25}H_{34}O_7$ (446.52): C, 67.23; H, 7.68. Found: C, 67.24; H, 7.88.

In another run with 2.7 g. of IV there was obtained 1.7 g. (52%) of Vb, m.p. 176–192°.

16α,21-Diacetoxy-17α-hydroxy-4,9(11)-pregnadiene-3,20-dione (VII). To a solution of 16α,21-diacetoxy-17α-hydroxy-9(11)-pregnene-3,20-dione (Vb, 600 mg., 1.34 millimoles) in 2 ml. of dimethylformamide and 11 mg. of *p*-toluenesulfonic acid monohydrate was added 4.0 ml. of a bromine solution (0.345*M* in dimethylformamide, 1.38 millimoles) dropwise over 5 hr. After this period, 50 ml. of water were added, the mixture was cooled, and 600 mg. of white glass (VI) was obtained.

The above glass was dissolved in 8 ml. of dimethylformamide containing 400 mg. of lithium chloride and was heated for 2.5 hr. at 100° under an atmosphere of nitrogen. Addition of water gave a yellow paste, which was dissolved in ethyl acetate, washed three times with water, treated with magnesium sulfate and activated carbon, filtered, and evapoated to give 540 mg. of glass which would not lend itself readily to purification.

Chromatography on 45 g. of silica gel gave 200 mg. of solid [eluted with ether-benzene (1:1)]. Two crystallizations from acetone–petroleum ether gave 55 mg. of VII, m.p. 187–189°; $\lambda_{max}^{abs.\ alc.}$ 239 mμ (ε 14,200). One further crystallization from the same solvents gave 20 mg., m.p. 193–194°; $[\alpha]_D^{25}$ +36° (*c*, 1.248). Infrared spectral analysis showed identity with an authentic sample of VII, and admixture melting point gave no depression.

Acknowledgment. We wish to thank Louis M. Brancone and associates for the analyses, and William Fulmor and associates for the infrared and ultraviolet absorption spectra and optical rotation data.

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O-Alkyl Substituted Hydroxycarbamates

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Certain carbamates are used in human and veterinary medicine.[1] Ethyl carbamate has been used in the treatment of neoplastic diseases and as a mild hypnotic in man and animals. Meprobamate, $CH_3C(n\text{-}C_3H_7)(CH_2OCONH_2)_2$, is widely employed as a mild hypnotic and skeletal muscle relaxant.

There is evidence that some, but not all, *O*-alkyl substituted hydroxylamine derivatives possess pharmacological properties similar to those of the related amines.[2–5]

In the present work, ethyl hydroxycarbamate, $HONHCOOC_2H_5$, and a number of its *O*-alkyl derivatives have been prepared and examined pharmacologically. Ethyl hydroxycarbamate has been synthesized by the method of Jones,[6] except that it has been possible to obtain the hydroxycarbamate analytically pure by distillation *in vacuo*.

The related compound, ethyl methoxythionocarbamate, $CH_3ONHCSOC_2H_5$, has been prepared by the following series of reactions:[7]

$$C_2H_5OCSSNa + ClCH_2COONa \longrightarrow C_2H_5OCSSCH_2COONa \xrightarrow{CH_3ONH_2} C_2H_5OCSNHOCH_3$$

Various 2,2-dialkyl-1,3-propanediol bis(alkoxyalkylcarbamates), $R,R'C[CH_2OCON(R'')OR''']_2$, where R'' = H or alkyl, have been prepared by the following series of reactions:

(1) Osol-Farrar, *U. S. Dispensatory*, 25th ed., J. B. Lippincott Co., New York, N. Y., 1955, pp. 1477, 1861, 2038.

(2) L. W. Jones and R. T. Major, *J. Am. Chem. Soc.*, 49, 1527 (1927).

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(5) R. T. Major and L. G. Peterson, *J. Org. Chem.*, 22, 579 (1957).

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TABLE I

2,2-DIALKYL-1,3-PROPANEDIOL BIS(CHLOROFORMATES), $R,R'C(CH_2OCOCl)_2$

R	R'	B.P., °C.	Yield	Formula	Calcd. C	Calcd. H	Found C	Found H
CH_3	CH_3	122–125 (17 mm.)	56%	$C_7H_{10}Cl_2O_4$	36.70	4.40	36.69	4.62
C_2H_5	C_2H_5	153–155 (24 mm.)	64%	$C_9H_{14}Cl_2O_4$	42.04	5.49	41.73	5.54
C_2H_5	n-C_4H_9	165–168 (20 mm.)	60%	$C_{11}H_{18}Cl_2O_4$	46.33	6.36	46.23	6.11

TABLE II

$R,R'C[CH_2OCON(R'')OR''']_2$

R	R'	R''	R'''	Method Used	B.P., °C.	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
CH_3	CH_3	CH_3	CH_3	I	183–184 (20 mm.)	$C_{11}H_{22}N_2O_4$	47.47	7.97	10.07	47.05	7.97	9.84
CH_3	CH_3	H	CH_3	I	194–195 (1 mm.)	$C_9H_{18}N_2O_4$	43.19	7.25	11.20	42.87	6.93	—
CH_3	CH_3	C_2H_5	C_2H_5	II	136–138 (0.15 mm.)	$C_{15}H_{30}N_2O_4$	53.87	9.04	8.38	54.43	9.06	8.07
CH_3	CH_3	H	C_2H_5	II	175–180 (0.5 mm.)	$C_{11}H_{22}N_2O_4$	47.47	7.97	10.07	47.47	7.95	10.04
C_2H_5	C_2H_5	CH_3	CH_3	II	163–165 (0.3 mm.)	$C_{13}H_{26}N_2O_4$	51.00	8.55	9.14	51.05	8.22	8.56
C_2H_5	C_2H_5	C_2H_5	C_2H_5	II	133–138 (0.1 mm.)	$C_{17}H_{34}N_2O_4$	56.33	9.45	7.73	56.32	9.25	7.89
C_2H_5	n-C_4H_9	CH_3	CH_3	II	166–169 (0.3 mm.)	$C_{15}H_{30}N_2O_4$	53.87	9.04	8.38	53.83	8.89	8.52
C_2H_5	n-C_4H_9	C_2H_5	C_2H_5	II	142–148 (0.2 mm.)	$C_{19}H_{38}N_2O_4$	58.43	9.81	—	58.62	9.63	—

$$R,R'C(CH_2OH)_2 \xrightarrow[\text{toluene}]{COCl_2} R,R'C(CH_2OCOCl)_2 \xrightarrow[K_2CO_3]{2R''NHOR'''} R,R'C[CH_2OCON(R'')OR''']_2$$

The chloroformates needed in this synthesis were prepared by the method of Ludwig and Piech[8]; the biscarbamates were produced from these intermediates in 60–86% yield.

Dr. Donald A. Clarke of the Sloan-Kettering Institute for Cancer Research, New York, N. Y., has tested the following compounds *in vivo* for Sarcoma 180 inhibition: ethyl hydroxycarbamate[6]; ethyl methoxycarbamate[9]; ethyl ethoxycarbamate[9]; ethyl methoxythionocarbamate; 2,2-dimethyl-1,3-propanediol bis(methoxycarbamate) and bis(ethoxycarbamate); and 2-ethyl-2-*n*-butyl-1,3-propanediol bis(methoxymethylcarbamate). None of these compounds inhibited Sarcoma 180 at nontoxic doses.

Dr. C. A. Stone of the Merck Institute for Therapeutic Research, West Point, Pa., has examined the pharmacological properties of many of the compounds described in this paper. He has reported that ethyl ethoxycarbamate[9] showed little effect in mice when administered intraperitoneally in Mazola oil in doses below the toxic level of 441 mg. per kg. Ethyl ethoxyethylcarbamate[3] produced depression in mice in doses at or near the lethal level of 1069 mg. per kg. administered intraperitoneally. However, a 1% suspension of this compound in tragacanth abolished the corneal reflex for 18 min. when instilled into the rabbit eye. The biscarbamates with the structure $R,R'C[CH_2OCON(R'')OR''']_2$, where $R,R',R'',R''' = CH_3$; $R,R' = CH_3$, $R'' = H$ and $R''' = C_2H_5$; $R,R' = CH_3$ and R'', $R''' = C_2H_5$; $R,R' = C_2H_5$ and R'', $R''' = CH_3$; and $R = C_2H_5$, $R' = n$-C_4H_9 and $R'',R''' = CH_3$, were inactive in tests designed to evaluate their meprobamate-like activity in mice.

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EXPERIMENTAL

All melting points and boiling points are uncorrected.

Ethyl hydroxycarbamate. To a stirred mixture of 195 g. (2.80 mole) of hydroxylamine hydrochloride and 380 g. (2.75 mole) of anhydrous potassium carbonate, both finely powdered, with 1500 ml. of ether was added 20 ml. of water. Subsequently, with ice cooling 300 g. (2.77 mole) of ethyl chloroformate was added to the stirred mixture within about 1 hr. Carbon dioxide was evolved immediately. After the addition was completed the mixture was stirred overnight at room temperature, the potassium chloride was removed by filtration, and the filtrate was evaporated under a slight vacuum. The remaining colorless oil had an ester-like odor. Distillation through a 15-cm. Vigreaux column afforded 103 g. (66%) of ethyl hydroxycarbamate, b.p. 113–116°(3 mm.), as a slightly hygroscopic odorless oil, which gave a deep purple color with aqueous ferric chloride.

Anal. Calcd. for $C_3H_7NO_3$: C, 34.28; H, 6.72; N, 13.33. Found: C, 34.47; H, 6.49; N, 13.72.

Ethyl methoxythionocarbamate. An aqueous solution of 0.30 mole sodium ethyl xanthate was prepared according to Davies and Maclaren.[7] To this was added an ice cold solution of sodium chloroacetate prepared by slowly neutralizing 39 g. (0.42 mole) of chloroacetic acid with 17 g. (0.42 mole) of sodium hydroxide in 180 ml. of cold water. After having stood overnight this mixture was evaporated to about 150 ml. on a water bath at reduced pressure. Methoxyamine (21 g., 0.45 mole) was added and the mixture kept at room temperature overnight. After being neutralized with acetic acid, it was extracted with ether. After the extract had been dried over sodium sulfate and the ether removed by evaporation at room temperature, a low melting solid remained; yield 37 g. (66%). Upon recrystallization from petroleum ether (30–60°), long needles were obtained, m.p. 33–36°.

Anal. Calcd. for $C_4H_9NO_2S$: C, 35.53; H, 6.72. Found: C, 35.27; H, 6.87.

2,2-Dialkyl-1,3-propanediol bis(chloroformates).[8] *See Table* I. *2,2-Dimethyl-1,3-propanediol bis(chloroformate).* To a stirred solution of 16.0 g. (1.17 mole) freshly distilled phosgene in 400 ml. of dry toluene was slowly added a solution of 220 g. (1.17 mole) of antipyrine and 70 g. (0.53 mole) of 2,2-dimethyl-1,3-propanediol in 500 ml. of chloroform. The temperature was kept between −10° and 0° with an ice salt mixture. After the addition was completed, the mixture was warmed to room temperature and was stirred overnight. The antipyrine hydrochloride was filtered (yield nearly theoretical), washed with ether, and the combined filtrates evaporated *in vacuo*. Distillation of the yellow oily residue furnished 86 g. (56%) of pure 2,2-dimethyl-1,3-propanediol bis(chloroformate), b.p. 122–125° (17 mm.).

2,2-Dialkyl-1,3-propanediol bis(alkoxyalkylcarbamates). See Table II. Method I. *2,2-Dimethyl-1,3-propanediol bis(methoxymethylcarbamate).* To a stirred mixture of 3.0 g. (0.05 mole) *N*-methoxymethylamine[9] in 30 ml. of absolute ether and 5.0 g. (0.04 mole) of powdered anhydrous potassium carbonate was added with ice cooling 5.0 g. (0.025 mole) of 2,2-dimethyl-1,3-propanediol bis(chloroformate). Carbon dioxide was evolved slowly. The mixture was stirred at room temperature for 24 hr., following which the ether was evaporated and the residue was dissolved in 25 ml. of water. An oil separated and was extracted with ether. Upon evaporation of the dried extract, the crude biscarbamate remained as an oil. It was purified by distillation, yield 5.0 g. (86%), b.p. 183–184° (20 mm.). The microanalytical data are recorded in Table II.

Method II.[8a] *2,2-Diethyl-1,3-propanediol bis(methoxymethylcarbamate).* To 25.7 g. (0.1 mole) of 2,2-diethyl-1,3-propanediol bis(chloroformate) in 150 ml. of absolute ether was added dropwise 30.5 g. (0.5 mole) of *N*-methoxymethylamine with shaking and cooling. The hydrochloride of *N*-methoxymethylamine separated immediately and was filtered after the mixture had stood overnight at room temperature. The filtrate was washed with 25 ml. of water, dried over sodium sulfate, and the solvents evaporated. The oily residue furnished upon distillation 18.0 g. (60%) of biscarbamate, b.p. 163–165° (0.3 mm.). The microanalytical data are recorded in Table II.

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Synthesis of Coprostane-3α,7α,12α-triol-27-C^{14}, Coprostane-3α,7α,12α-triol-24-one-27-C^{14}, and Coprostane-3α,7α,12α,24ξ-tetrol-27-C^{14}

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A synthesis of coprostane-3α,7α,12α-triol (I), coprostane-3α,7α,12α-triol-24-one (II), and coprostane-3α,7α,12α,24-ξ tetrol (III) labeled at C_{27} with carbon-14 was required for studies of their metabolism and possible role as intermediates in the enzymatic conversion of cholesterol to cholic acid. Two methods of synthesizing I have been reported[2–4] These procedures were found to be unsuitable for the purpose intended because a large excess of relatively inaccessible carbon-14 intermediate was required or yields proved to be very poor in our hands. Cole and Julian[5] have reported an elegant method for the synthesis of steroid compounds with a ketonic group in the side chain. We have applied this procedure to prepare II using triformylcholyl chloride and diisopropylcadmium as the starting materials.

A preliminary report on the synthesis has already been given.[6]

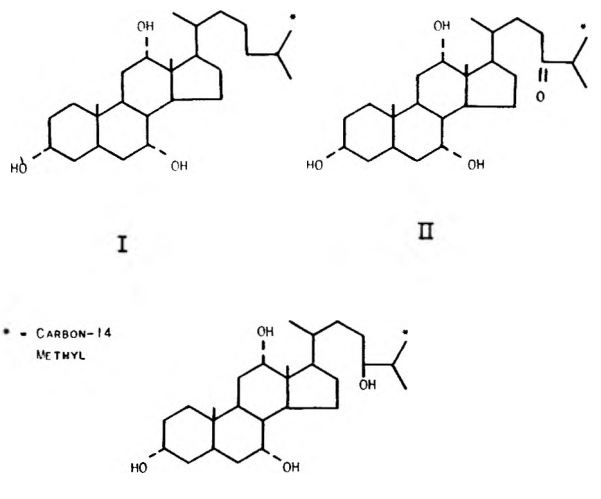

Figure 1.

EXPERIMENTAL

Materials. Triformylcholyl chloride was prepared from cholic acid by the method of Cortese and Bauman.[7] By modifying their crystallization procedure using benzene–petroleum ether (b.p. 60–80°) as solvent, triformylcholic acid was obtained as crystalline solid with m.p. 209–211°. This was converted to the acid chloride by treatment with oxalyl chloride. 2-Propanol-1,3-C^{14} [8] (specific activity 1.0 millicurie per millimole) was diluted twenty-fold with unlabeled 2-propanol and then converted to 2-bromopropane-1,3-C^{14} by reaction with phosphorus tribromide on a semimicro scale.

Coprostane-3α,7α,12α-triol-24-one-27-C^{14}. A Grignard re-

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(7) F. Cortese and L. Bauman, *J. Am. Chem. Soc.*, **57**, 1393 (1935).

(8) Obtained from Nuclear Instrument and Chemical Corp., Chicago, Ill.

agent was prepared from 2.40 g. 2-bromopropane-1,3-C^{14} (specific activity, 0.050 millicurie per millimole) and 0.600 g. magnesium turnings in 25 ml. anhydrous ethyl ether. The solution was cooled in an ice bath and stirred while 7.5 g. powdered anhydrous cadmium bromide (dried for 3 hr. at 120°) were added. After stirring for 30 min., the ice bath was removed and a solution of 1.50 g. triformylcholyl chloride, dissolved in 8 ml. anhydrous benzene, was added dropwise. Stirring was continued for 30 min. after the addition and the reaction mixture was heated to reflux for 1 hr. The mixture was then allowed to stand overnight. Ice water followed by sufficient 3*N* HCl solution to dissolve the precipitate was added to the reaction mixture. The benzene-ether layer was separated and washed with water until the washings were neutral. The washed solvent layer was then evaporated to dryness and the residual gum was dried *in vacuo*. This residue was saponified by heating for 1 hr. with 10 ml. 5% KOH in methanol solution. The saponification mixture was diluted with 100 ml. water and this solution was extracted with ethyl ether. The ether extract was evaporated to dryness. The residual crude ketone was subjected to chromatography on a silicic acid column. The column was washed through with benzene first and the ketone was eluted with ethyl ether–benzene (1:2). After evaporation of this eluate, 0.698 g. coprostane-3α,7α,12α-triol-24-one-27-C^{14} were obtained. Upon crystallizing twice from acetone solution, colorless crystals melting at 151–152° were obtained. This product had a specific activity of 0.051 millicurie per millimole. The infrared spectrum of this ketone exhibited a characteristic carbonyl absorption peak at 5.82 μ.

Anal. Calcd. for $C_{27}H_{46}O_4$: C, 74.60; H, 10.67. Found: C, 74.26; H, 10.63.

Coprostane-3α,7α,12α-triol-27-C^{14}. To 0.500 g. coprostane-3α,7α,12α-triol-24-one-27-C^{14} dissolved in 1 ml. ethanol, 1 ml. hydrazine hydrate (99%) was added. The mixture was swirled for a few minutes until a homogeneous solution resulted. To this solution was added 10 ml. triethylene glycol and 1 g. KOH. The mixture was heated and allowed to reflux for 30 min. The reflux condenser was then removed and the mixture heated at 180–200° for 2 hr. At the end of this period the reaction mixture was allowed to cool in a stream of nitrogen gas and it was then poured into 50 ml. of water. The precipitated compound was filtered, washed with water, and dried. The crude product was crystallized from acetone, 0.269 g. coprostane-3α,7α-12α-triol-27-C^{14} melting at 184–185° were obtained. Upon mixing with coprostane-3α,7α,12α-triol prepared by the previously cited procedure,[2] no depression in melting point was observed. The infrared spectra of the two samples were identical. Major absorption peaks were observed at 2.94 μ, 3.42 μ, 6.80 μ, 7.26 μ, 7.95 μ, 9.28 μ, 9.60 μ, 10.21 μ, 10.55 μ, 10.96 μ, and 11.70 μ.

Anal. Calcd. for $C_{27}H_{48}O_3$: C, 77.08; H, 11.50. Found: C, 77.04; H, 11.49.

Coprostane-3α,7α,12α,24ξ-tetrol-27-C^{14}. A solution containing 0.150 g. lithium aluminum hydride in 25 ml. anhydrous ethyl ether was prepared. To this solution in a flask provided with a magnetic stirrer and reflux condenser was slowly added a solution of 0.300 g. coprostane-3α,7α,12α-triol-24-one-27-C^{14} in 25 ml. anhydrous ethyl ether. Stirring was continued for 1.5 hr. at room temperature. The reaction mixture was cooled in ice and 20 ml. 2*N* H_2SO_4 solution was added slowly. The acidified reaction mixture was stirred for a few minutes and the ether layer separated and washed with water until the washings were neutral. The ether extract was then dried and evaporated to dryness. The residue was crystallized from acetone or benzene-petroleum ether to yield 0.102 g. coprostane-3α,7α,12α,24-ξ-tetrol-27-C^{14} melting at 169–170°. The infrared spectrum of this compound was qualitatively similar to that of compound I but showed an enhanced C—OH absorption peak at 2.94 μ.

Anal. Calcd. for $C_{27}H_{48}O_4$: C, 74.25; H, 11.08. Found: C, 74.14; H, 10.95.

Radiochemical purity of Compounds I, II, and III above was determined as follows: (1) A mixture of each radioactive compound and a large excess of corresponding unlabeled compound was recrystallized three times. No substantial changes (±5%) in specific activity were observed. (2) Samples of the radioactive compounds were chromatographed on paper together with samples of corresponding unlabeled compounds using the phenoxyethanol and heptane system of Neher and Wettstein[9] and the acetic acid and isopropyl ether–heptane system of Sjövall.[10] In each case practically all (90% or more) of the radioactivity was recovered from the spot corresponding to the unlabeled substance. (3) Compounds I and II were subjected to the reversed-phase partition column chromatographic procedure of Danielsson[11] modified by the use of 1:1 2-propanol–water mixture as the mobile phase. The weight and radioactivity curves of the eluted substances coincided in each case and the elution volumes corresponded to those obtained with unlabeled samples of each compound.

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Synthesis of Potential Anticancer Agents. XVIII. Analogs of Carbamoyl Phosphate[1]

Rudolf W. Balsiger, Dale G. Jones, and John A. Montgomery

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In an effort to uncover new classes of anticancer agents we have directed our attention to the synthesis of carbamoyl phosphate analogs, since carbamoyl phosphate has been shown to be involved in the *de novo* biosynthesis of pyrimidines, where it acts as the cofactor in the formation of *N*-carbamoylaspartic aicd.[2,3] The identity of this natural carbamoyl donor has been further corroborated by Hall,[4] who, in addition, has compiled a comprehensive bibliography on the subject.

(1) This work was supported by funds from the National Institutes of Health Contract No. SA-43-ph-1740 and from the C. F. Kettering Foundation. Part XVII. H. J. Schaeffer and R. D. Weimer, *J. Am. Chem. Soc.*, **81**, 197 (1959).
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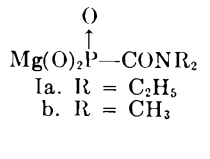
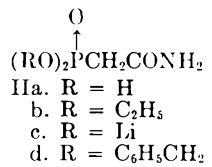
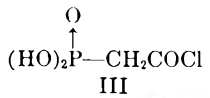


Ia. R = C_2H_5
b. R = CH_3



IIa. R = H
b. R = C_2H_5
c. R = Li
d. R = $C_6H_5CH_2$



III

In an attempt to prepare a compound which might interfere with this carbamoylation reaction, we synthesized the magnesium salt of diethylcarbamoyl phosphate (Ia). Methylcarbamoyl chloride was phosphorylated with silver dibenzyl phosphate according to the method of Zervas,[5] adapted to the preparation of mixed anhydrides of phosphoric and acetic acids by Lynen[6]; and the intermediate dibenzyl diethylcarbamoyl phosphate was catalytically hydrogenolyzed with a palladium-on-charcoal catalyst in ethanol in the presence of magnesium oxide yielding hydrated magnesium diethylcarbamoyl phosphate (Ia). Magnesium dimethylcarbamoyl phosphate (Ib), which can be obtained by a similar reaction sequence, was identified by the comparison of its infrared absorption spectrum with that of the diethyl analogy Ia; however, satisfactory elemental analyses were not obtained because of the instability of the compound, even at room temperature. There was no reaction between silver dibenzyl phosphate and diphenylcarbamoyl chloride even after prolonged refluxing of an ether suspension of the two substances.

(Carbamoylmethyl)phosphonic acid (IIa), which is sterically very similar to carbamoyl phosphate but is incapable of donating the carbamoyl group to an enzyme substrate, was also synthesized. An attempt to adapt reported procedures[7-9] for the preparation of phosphonacetic acid to the preparation of (carbamoylmethyl)phosphonic acid (IIa) was unsuccessful, since selective hydrolysis of the phosphonester group of diethyl (carbamoylmethyl)phosphonate (IIb) is not possible under the conditions described; phosphonacetic acid was obtained instead. The desired (carbamoylmethyl) phosphonic acid (IIa) was obtained by two methods: (1) Phosphonacetic acid was converted to phosphonacetyl chloride (III),[10] which upon treatment with ammonia gave the monoammonium salt of (carbamoylmethyl)phosphonic acid. The acid was purified through its dilithium salt (IIc). (2) The reaction of dibenzyl phosphite and 2-chloroacetamide according to Nylen[9] gave dibenzyl (carbamoylmethyl)phosphonate (IId) in 30% yield; catalytic hydrogenolysis of IId gave the desired (carbamoylmethyl)phosphonic acid (IIa).

Neither carbamoyl phosphate analog has shown activity against Sarcoma 180 in Swiss mice.

(5) L. Zervas, *Naturwissenschaften*, **27**, 317 (1939).
(6) F. Lynen, *Ber.*, **73**, 367 (1940).
(7) A. E. Arbuzov and A. A. Dunin, *Ber.*, **60**, 291 (1927).
(8) G. M. Kosolapoff and J. S. Powell, *J. Am. Chem. Soc.*, **72**, 4198 (1950).
(9) P. Nylen, *Ber.*, **59**, 1119 (1926).
(10) This acid chloride could not be purified by distillation *in vacuo*. The distillable acid chloride obtained by P. Nylen[11] from the reaction of phosphonacetic acid and phosphorus pentachloride was shown to be the trichloride.
(11) P. Nylen, *Ber.*, **57**, 1023 (1924).

EXPERIMENTAL[12]

Dibenzyl diethylcarbamoyl phosphate. A solution of diethylcarbamoyl chloride (1.1 g., 7.8 mmoles) in 20 ml. of ether was added to silver dibenzyl phosphate[13] (3.3 g., 8.6 mmoles) in an atmosphere of nitrogen. The mixture was stirred with a Vibro-mixer for 3 hr. and then filtered to remove the silver salts. After evaporation of the ether *in vacuo*, the residue was heated to 80° at 8 mm. pressure to remove the last traces of unreacted diethylcarbamoyl chloride. The remaining brown oil, weighing 1.9 g. (53%), was used without further purification in the next step.

Spectral data. ν in cm.$^{-1}$ (film): 3060 (aromatic CH), 2995, 2905 (aliphatic CH); 1730 (C=O); 1640, 1505 (phenyl); 1460, 1440 (CH); 1290, 1270 (P → O); 1020, 980 (P—O—C); 740, 695 (monosubstituted benzene).

A second run yielded 5.2 g. (79%) from 6.6 g. of silver dibenzyl phosphate.

Magnesium salt of diethylcarbamoyl dihydrogen phosphate (Ia). A solution of crude dibenzyl diethylcarbamoyl phosphate (5.2 g., 14 mmoles) in 50 ml. of ethanol containing palladium catalyst on charcoal (1 g.) and magnesium oxide (0.5 g.) was shaken overnight with hydrogen in a steel bomb at 1000 p.s.i. The catalyst was removed by filtration and washed with ethanol. Two thirds of the solvent was evaporated under reduced pressure at room temperature. The addition of petroleum ether caused the precipitation of the magnesium salt, which was collected and dried *in vacuo* over phosphorus pentoxide at room temperature; yield, 2.3 g. (65%).

Spectral data. ν in cm.$^{-1}$ (KBr): 3430 (OH water); 2960 (aliphatic CH); 1660 (C=O); 1490 (CH); 1200–1070 (ionic phosphate); 980 (P—O—C).

Anal. Calcd. for $C_5H_{10}MgNO_5P.2^1/_2H_2O$: C, 22.75; H, 5.68; N, 5.30; P, 11.75. Found: C, 23.10; H, 5.99; N, 5.08; P, 11.15.

Drying at 60° *in vacuo* in an attempt to obtain anhydrous material resulted in decomposition of the molecule.

Diethyl (carbamoylmethyl)phosphonate (IIb). A mixture of 2-chloroacetamide (9.3 g., 0.1 mole) and triethyl phosphite (16.7 g., 0.1 mole) was heated at 145° for 2 hr. Unreacted 2-chloroacetamide (2 g.) was removed by vacuum distillation (1 mm.). The residue was dissolved in benzene, and the resulting solution was treated with decolorizing carbon, filtered, and then concentrated *in vacuo*. The crystalline product was removed by filtration and dried; yield, 17.4 g. (63.5%).

The analytical sample was obtained by recrystallization of the crude material once from ethyl acetate and twice from benzene (with charcoal treatment). The white crystals so obtained melted at 78–79° (lit.,[11] 78–80°). After completion of this work a recent publication has been brought to our attention [A. J. Speziale and R. C. Freeman, *J. Org. Chem.*, **23**, 1883 (1958)] describing the preparation of this compound by essentially the same procedure.

Spectral data. ν in cm.$^{-1}$ (KBr): 3360, 3160 (NH); 2972, 2915 (aliphatic CH); 1660 (amide C=O); 1625 (amide

(12) Melting points were determined on a Kofler Heizbank.
(13) Prepared by the method of Atherton *et al.*[14] except that the intermediate dibenzyl hydrogen phosphate was isolated pure.
(14) F. R. Atherton, H. T. Openshaw, and A. R. Todd, *J. Chem. Soc.*, 382 (1945).

NH); 1485, 1433, and 1378 (CH); 1240 (P → O); 1164, 1024, 975 (P—O—C).

Anal. Calcd. for $C_6H_{14}NO_4P$: N, 7.18. Found: N, 7.30.

Attempted selective hydrolysis of this compound to (carbamoylmethyl)phosphonic acid resulted in complete hydrolysis to phosphonacetic acid.

Diisopropyl (methoxycarbonylmethyl)phosphonate. Methyl bromoacetate (153 g., 1 mole) was added dropwise to hot triisopropyl phosphite (200 g., 1 mole) at a rate which maintained boiling. Distillation of the resulting solution gave a fraction boiling between 88° and 94° at 0.08–0.4 mm. This colorless liquid was redistilled, and the fraction boiling at 93–96°/0.09 mm. was collected and analyzed; yield, 172 g. (72%).

Spectral data. ν in cm.$^{-1}$ (film): 2980 (aliphatic CH); 1740 (ester C=O); 1445, 1395, 1385 (CH); 1280 (P → O); 1180, 1110, 985 (P—O—C).

Anal. Calcd. for $C_9H_{19}O_5P$: C, 45.38; H, 8.04; P, 13.01. Found: C, 45.78; H, 8.75; P, 12.58.

Phosphonacetic acid. Diisopropyl (methoxycarbonylmethyl)phosphonate (72 g., 0.3 mole) was heated with concentrated hydrochloric acid (300 ml.) on a water bath for 4 hr. A portion of the hydrochloric acid (150 ml.) was removed by distillation at atmospheric pressure, and the remainder was removed under reduced pressure. Distillation with benzene removed the last traces of water azeotropically. Evaporation of the benzene gave an oil which crystallized on standing overnight in a desiccator over phosphorus pentoxide and potassium hydroxide. Recrystallization from acetic acid gave 33.2 g. (79%) of the free acid, m.p. 143° (lit.[8] m.p. 142–143°).

Spectral data. ν in cm.$^{-1}$ (KBr): 2900 (acidic hydrogen); 2300 (shoulder, P—OH); 1705 (acid C=O); 1410 (CH); 1125 (P → O, hydrogen bonded).

Anal. Calcd. for $C_2H_5O_5P$: C, 17.16; H, 3.60; P, 22.13. Found: C, 17.43; H, 3.43; P, 21.78.

Dibenzyl (carbamoylmethyl)phosphonate (IId). Molten sodium (2.3 g., 0.1 mole) was shaken with a Vibro-mixer in boiling toluene (50 ml.), and the fine dispersion was allowed to cool with shaking to give powdered sodium. The toluene was decanted and replaced with ether (200 ml.). Absolute ethanol (4.6 g., 0.1 mole) was added and the suspension was refluxed until all the sodium had disappeared (8 hr.). A solution of dibenzyl phosphite (26.3 g., 0.1 mole) in 50 ml. of ether was added dropwise in an atmosphere of nitrogen to give a clear solution of sodium dibenzyl phosphite. This solution was added dropwise to a suspension of 2-chloroacetamide (9.3 g., 0.1 mole) in ether with stirring and cooling. After the addition was completed, the mixture was heated under reflux for 1 hr. The ether was decanted from the gummy precipitate which had formed, and was washed with water (3 × 100 ml.), dried over magnesium sulfate, and evaporated under reduced pressure. The residue (3.6 g.) from the ether evaporation crystallized when the walls of the vessel containing it were scratched. Recrystallization of a sample of this material from water gave long, colorless needles, m.p. 93°.

The gummy residue from the ether decantation was dissolved in benzene and washed with water (3 × 100 ml.) to remove sodium chloride. Evaporation of the benzene solution, which had been dried over magnesium sulfate, gave a residue (5.8 g.) which crystallized when scratched. After recrystallization from water, the product melted at 93–94°; total yield, 9.4 g. (29%).

Spectral data. ν in cm.$^{-1}$ (KBr): 3360, 3180 (NH); 3050 (aromatic CH); 2980, 2905 (aliphatic CH); 1665 (amide C=O); 1645 (amide); 1505 (phenyl); 1430, 1410, 1390 (CH); 1240 (P → O); 1005, 980 (P—O—C); 750, 700 (monosubstituted benzene).

Anal. Calcd. for $C_{16}H_{18}NO_4P$: C, 60.19; H, 5.68; N, 4.39; P, 9.70. Found: C, 60.67; H, 5.46; N, 4.32; P, 9.75.

(Carbamoylmethyl)phosphonic acid (IIa) (*A*). *Free acid.* A solution of dibenzyl (carbamoylmethyl)phosphonate (1 g., 3 mmoles) in 25 ml. of absolute ethanol was hydrogenated in the presence of 5% palladium-on-charcoal catalyst (0.5 g.). Hydrogen uptake stopped after 165 ml. had been consumed (calculated 155 ml.). The catalyst was removed by filtration and washed with ethanol. The residue from the evaporation of the combined filtrate and washings was recrystallized from methanol; yield of white needles, 0.3 g. (68%); m.p. 171°.

Spectral data. ν in cm.$^{-1}$ (KBr): 3375, 3220 (NH); 2400–2300 (P—OH); 1675 (amide C=O); 1605 (amide NH); 1460, 1405 (CH); 1170 (P → O, hydrogen bonded).

Anal. Calcd. for $C_2H_6NO_4P$: C, 17.27; H, 4.35; N, 10.08; P, 22.28. Found: C, 17.58; H, 4.42; N, 10.22; P, 22.41.

B. Dilithium salt (IIc). Phosphonacetic acid (14 g., 0.1 mole) and 70 g. of thionyl chloride were mixed. Immediate evolution of hydrogen chloride occurred. When the evolution began to slow down, heat was applied. After completion of the reaction, excess thionyl chloride was removed under reduced pressure with the addition of several portions of benzene. The residue, a reddish yellow oil free of thionyl chloride odor, was dissolved in dry dioxane (180 ml.), and gaseous ammonia was bubbled through the solution for 1 hr. The yellow precipitate that formed was filtered off rapidly and extracted with hot glacial acetic acid. Most of the ammonium chloride remained undissolved, but a small amount crystallized from the acetic acid on cooling. It was removed by filtration, and the acetic acid was evaporated under reduced pressure. The remaining orange-colored oil was dissolved in 200 ml. of 5% hydrochloric acid. Neutralization with a saturated solution of lithium hydroxide, followed by the addition of an equal volume of ethanol, gave an almost white precipitate, which was collected by filtration and dried *in vacuo* over phosphorus pentoxide at 110°.

Spectral data. ν in cm.$^{-1}$ (KBr): 3200 (NH); 1660 (amide C=O); 1610 (amide NH); 1440, 1390 (CH); 1105, 1085 (ionic phosphonate); 1005 (P—C).

Anal. Calcd. for $C_2H_4Li_2NO_4P$: C, 15.92; H, 2.67; N, 9.29; P, 20.53. Found: C, 16.24; H, 3.02; N, 9.39; P, 20.36.

Acknowledgment. The authors are indebted to Mr. J. P. Holmquist and Mr. J. W. Murphy for most of the microanalytical results reported; to Dr. W. C. Coburn and Mr. W. A. Rose for the determination and interpretation of the infrared spectra; and to Virginia-Carolina Chemical Corp., Richmond, Va., for a gift of triisopropyl phosphite. Some of the microanalytical determinations were performed by the Galbraith Microanalytical Laboratories, Knoxville, Tenn.

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An Extension of the Woodward Rules Concerning Alkyl Substituents in Conjugated Aliphatic Systems

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It is known[1a,b] that alkyl substitution in α,β-unsaturated aldehydes and ketones affords ap-

(1) (a) R. B. Woodward, *J. Am. Chem. Soc.*, **63**, 1123 (1941); **64**, 76 (1942); (b) L. K. Evans and A. E. Gillam, *J. Chem. Soc.*, 815 (1941); 565 (1943).

TABLE I

RELATIONSHIPS BETWEEN WAVE LENGTH OF MAXIMAL ABSORPTION AND SUBSTITUTION IN α,β-UNSATURATED ALDEHYDES AND KETONES

Compound	In Ethanol		In Cyclohexane	
	λ_{max}, mμ	Displacement on replacement of β-hydrogen atom by methyl, mμ	λ_{max}, mμ	Displacement on replacement of β-hydrogen atom by methyl, mμ
CH_2=CH·CHO	207		203	
CH_3·CH=CH·CHO	218	11	213	10
$(CH_3)_2$C=CH·CHO	235.5	17.5	228	15
CH_2=C(CH_3)·CHO	216		213	
CH_3·CH=C(CH_3)·CHO (Tiglaldehyde)	226	10	222.5	9.5
$(CH_3)_2$C=C(CH_3)·CHO	245	19	240	17.5
CH_2=CH·CO·CH_3	208.5		205	
CH_3·CH=CH·CO·CH_3	220	11.5	215	10
$(CH_3)_2$C=CH·CO·CH_3	236	16	231	16
CH_2=C(CH_3)·CO·CH_3	217.5		214.5	
CH_3·CH=C(CH_3)·CO·CH_3	228	10.5	223	8.5
$(CH_3)_2$C=C(CH_3)·CO·CH_3	245.5	17.5	238.5	15.5

TABLE II

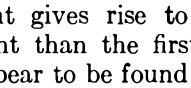
EFFECT OF TERMINAL METHYL GROUPS ON WAVE LENGTH OF MAXIMAL ABSORPTION IN CONJUGATED DIENES

Compound	In Ethanol		In Cyclohexane	
	λ_{max}, mμ	Displacement on replacement of hydrogen atom by methyl, mμ	λ_{max}, mμ	Displacement on replacement of hydrogen atom by methyl, mμ
CH_2=CH·CH=CH_2	217.5		218.5	
CH_3·CH=CH·CH=CH_2	223	5.5	224	5.5
$(CH_3)_2$C=CH·CH=CH_2	232.5	9.5	234	10
CH_3·CH=CH·CH=CH·CH_3	226	8 5/2	226.5	8/2
$(CH_3)_2$C=CH·CH=C(CH_3)$_2$	241	15/2	242	15.5/2

proximately constant, additive, displacements in the wave length of maximal absorption. A β-alkyl group gives a larger displacement than an α-alkyl group[1b] and for α,β-unsaturated ketones average figures of 12 and 10 mμ, respectively, have been quoted.[2]

We have recently examined the spectra of methyl substituted derivatives of acrolein and methyl-vinyl ketone and have observed that a second β-methyl substituent gives rise to a considerably larger displacement than the first (see Table I). Similar figures appear to be found for a number of cyclic α,β-unsaturated ketones. In alcohol, 1-acetyl-cyclopentene has λ_{max} 239 mμ, 1-acetyl-2-methyl-cyclopentene has λ_{max} 253 mμ,[3] a displacement of 14 mμ; 1-acetylcyclohexene has λ_{max} 232–233 mμ, 2-methyl-1-acetylcyclohexene has λ_{max} 249 mμ,[3] a displacement of 16–17 mμ. A related phenomenon is shown by the infrared carbonyl bands of the aldehydes. In carbon tetrachloride, acrolein shows a carbonyl band at 1704 cm.$^{-1}$, crotonaldehyde at 1696 cm.$^{-1}$,[4] and β-methylcrotonaldehyde at 1683 cm.$^{-1}$ [5]

Table II shows an analogous effect for conjugated dienes. It is of interest that an empirical correlation of maximal wave length for conjugated dienes with structure suggested the use of a parameter 0.13 for R and 0.17 for R′ in compounds with



an C= structure.[6]

The point arises whether the effect of the second group is caused by its occurrence as part of a gem-dimethyl group, or whether it is caused by the second group usually taking up a position *cis* to the carbonyl or second vinyl group. This question is being investigated. Frequently the *cis*-isomer would be anticipated to absorb at shorter wave length because of steric interactions.[7] However,

(2) L. F. Fieser and M. Fieser, *Natural Products Related to Phenanthrene*, Reinhold Publishing Corp., New York, 1949, p. 192.

(3) W. M. Schubert and W. A. Sweeney, *J. Am. Chem. Soc.*, **77**, 2297 (1955).

(4) D. Cook, *J. Am. Chem. Soc.*, **80**, 49 (1958).

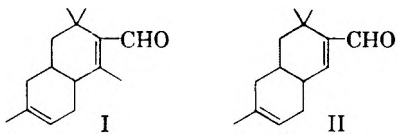
(5) C. J. Timmons, private communication.

(6) K. Hirayama, *J. Am. Chem. Soc.*, **77**, 373 (1955).

(7) W. F. Forbes and W. A. Mueller, *Can. J. Chem.*, **35**, 488 (1957).

there is evidence that sometimes the *cis*-isomer absorbs at *longer* wave length in spite of steric interactions. For example, in ethanol, angelic acid has λ_{max} 215.5 mμ, whereas tiglic acid has λ_{max} 212.5 mμ.[8] In *n*-heptane, *cis*-piperylene has λ_{max} 226 mμ, whereas *trans*-piperylene has λ_{max} 223 mμ, and the same order is found in the vapor phase.[9]

In contrast to our observations, the wave length displacement between compounds I and II is only



I II

5 mμ,[10] and the displacement between 1-vinylcyclohexene (λ_{max} 230 mμ) and 2-methyl-1-vinylcyclohexene (λ_{max} 233 mμ) is only 3 mμ.[11] In the former set of data, the structures have, however, been assigned only tentatively, and both sets of data are not recent. We, therefore, consider it probable that some of these spectral data are in error.

EXPERIMENTAL

Spectra were determined by standard methods on a Unicam SP 500 or Beckman DU spectrophotometer. The purification of the compounds, the absorption intensity values, and the spectral curves will be described separately in a fuller discussion of the relevant compounds.

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(8) A. S. Dreiding and R. J. Pratt, *J. Am. Chem. Soc.*, **76**, 1902 (1954).

(9) L. E. Jacobs and J. R. Platt, *J. Chem. Phys.*, **16**, 1137 (1948); American Petroleum Institute Research Project 44. Ultraviolet Spectral Data. Contributions from Shell Laboratory, Nos. 46, 48.

(10) J. W. Batty, I. M. Heilbron, and W. E. Jones, *J. Chem. Soc.*, 1556 (1939).

(11) H. Booker, L. K. Evans, and A. E. Gillam, *J. Chem. Soc.*, 1453 (1940).

Near Infrared Studies. Rate Constants for the Alcohol/Aryl Isocyanate Reaction

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In the near infrared spectrum (14,300–4000 cm.$^{-1}$) are found the overtone and combination frequencies of the OH, NH, CH, and SH fundamental stretching vibration. In a recent paper, we have shown that this region can be used to reveal the presence of an intramolecular hydrogen bond in aryl allophanates and biurets.[1] Similarly, the kinetics of the alcohol/isocyanate reaction can be studied by using the near infrared spectrum to follow the course of the reaction.

Davis and McC. Farnum[2] were the first to study the relative reactivity of phenyl isocyanate with lower aliphatic alcohols. The kinetics of the tertiary amine catalyzed reaction of aromatic monoisocyanates with methanol were studied by Baker and Holdsworth.[3] They showed that the reaction of an alcohol with phenyl isocyanate follows second order kinetics. Baker and Gaunt[4] studied both the base-catalyzed and uncatalyzed reactions of phenyl isocyanate with lower alcohols in di-*n*-butyl ether and in benzene and have obtained kinetic evidence for the mechanism of this reaction.

EXPERIMENTAL

Materials. Every effort was made to exclude water from the solvent and reactants in order to keep hydrolysis to a minimum. Ethyl alcohol was dried by the method of Fieser.[5] Eastman Kodak phenyl, *p*-tolyl, and *o*-tolyl isocyanate and Du Pont toluene-2,4-diisocyanate and toluene-2,6-diisocyanate were carefully redistilled into preflamed 10-ml. glass ampoules and sealed under dry nitrogen. A reagent grade of carbon tetrachloride was used without further purification. Triethylamine was purified by distillation over lithium aluminum hydride into ampoules and sealed under dry nitrogen.

Spectrophotometric method. The intense absorption of near infrared radiation at a wave length of approximately 6750 cm.$^{-1}$ caused by the NH group of a carbanilate provides an excellent method for following the rate of reaction between ethyl alcohol and an aryl isocyanate. The rate of increase of carbanilate formed from the alcohol/isocyanate reaction was noted by the increase in absorption at 6750 cm.$^{-1}$ at regularly timed intervals. Measurements were made in a 10.0-cm. quartz cell using the Cary Spectrophotometer model No. 14. The instrument was provided with a thermostatically controlled cell holder and was held at 28 ± 0.2°.

The concentration of carbanilate at time t was determined from the absorption log I_0/I by the Beer-Lambert formula where log I_0/I is the intensity of absorption, L is the length of the cell in centimeters, c is the concentration of carbanilate in moles per liter, and e is the molar absorptivity.

$$\text{Log } I_0/I = eLc \qquad (1)$$

The molar absorptivity for ethyl carbanilate (I), ethyl-4-methylcarbanilate (II), ethyl-2-methylcarbanilate (III), ethyl-3-isocyanato-4-methylcarbanilate (IV), and ethyl-3-isocyanato-2-methylcarbanilate (V) was obtained from the slope of the straight line by plotting log I_0/I against concentration of carbanilate. A typical plot is shown in Fig. 1. The strong polar effect of ethyl alcohol upon the absorption of radiation by the NH group and, therefore, upon the molar absorptivity for the carbanilates was taken into consideration in the following manner. A sufficient quantity of ethyl alcohol was present in each solution of carbon tetrachloride and carbanilate (representing a point on the straight

(1) I. C. Kogon, *J. Am. Chem. Soc.*, **79**, 2253 (1957).

(2) T. L. Davis and J. McC. Farnum, *J. Am. Chem. Soc.*, **56**, 883 (1934).

(3) J. W. Baker and J. B. Holdsworth, *J. Chem. Soc.*, 714 (1947).

(4) J. W. Baker and J. Gaunt, *J. Chem. Soc.*, 9, 14, 24, 27 (1949).

(5) L. Fieser, *Experiments in Organic Chemistry*, D. C. Heath and Co., New York, 1941, p. 358.

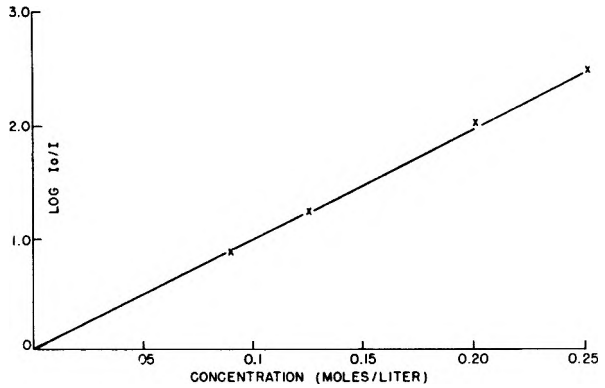


Fig. 1. Plot of log I_0/I *vs.* the concn. of ethyl carbanilate in CCl_4 and ethyl alcohol at 28 ± 0.2°

line) to maintain a total molarity of 0.250. The values of e were found to be 0.985, 1.116, 0.820, 1.109, and 0.809 for I–V, respectively.

The rate constants were calculated from the customary second order rate expression (2 and 3) for equal and unequal reactant concentrations, where a is equal to the initial concentration of ethyl alcohol, b is equal to the initial concentration of isocyanate, and x is the concentration of carbanilate at time t.

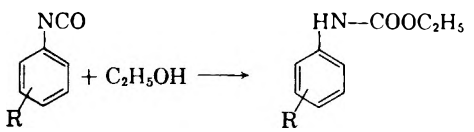
$$k = 1/t \frac{x}{b(b - x)} \quad (2)$$

$$k = 1/t \frac{2.303}{a - b} \log \frac{b(a - x)}{a(b - x)} \quad (3)$$

The second order rate constants are listed in Table I and Table II and Figs. 2, 3, and 4.

TABLE I

RATE CONSTANTS FOR THE BASE CATALYZED REACTION OF AN AROMATIC ISOCYANATE WITH ETHYL ALCOHOL IN CARBON TETRACHLORIDE AT 28 ± 0.2°



No.	R	$(C_2H_5)_3N$ × 10^2 Moles/ Liter	K × 10^4 Liter, $Mole^{-1}$ $Sec.^{-1}$	Relative Reactivity
1	H	7.2	43.30	1.0
2	p-CH_3	7.2	18.42	0.47
3	o-CH_3	7.2	5.16	0.118

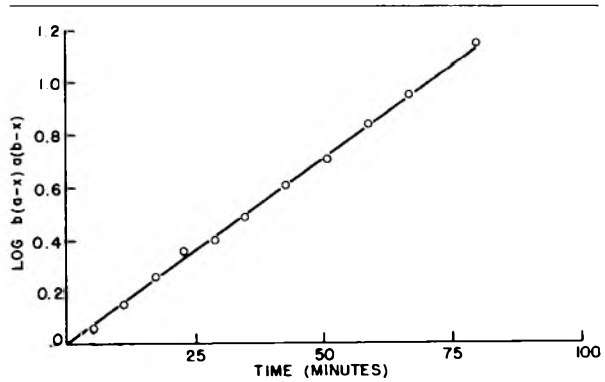
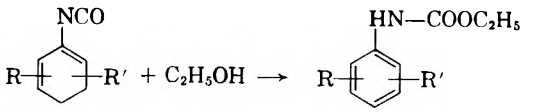


Fig. 2. Second order rate plot for phenyl isocyanate with ethyl alcohol in CCl_4 catalyzed by triethylamine at 28 ± 0.2°.

TABLE II

RATE CONSTANTS FOR THE UNCATALYZED REACTION OF AROMATIC ISOCYANATES WITH ETHYL ALCOHOL IN CARBON TETRACHLORIDE AT 28 ± 0.2°



No.	R	R′	K × 10^4 Liter, $Mole^{-1}$ $Sec.^{-1}$	Relative Reactivity
1	H	H	2.50	1.0
2	2-CH_3	5-NCO	10.70	4.0
3	2-CH_3	3-NCO	2.46	0.98

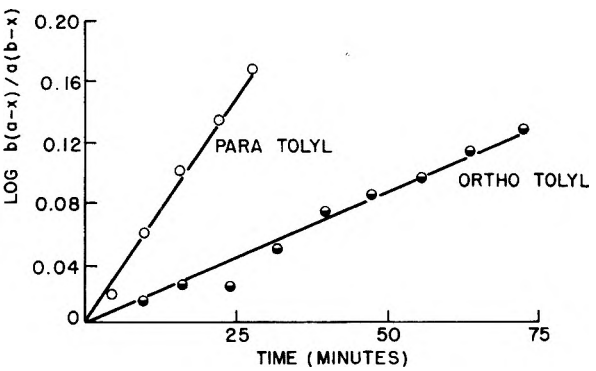


Fig. 3. Second order rate plot for *o*- and *p*-tolylisocyanate with ethyl alcohol in CCl_4 catalyzed with triethylamine at 28 ± 0.2°.

The second order plot for the triethylamine catalyzed reaction of phenyl, *p*-tolyl, and *o*-tolyl isocyanate was good up to 70–96% completion of the reaction, *e.g.*, Fig. 2. The second order plot for the uncatalyzed reaction of toluene-2,4-diisocyanate with ethyl alcohol resulted in a straight line up to approximately 60% of reaction. Several workers[6,7] have shown that the two isocyanato groups of toluene-2,4-diisocyanate differ in reactivity by a factor of ten. Isolation studies by Arnold and Simons[8] have unequivocally shown that the 4-isocyanato group of toluene-2,4-diisocyanate reacts faster toward aniline than the 2-isocyanato group. Therefore we have assumed that the 2-isocyanato group does not react in sufficiently high rate to interfere with our calculations for obtaining a rate constant for the 4-isocyanato group.

On the other hand the two isocyanato groups of toluene-2,6-diisocyanate are equivalent in reactivity and this was taken into consideration in the calculation of the rate constant. A linear rate plot was obtained only up to 30% of reaction. This is due to the fact that ethyl-3-isocyanato-2-methyl carbanilate is five times less reactive than toluene-2,6-diisocyanate.[9]

(6) M. Morton and M. A. Deisy, presented before the Division of Paints and Plastics at the 130th national meeting of the American Chemical Society, Atlantic City, N. J., September 1956.

(7) J. J. Tazuma and H. K. Latourette, presented before the Division of Paints and Plastics at the 130th national meeting of the American Chemical Society, Atlantic City, N. J., September 1956.

(8) R. G. Arnold and D. M. Simons, *J. Am. Chem. Soc.*, **78**, 1658 (1956).

(9) M. E. Bailey, V. Kirss, and R. G. Spaunburgh, *Ind. Eng. Chem.*, **48**, 794 (1956).

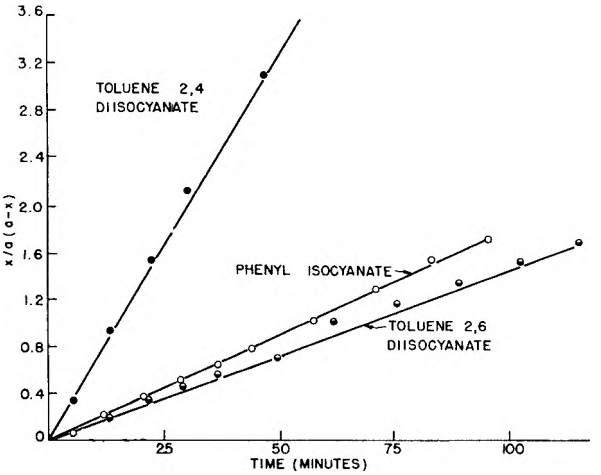


Fig. 4. Second order rate plot for phenyl isocyanate, toluene-2,4, and 2,6-diisocyanate with ethyl alcohol in CCl_4 at 28 ± 0.2°.

Solutions. For a kinetic run involving triethylamine as the catalyst (*a*) 100 ml. of 0.5 molar absolute ethyl alcohol and 0.072 molar triethylamine in carbon tetrachloride and (*b*) 100 ml. of 0.250 molar of phenyl, *o*-, or *p*-tolyl isocyanate in carbon tetrachloride were prepared at 28 ± 0.2°. For an uncatalyzed run (*c*) 100 ml. of 0.250 molar absolute ethyl alcohol in carbon tetrachloride and (*d*) 100 ml. of 0.250 molar toluene-2,4- or 2,6-diisocyanate or phenyl isocyanate in carbon tetrachloride were made up at 28 ± 0.2°.

For a typical kinetic measurement 50 ml. of solution (*a*) or (*c*) and 50 ml. of (*b*) or (*d*) were mixed at 28° and this mixture used to fill a 10.0-cm. quartz cell. The time at which the two solutions were mixed was taken as t_0.

DISCUSSION

The order of reactivity of the second order rate constants for the triethylamine-catalyzed reaction of phenyl, *p*-tolyl, and *o*-tolylisocyanate with ethyl alcohol is 1.0:0.47:0.118 (Table I). Thus the presence of a methyl group para or ortho to an isocyanato group, decreases the rate to one half and one eighth, respectively, of the value obtained for the unsubstituted phenyl isocyanate.

The deactivating influence of a methyl group upon an isocyanato group is also revealed by the results in Table II. The second order rate constant for the first isocyanato group of toluene-2,6-diisocyanate is less than the second order rate constant for the 4-isocyanato group of toluene-2,4-diisocyanate by a factor of approximately 4.8.

The influence of an isocyanato group meta to another was not measured directly, but its effect can be deduced from the rate constant data in Tables I and II, assuming that triethylamine has the same accelerating effect on each of the alcohol/-aryl isocyanate reactions. The electron releasing methyl group para to an isocyanato group (*e.g.*, *p*-tolylisocyanate) decreases the rate of reaction by a factor of approximately 2 (Table I, Nos. 1 and 2). The introduction of an isocyanato group into the 2-position of 4-isocyanato-toluene (to give toluene-2,4-diisocyanate) leads to a fourfold increase in the rate of reaction of the 4-isocyanato group when compared to phenyl isocyanate (Table II, Nos. 1 and 2). Therefore, the electron activating effect of a meta-isocyanato group (toluene-2,4-diisocyanate *vs.* *p*-tolylisocyanate) increases the rate of reaction of an isocyanato group (para NCO) with ethyl alcohol by a factor of 8. The same results are obtained when the relative reactivity of *o*-tolylisocyanate and toluene-2,6-diisocyanate are compared (Table I, Nos. 1 and 3 and Table II, Nos. 1 and 3). Recently, Burkus and Eckert obtained a factor of 7 for the electron activating affect of a meta-isocyanato group.[10]

CONTRIBUTION NO. 246
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(10) J. Burkus and C. F. Eckert, presented before the Division of Paints and Plastics at the 132nd national meeting of the American Chemical Society, New York City, New York, September 1956.

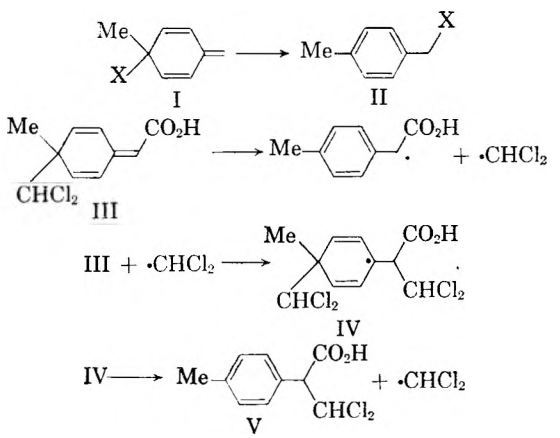
Communications TO THE EDITOR

The Mechanism of the von Auwers Rearrangement of Derivatives of 4-Methyl-4-polyhalomethyl-1-methylenecyclohexa-2,5-diene

Sir:

The rearrangement of the "semibenzenes" I (X = $CHCl_2$ or CCl_3) and their derivatives to the aromatic isomers II, discovered by von Auwers,[1] has tentatively been assigned an ionic mechanism.[2] We now present evidence to show that, at least in the case of the acid[3] III, the rearrangement involves a free-radical chain reaction.

The kinetics of the rearrangement of III to V have been measured spectrophotometrically in 20% (v/v) aqueous ethanol. The reaction exhibits a temperature-dependent induction period, and then obeys first order kinetics. From the change in length of the induction period with temperature between 130° and 152° an activation energy can be calculated for the initiation reaction of about 40 kcal./mole, which is of the expected order of magnitude.[4] Addition of benzoyl peroxide reduces the induction period without affecting the subsequent reaction. The rearrangement is inhibited by duroquinone. Ultraviolet irradiation of a solution of the triene III in petroleum ether yields the rearranged acid V even at room temperature.



We conclude that the rearrangement proceeds by a reaction in which the chain-carrier is the dichloromethyl radical. Other 4-halomethylsemibenzenes (I; X = CCl_3, $CHBr_2$, or CBr_3) appear to isomerize by an analogous process. The postulated intermediate radical IV is interesting, since it has the same electronic structure as the intermediate in radical aromatic substitution.

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(1) K. v. Auwers and G. Keil, *Ber.*, **36**, 1861 (1903); K. v. Auwers and W. Jülicher, *Ber.*, **55**, 2167 (1922), and earlier papers.

(2) R. L. Tse and M. S. Newman, *J. Org. Chem.*, **21**, 638 (1956).

(3) K. v. Auwers, *Ber.*, 44, 588 (1911).

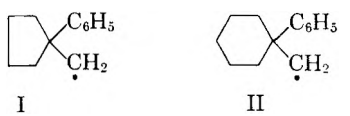
(4) C. Walling, *Free Radicals in Solution*, John Wiley and Sons, Inc., New York, 1957, Chap. 2; W. A. Roth, *Z. Elektrochem.*, **16**, 658 (1910).

The Effect of Incorporated Cycloalkyl Rings upon the Rearrangement of Neophyl-like Radicals

Sir:

The generation of carbon radicals in solution in order to study their possible rearrangement is perhaps best achieved by the di-*t*-butyl peroxide-induced decarbonylation of the appropriate aldehydes.[1]

Using this technique, we have investigated the rearrangement ability of some neophyl-like[2] radicals possessing incorporated cycloalkyl ring structures (I and II below).



The results indicate that the size of the ring present in such a radical affects its rearrangement ability appreciably. Little information on such a point seemed available heretofore.[3]

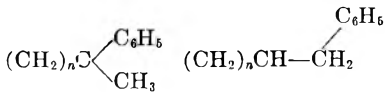
1-Phenylcyclopentylacetaldehyde (III, b.p. 106° at 1 mm., $n_D^{20.5}$ 1.5352, d_4^{20} 1.065, *Anal.*, Calcd. for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 82.69; H, 8.37. 2,4-DNP m.p. 132–133°, *Anal.*, Calcd. for $C_{19}H_{20}N_4O_4$: N, 15.21. Found: N, 15.25) and 1-phenylcyclohexylacetaldehyde (IV, b.p. 112° at 0.5 mm., n_D^{20} 1.5395, d_4^{20} 1.080, *Anal.*, Calcd. for

(1) Among others, S. Winstein and F. H. Seubold, Jr., *J. Am. Chem. Soc.*, **69**, 2916 (1947); W. H. Urry and N. Nicolaides, *J. Am. Chem. Soc.*, **74**, 5163 (1952); D. Y. Curtin and M. J. Hurwitz, *J. Am. Chem. Soc.*, **74**, 5381 (1952); and F. H. Seubold, Jr., *J. Am. Chem. Soc.*, **75**, 2532 (1953).

(2) The neophyl radical itself is $C_6H_5C(CH_3)_2\dot{C}H_2$.

(3) M. A. Muhs, dissertation (University of Washington, 1954), quoted in H. Breederveld and E. C. Kooyman, *Rec. trav. chim.*, **76**, 305 (1957), has noted *no* rearrangement in radicals analogous to I and II with a methyl group in place of the phenyl group. Thus far alkyl groups have never been observed to rearrange in decarbonylation reactions.

$C_{14}H_{18}O$: C, 83.14; H, 8.95. Found: C, 82.95; H, 9.09. 2,4-DNP m.p. 163–164°, *Anal.*, Calcd. for $C_{20}H_{22}N_4O_4$: N, 14.65. Found: N, 14.53) have been prepared[4] and decarbonylated with di-*t*-butyl peroxide (10–20 mole %) to mixtures of the hydrocarbons V and VI in yields of 64–74% (n = 4)



V n = 4,5 VI

and 21–47% (n = 5). The conditions used and the rearrangement percentages obtained (infrared analysis by comparison with known mixtures of authentic V and VI) are shown in Table I.

TABLE I

Acetaldehyde	Rearrangement (%)[5] at Various Temperatures (Bath, °C) 140°[a]	190°[a]	132°[b]	160°[c]
1-Phenylcyclopentyl (III)	63	71	92	<3
1-Phenylcyclohexyl (IV)	89	91	94	50

[a] Pure aldehyde. [b] Aldehyde 1*M* in chlorobenzene. [c] Benzyl mercaptan (20 mole %) present.

The decarbonylation of β-phenylisovaleraldehyde to mixtures of iso- and *t*-butylbenzene has been previously reported to give the following rearrangement percentages: 57 (130°, 150°)[5,6]; 63 (170°)[5,6]; ~80 (130°, aldehyde 1*M* in chlorobenzene)[6]; and "the amount of rearrangement . . . decreases as benzyl mercaptan is added."[7] It is apparent from Table I that the cyclopentyl ring in I is somewhat comparable to the *gem*-dimethyl function in the neophyl radical[2] in its effect upon this radical rearrangement, while the cyclohexyl ring in II increases the amount of rearrangement significantly.

At some initial aldehyde concentration, two factors determine the amount of rearrangement of a neophyl-like radical: the *half-life* of the radical (a measure of its stability); and the *chain transfer ability* of the parent aldehyde (a measure of the ease of aldehydic hydrogen atom abstraction by chain-carrying radicals). Scale models[8] of the radicals I and II indicate that serious steric hindrance to benzene ring rotation about the cycloalkyl ring-phenyl bond is present in the cyclopentyl case and absent in the cyclohexyl case. Such additional rotational freedom in II should increase its half-life (stability) relative to I and thereby allow II more time to rearrange. This restricted rotation in I hinders maximum overlap of the carbinyl carbon p (or sp^3) orbital (possessing the unpaired electron) with the π-molecular orbital of the benzene ring. Since such overlap is considered to be a prerequisite for the ready migration of the phenyl group,[9] this hindrance should slow the rearrangement process in the cyclopentyl instance.[10] On the other hand, qualitative rate data show that under comparable conditions III is decarbonylated two to four times faster than is IV and to an extent nearly twice that of IV. Such data can be accommodated if III has the more easily abstracted aldehydic hydrogen atom (greater chain transfer ability).[11] Confirmation of this point may be found in the apparently greater chain length process with III. Here 10 mole % of di-*t*-butyl peroxide suffices for nearly complete decarbonylation, while 20 mole % peroxide is needed for half-complete decarbonylation in IV.

These results will be presented soon in detail. The rearrangement ability of neophyl-like radicals with other incorporated cycloalkyl rings is also under investigation in this laboratory.

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(4) The appropriate 2-phenylcycloalkanone was substituted at C-2 with allyl chloride using sodium amide. Huang-Minlon reduction to the hydrocarbon, followed by performic acid hydroxylation of the allylic double bond and subsequent cleavage of the vic-glycol with lead tetraacetate afforded the appropriate aldehyde.

(5) The results are ±3%.

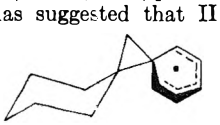
(6) F. H. Seubold, Jr., *loc. cit.*

(7) S. Lapporte, unpublished work mentioned by S. Winstein *et al.*, *Experientia*, 12, 138 (1956).

(8) Fisher-Taylor-Hirschfelder models were used with the carbinyl carbon (radical) portion *either* trigonal planar (sp^2) *or* tetrahedral (sp^3), and, in II, with the phenyl group equatorial on a chair-form cyclohexane ring.

(9) J. Hine, *Physical Organic Chemistry*, McGraw-Hill Book Co., New York, N. Y., 1956, p. 448.

(10) A referee has suggested that II may be *bridged*,



thereby allowing relief from the steric strain due to the axial —CH_2·, and accommodating the apparent insensitivity of the rearrangement to concentration. While extensive discussion will properly be reserved until later, we feel that the decreased rearrangement in the presence of mercaptan argues against such a bridged structure.

(11) Concerning this point, the above referee has pointed out that the axial conformation of the —CH_2CHO in IV renders its aldehydic hydrogen relatively inaccessible.

Glucosides of Vanillic and Syringic Acids in Deciduous Woods

Sir:

During the course of our investigations on the extractives of representative deciduous woods it was found that the 75% *n*-propyl alcohol extractives of each of 46 different species tested yielded vanillin, syringaldehyde, vanillic acid, and syringic acid upon alkaline hydrolysis.[1] Because of the proven presence of coniferaldehyde and sinapaldehyde in the extractives of these woods and because of the known formation of vanillin and syringaldehyde from these two cinnamaldehydes in alkaline solution by a reverse "aldol" mechanism, it was suggested that such a mechanism was responsible for vanillin and syringaldehyde in these alkaline hydrolysates. Further, it was suggested that because oxygenated three-carbon side chains in guaiacyl and syringyl model compounds are known to rearrange to "acyloin" configurations during isolation procedures and because many acyloins hydrolyze to the corresponding benzoic acids by boiling with alkali, an alkaline hydrolysis of "acyloin" side chains might be responsible for the presence of vanillic and syringic acids in the alkaline hydrolysates of the extractives of these deciduous woods.

We have recently subjected these same 75% *n*-propyl alcohol extractives to hydrolysis with 0.5*N* sulfuric acid and have analyzed the hydrolysates for sugars and for phenolic materials. Again, vanillin, syringaldehyde, vanillic acid, and syringic acid were found in the hydrolysates of all 46 hardwood extractives. The vanillin and syringaldehyde yields were approximately of the same order of magnitude as those found in the alkaline hydrolysates of the same extractives. However, the yields of vanillic and syringic acids were substantially greater in the case of the acid hydrolyses. In some instances, the increase was manifold. In all instances, the increase in vanillic and syringic acids was accompanied by an increase in glucose yield, and in those experiments that produced manifold increases in vanillic and syringic acid yield, the yield of glucose produced by acid hydrolysis was correspondingly great.

Although these recent data do not prove, they certainly do suggest that all deciduous woods contain as extractives glucosides of vanillic and syringic acids. Such phenolic glucosides would yield the free phenolic acids to a limited degree upon alkaline hydrolysis[2] but would be hydrolyzed completely by boiling with dilute sulfuric acid.

Detailed analytical results on all of the sugars and phenolic compounds obtained in the acid hydrolyses of the 46 representative hardwoods and their significance to taxonomy and to biosynthesis will be reported at a later date. Experiments are now under way on the isolation and identification of the above noted glucosides of vanillic and syringic acids from those extractives which appear to have them in largest quantity.

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(1) I. A. Pearl, D. L. Beyer, S. S. Lee, and D. Laskowski, *Tappi*, **42**, 61 (1959).

(2) C. E. Ballou, *Advances in Carbohydrate Chem.*, **9**, 59 (1954).

Organic Sulfur Compounds. I. Hydroperoxide Intermediates in the Co-oxidation of Mercaptans and Olefins

Sir:

Substituted hydroxyethyl sulfoxides were obtained by Kharasch and co-workers[1] by a co-oxidation reaction of mercaptans and olefins. They proposed two tentative chain mechanisms for the co-oxidation which involved the formation of peroxide intermediates. Recently Ford and co-workers[2] obtained 2-phenylmercapto-1-indanyl hydroperoxide by the co-oxidation of indene and benzenethiol at room temperature in 70% yield, although they did not isolate the product.

It was found, in these laboratories, that on introducing air into hydrocarbon solutions of aromatic mercaptans (benzenethiol, *p*-toluenethiol, 4-chlorobenzenethiol, 2-naphthalenethiol) and reactive olefins (styrene, α-methylstyrene, indene) at 0° or at lower temperatures, the peroxide intermediates of such co-oxidation reactions can be obtained. Intermediates of high hydroperoxide content separate as viscous liquids in the bottom of such solutions.

The new hydroperoxides containing sulfur usually rearrange at room temperature to the corresponding hydroxyethyl sulfoxides.

$$RSCH(R')C(R'')_2OOH \longrightarrow RS(O)CH(R')C(R'')_2OH$$

This rearrangement is accompanied by the loss of peroxide content, by a stronger absorption in the infrared at 3 microns (OH) and between 9–10 microns (SO), and by solidification where the hydroperoxides were liquid.

The co-oxidation product of 2-naphthalenethiol and indene, 2-(2-naphthylmercapto)-1-indanyl hydroperoxide, showed exceptional stability, m.p. 70° from benzene-*n*-heptane. (*Anal.* Calcd. for

(1) M. S. Kharasch, W. Nudenberg, and G. H. Mantell, *J. Org. Chem.*, **16**, 524 (1951).

(2) J. F. Ford, R. C. Pitkethly, and V. O. Young, *Tetrahedron*, **4**, 325 (1958).

$C_{19}H_{15}O_2S$· C, 73.99; H, 5.23; S, 10.40. Found C, 74.12; H, 5.43; S, 10.3. Peroxide content by the iodide method 98%.) The pure compound was stable up to 70°. In benzene solution at 40° it was found to rearrange giving mainly 2-(2-naphthylsulfinyl)-1-indanol, mp. 138.5–139.5° with decomposition. (*Anal.* Calcd. for $C_{19}H_{15}O_2S$: C, 73.99; H, 5.23; S, 10.40. Found C, 74.26; H, 5.48; S, 10.3.) Other hydroxysulfoxide isomers now under investigation were also obtained on rearrangement.

A typical member of the new hydroperoxides is 2-hydroperoxy-2-phenylpropyl 2-naphthyl sulfide. This is obtained by co-oxidation of 2-naphthalenethiol and α-methylstyrene. (m.p., 10° by the freezing curve method, peroxide content 85% by the iodide method). A benzene solution containing 0.3 mole/l. of this compound deposits 2.3 g./100 ml. sediment on standing 16 hr. at 40°. After recrystallization from benzene this sediment melts between 114 and 118°. (*Anal.* Calcd. for 2-hydroxy-2-phenylpropyl 2-naphthyl sulfoxide, $C_{19}H_{18}O_2S$: C, 73.52; H, 5.84; S, 10.3 Found: C, 72.80; H, 5.85; S, 10.2.)

It is proposed that the co-oxidation of olefins and mercaptans which results in the formation of hydroperoxide intermediates is largely responsible for the peroxidation and subsequent color, gum, and sediment formation in untreated petroleum distillates.

Details of work on the co-oxidation of mercaptans and olefins will be reported later.

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