THE JOURNAL OF Organic Chemistry

Volume 22

JANUARY–JUNE, 1957

(Pages 1–718)

EASTON, PENNSYLVANIA
MACK PRINTING CO.
1957

THE JOURNAL OF Organic Chemistry®

Volume 22, Number 1

~~March~~ January 5, 1957

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

Grignard Synthesis of 2-Phenyl-2-butanol in Optically Active Solvents

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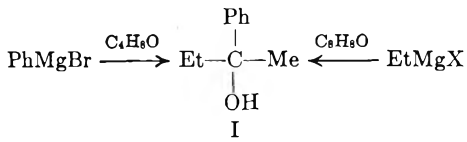
Received Aug. 3, 1956

1. The preparation of 2-phenyl-2-butanol in benzene and (+)2,3-dimethoxybutane from ethyl halides and acetophenone gives a degree of enantiomeric preponderance varying as Cl < I < Br. 2. The optical activity of 2-phenyl-2-butanol prepared in benzene and (+)2,3-dimethoxybutane from bromobenzene and 2-butanone is about 5 times that of the product from ethyl bromide and acetophenone. 3. The 2-phenyl-2-butanol prepared in benzene and hexamethyl mannitol or pentamethyl arabitol is obtained in yield lower than is the case with comparable reaction in dimethoxybutane. Also the optical rotation is opposite in sign. 4. The asymmetric resolution of 2,3-diphenylpropanoic acid from 1,2-diphenylchloroethane and phenylisocyanate is cited as an instance where bulkiness of the entering organic group tends to increase the optical activity of the product over that of smaller groups.

Although Cohen and Wright[1] performed a partial asymmetric synthesis by addition of ethyl chloride and bromide Grignard reagents to ethyl benzoylformate in a benzene and (+)2,3-dimethoxybutane medium, the example was unfavorable from the aspect of interpretation. Because of the presence of the carboethoxy group it was considered advisable to use "inverse" addition (of Grignard reagent into the ketoester), but even this limitation could not eliminate the possibility that the ester group partook of coordination in the system. In consequence, we have chosen another reaction which is simpler and more amenable to variations.

By choice of 2-phenyl-2-butanol as a product, the extent of asymmetric synthesis can be calculated easily because this tertiary alcohol has been resolved,[2] $[\alpha]_D^{22}$ +17.45°. Moreover the carbinol can be obtained by the alternative paths: ethyl halide Grignard reagents with acetophenone or bromobenzene Grignard reagent with 2-butanone. Finally, these Grignard reagents are preparable in the optically active ether-benzene media which we have chosen to use.



I

In addition to the (+)2,3-dimethoxybutane ($C_6H_{14}O_2$) described previously,[1] we have prepared and used three other optically active ethers. D(+)mannitol hexamethyl ether ($C_{12}H_{26}O_6$) has been prepared by a modification of the previous preparation[3] while D(−)arabitol pentamethyl ether, ($C_{10}H_{22}O_5$) has been prepared anew. Only the third (+)1-methoxy-2-methylbutane ($C_6H_{14}O$),[4,5] prepared from sodium 2-methylbutoxide and methyl *p*-toluenesulfonate, is ineffective for induction of optical activity into the product. This behavior conforms with the previous observation[1,6] that monoethers will not function in the asymmetric synthesis, and extends the observation to an ether in which both alkyl groups attached to oxygen in the ether are primary. The reactions which we have carried out in the various ethers are recorded in Table I.

Effect of variation in halogen. Table I shows that the specific activity of 2-phenyl-2-butanol prepared from ethyl Grignard reagents and acetophenone

(1) H. L. Cohen and G. F Wright, *J. Org. Chem.*, **18**, 432 (1953).

(2) H. H. Zeiss, *J. Am. Chem. Soc.*, **73**, 2391 (1952).

(3) W. Freudenberg and J. T. Sheehan, *J. Am. Chem. Soc.*, **62**, 558 (1940).

(4) Guye and Chavanne, *Bull. soc. chim.* [3] **15**, 301 (1896).

(5) H. G. Rule, E. B. Smith, and J. Harrower, *J. Chem. Soc.*, 376 (1933).

(6) D. S. Tarbell and M. C. Paulson, *J. Am. Chem. Soc.*, **64**, 2842 (1942).

TABLE I

REACTIONS PRODUCING 2-PHENYL-2-BUTANOL

Expt. No.	Halide	Ether	Grignard Yield, %	Ketone	2-Phenyl-2-butanol Yield, %	$[\alpha]_D$ at T	°C.
1	C_2H_5Br	$C_4H_{10}O$	91	C_8H_8O	85		
2	Same	$C_6H_{14}O_2$	76	Same	45	$+0.62 \pm 0.04$	21
3	Same	Same	80	Same	50	$+0.55 \pm 0.02$	25
4	Same	Same	[a]	Same	40	$+0.61 \pm 0.04$	24
5	Same	Same	79[b]	Same	54	$+0.51 \pm 0.02$	21
6	C_2H_5I	Same	—	Same	42	$+0.44 \pm 0.06$	21
7	Same	Same	—	Same	38	$+0.50 \pm 0.05$	26
8	C_2H_5Cl	Same	82	Same	58	$+0.08 \pm 0.05$	21
9	Same	Same	80	Same	61	$+0.09 \pm 0.01$	24
10	C_6H_5Br	Same	56	C_4H_8O	54[c]	$+3.04 \pm 0.06$	20
11	C_2H_5Br	$C_{12}H_{26}O_6$	50	C_8H_8O	17	-2.00 ± 0.14[d]	21
12	C_2H_5Cl	Same	66	Same	17	-0.42 ± 0.15[d]	21
13	C_6H_5Br	Same	47	C_4H_8O	11	-0.75 ± 0.10[d]	20
14	C_2H_5Br	$C_{15}H_{22}O_5$	33	C_8H_8O	14	-1.15 ± 0.07[d]	20
15	C_6H_5Br	Same	24	C_4H_8O	7[e]	$+0.4 \pm 0.4$[b]	20
16	Same	$C_6H_{14}O$	42	Same	55[f]	-0.02 ± 0.08	22

[a] Excess magnesium filtered off. [b] Molar equivalent of magnesium bromide added. [c] Yield calculated from rotations of crude and final products. [d] Minimum value of rotation calculated after dilution with inactive carbinol. [e] Yield calculated on the Grignard reagent basis. [f] Crude material.

(C_8H_8O) varies from a low of $(+)0.08 \pm 0.05°$ when ethyl chloride is used to a high value of $(+)0.62 \pm 0.04°$ from the ethyl bromide Grignard reagent, the medium being benzene plus one molar equivalent of (+)2,3-dimethoxybutane. However, this order is not directly related to the ordinary reactivity of alkyl halides since the phenylbutanol from ethyl iodide Grignard reagent shows $[\alpha]_D$ $(+)0.44 \pm 0.06$ which is intermediate between the optical activity of the product from the other two halides. However, it should be noted that the same order is found with respect to enolate formation, since about 10% of acetophenone is recovered from the systems involving ethyl bromide and iodide, but none is recovered from the system containing chloride. The duplicate experiments, 2 and 3, 6 and 7, 8 and 9, show that the results are reproducible. Moreover the same order of effectiveness is shown (experiments 11 and 12) when the medium is benzene containing one molar equivalent of mannitol hexamethyl ether. These results are contrary to those observed by Cohen and Wright[1] but the two studies may not be comparable. The present Grignard reagents (except those from methyl iodide) are homogeneous whereas the earlier ones consisted of two phases. Furthermore, inverse addition of reagent to the ketoester was employed by Cohen and Wright.

An explanation of these results cannot be expected on the basis of the limited data of these two studies. However, we suggest tentative consideration of the R_2Mg and $RMgX$–MgX_2 content of these systems. The amount of diethylmagnesium in a diethyl ether solution of ethyl chloride Grignard reagent has been reported as 42% in comparison with 29% of Et_2Mg in ethyl bromide Grignard reagent.[7,8] But diethylmagnesium seems not to coordinate appreciably, at least with diethyl ether.[9] In so far as diethylmagnesium would not coordinate with the optically active ether, but would coordinate with acetophenone, the 2-phenyl-2-butanol thus formed would be optically inactive.

The argument is weak in several aspects. The diethylmagnesium content of ethyl iodide Grignard reagent is about the same (29%) as that of the analogous bromide yet the optical rotation of the product from the iodide is about 70% of the phenylbutanol from the bromide. But this discrepancy is not serious in view of the quantitative unreliability of the precipitation analysis of the "Schlenk Equilibrium."[7] Likewise the significance of the diethylmagnesium content of these systems might seem to be vitiated by experiment 5, Table I, in which an equivalent of added magnesium bromide did not appreciably alter the optical rotation of the product. But, again, it has been shown that such attempts to shift the Schlenk equilibrium[10] are not quantitatively successful[11] and, indeed, very little of the magnesium bromide seemed to dissolve in the reagent of experiment 5, Table I. This is of interest although it is not necessarily surprising in view of the fact that the alkoxy group content of the system was only adequate on the 2ROR.1RMgX basis for the magnesium salts in solution before the introduc-

(7) M. S. Kharasch and O. Reinmuth, *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, New York (1954), p. 105.

(8) C. G. Swain and H. B. Boyles, *J. Am. Chem. Soc.*, **73**, 870 (1951).

(9) W. Schlenk, Jr., *Ber.*, **64**, 736 (1931).

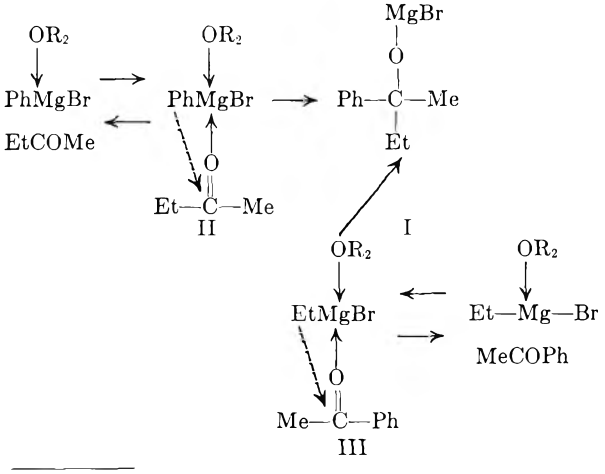
(10) W. Schlenk and W. Schlenk, Jr., *Ber.*, **62**, 920 (1929).

(11) C. R. Noller and D. C. Raney, *J. Am. Chem. Soc.*, **62**, 1749 (1940).

tion of additional magnesium bromide. In short, the argument concerning the significance of diethylmagnesium in these systems is not weak *per se* but only because of our ignorance of the constitutional nature of Grignard reagents. It is increasingly necessary that this situation, persisting for more than 50 years, be improved.

Effect of variation in organo group of the reagent. At any rate the R_2Mg content of the Grignard systems cannot account for the marked difference in asymmetric induction shown by experiments 3 and 10. Both experiments have been carried out identically in benzene-dimethoxybutane. Yet acetophenone added to ethyl bromide Grignard reagent yields 2-phenyl-2-butanol which is enantiomeric to the extent of 3.6% while the same carbinol (although in lower yield) from 2-butanone into bromobenzene Grignard reagent is 17.4% preponderant in one enantiomer. This is the most asymmetry yet induced by the influence of an optically active ether, and is of the same magnitude as was obtained by Mosher and LaCombe[12] by use of an optically active Grignard reagent. When one equivalent of the ether can induce as much activity as the Grignard reagent itself, it is obvious that the ether is of primary importance in the reaction.

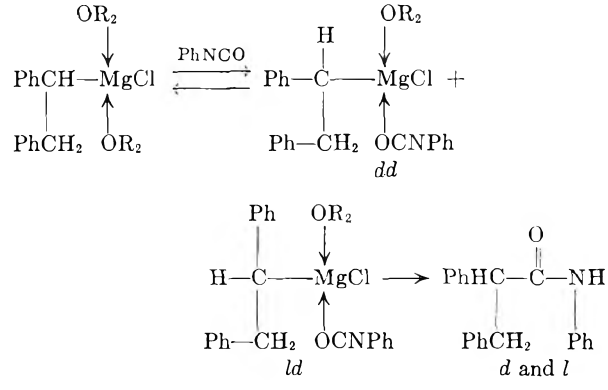
Therefore it is important to consider the possible ether-Grignard reagent-ketone complexes which would be involved in the reactions of experiments 2 and 10, which lead irreversibly to the same bromomagnesium *tert*-alkoxide, I. For simplicity the concepts of 6-atom quasicyclic transitory states (reference 7, p. 142) or of hexacovalent anions[13] are disregarded in favor of a 1:1:1 ether-magnesium-ketone complex. The complexes comprised of 2,3 or 4 monoether to 2 magnesium to 1 ketone which are described in references 7 and 13 probably do not contribute to the present problem and, at any rate, undoubtedly are only approximations to Grignard reagent structure, especially when colloidal agglomeration is possible.[13]



According to the formulation the difference in behavior of the 1:1:1 complexes, II and III, involves the steric preference depending on whether a phenyl or an ethyl group is undergoing transfer, but equally important are the mobile equilibria[1] among II, III, and their component parts. While either of the transitory diastereomers comprising II or III would react eventually to form the alkoxide I if they were formed irreversibly, the obvious reversibility of this transitory diastereomer formation will accentuate the tendency of either *dd* or *dl* II or III toward conversion to *d* or *l* I because of the difference in activation energy of the system *dd* II (or III) → *d* I *versus* *dl* II (or III) → *l* I.

One is tempted to attribute these steric preferences to bulkiness of the transferring group, admittedly upon the questionable assumption that migration is occurring in an otherwise rigid constellation of atoms. One cannot expect that this simple concept will be rigorously applicable. Nevertheless, we find that in a related instance of asymmetric resolution (in which the transition state must resemble that postulated for asymmetric synthesis), there is a trend toward higher optical activity as the bulk of the organic group becomes greater.

Previously it has been shown[1] that 2-methylbutanoic acid was 1.6% enantiomeric when it was prepared *via* 2-chlorobutane Grignard reagent and phenyl isocyanate in benzene-(+)2,3-dimethoxybutane. Under the same circumstances 1-chloro-1-phenylethane yielded 2-phenylpropanoic acid which was 2.6% enantiomeric. Now we have treated the Grignard reagent from 1,2-diphenylchloroethane [in benzene and (+)dimethoxybutane] with phenyl isocyanate.



The pure 2,3-diphenylpropanoic acid derived from the anilide has specific rotation $[\alpha]_D^{25}$ (+)3.16 ± 0.10°. Since the rotation of the pure enantiomer[14] is $[\alpha]_D^{20}$ (+)94° our reaction product is about 3.4% enantiomeric. In this series the extent of enantiomeric preponderance in the product seems to be related to the bulkiness of the group involved in the irreversible rearrangement.

Effect of variation in ethers. Polyethers such as

(12) H. S. Mosher and E. LaCombe, *J. Am. Chem. Soc.*, **72**, 3994 (1950).

(13) M. S. Newman, *Steric Effects in Organic Chemistry*, John Wiley & Sons, Inc., New York, 1956.

(14) H. Rupe and W. Kerkovins, *Ber.*, **45**, 1398 (1912).

hexamethylmannitol and pentamethylarabitol are of little value for the study of coordination with a Grignard reagent because of their complexity. They were used mainly as easily obtainable enantiomers with which the study could be extended beyond the use of (+)dimethoxybutane. However, two characteristics of their use are worthy of mention. First, the rotations of 2-phenyl-2-butanol prepared in benzene and (+)hexamethylmannitol or (−)pentamethylarabitol tend to be opposite in sign from 2-phenyl-2-butanol prepared in (+)2,3-dimethoxybutane. Second, the low yields of carbinol which are recorded in experiments 11–15, inclusive, are quite consistent. These yields probably reflect the high electron-donating tendencies which have been observed before[15] in polyethers. Because of such high coordination energy the displacement of ether by carbonyl would be inhibited, with consequent low yield of carbinol.[16]

EXPERIMENTAL[17]

General reagents. Sublimed magnesium (Dominion Magnesium Co., Haley, Ontario) was broken up and finely ground in a coffee mill giving fibrous particles up to 1 × 1 × 5 mm. This metal was activated by etching away 2% by means of bromobenzene in dry ether; the Grignard mixture was hydrolyzed briefly with dilute hydrochloric acid. The metal was thoroughly washed with water, acetone, and ethanol and was then vacuum dried. It contained 34 p.p.m. of iron,[18] 2.5 p.p.m. of copper (sodium diethyldithiocarbamate method) and traces of manganese, zinc, calcium, strontium (?), and silicon (?) that were barely detectable by arc spectrum.

Organic halides were washed with 75–95% (w./v.) sulfuric acid, water, 10% aqueous bicarbonate, saturated sodium chloride and were dried with calcium chloride prior to distillation under anhydrous conditions. Magnesium bromide was prepared by Noller's method.[11] Benzene was purified from sodium benzophenone ketyl but was distilled from sodium just prior to use. The (+)2,3-dimethoxybutane,[1] b.p. 111° uncor., d_4^{20} 0.853, n_D^{2c} 1.3935, $[\alpha]_D^{23}$ +3.76° ± 0.03, was treated likewise.

Arabitol pentamethyl ether. To a 5-l. three-necked flask equipped with dropping funnel, strong stainless steel stirrer and condenser for downward distillation was added 50 g. (0.328 mole) ($[\alpha]_D^{20}$ 8.0 ± 0.4°, c, 9.27 in saturated aqueous borax solution, m.p. 100–102°) of D-arabitol (kindly supplied by Prairie Regional Research Laboratory, National Research Council, Saskatoon, Saskatchewan) and 40 ml. of water. With a surrounding water bath at 55°, a solution of 240 ml. (2.5 moles) of dimethyl sulfate in 350 ml. of carbon tetrachloride was introduced with rapid stirring (throughout the reaction). Then 1 l. of 60% aqueous sodium hydroxide was added at 2–3 drops per second so as to maintain the temperature at 55°. After 20 min., when the distillation of carbon tetrachloride ceased, the remaining alkali was added quickly. The bath temperature was raised to 70° and maintained at 70–75° while 390 ml. (4.1 moles) of dimethyl sulfate was added at 5 drops per second. When addition was complete the heating bath was raised to 100° for 30 min., then cooled at 25°, when 1.5 l. of water was added to dissolve sodium sulfate. Fourfold extraction with chloroform gave a liter of nonaqueous solution which was dried with sodium sulfate and distilled, finally at 0.05 mm., b.p. 77–87°, 61.9 g. (85%), n_D^{20} 1.4310, d_4^{20} 1.021, $[\alpha]_D^{20}$ −5.57 ± 0.06° (neat).

This initial methylation[19] was supplemented by treatment of the 61.9 g. under nitrogen in a 2-l. three-necked flask equipped with strong sealed stirrer, ammonia inlet with acetone–Dry-Ice cooled condenser and introduction tube for 17.5 g. (0.45 g. atom) of metallic potassium[20] with 200 ml. of dry (condensed) liquid ammonia. Gaseous ammonia was then introduced slowly while the potassium was added during 14 hr. Then, when the color of dissolved potassium persisted, the reflux condenser and metal-addition tube were replaced by a dropping funnel and condenser for downward distillation. The ammonia was evaporated off in a nitrogen stream, then 200 ml. of benzene was added and evaporated *in vacuo* with the flask at 40°.

The condenser of the flask was replaced for cold water and Dry-Ice cooling so as to retain the 130 g. (0.9 mole) of methyl iodide which was now added in 300 ml. of benzene. After 3 hr. of stirring and reflux the volatile components were removed *in vacuo* at 45°. This entire methylation was then repeated with additional 7 g. (0.18 g.-atom) of potassium and 57 g. (0.4 mole) of methyl iodide. The final residue was dissolved in water under nitrogen and then extracted four times with chloroform. The 500 ml. of extract was distilled, finally at 0.04 mm., b.p. 71–73°, 44.4 g. (over-all, 61%), d_4^{20} 1.013, n_D^{20} 1.4294, $[\alpha]_D^{20}$ −5.22 ± 0.03° (neat).

For use in the Grignard reaction the ether was dissolved in 40 ml. of benzene, refluxed over sodium for 4 hr. and distilled finally at 0.02 mm., b.p. 67–70°, d_4^{20} 1.010, n_D^{20} 1.4290 $[\alpha]_D^{20}$ −5.21 ± 0.02° (neat).

Anal. Calc'd for $C_{10}H_{22}O_5$: C, 54.0; H, 9.98. Found: C, 54.2; H, 9.82.

The ether is miscible with water. It cannot be made to crystallize at −60° but it is chromatographically homogeneous when it is eluted from silicic acid by chloroform + 2% ethanol.

Mannitol hexamethyl ether. This ether, prepared in 65% yield essentially as described above for pentamethylarabitol, was a solid, fusion point 18.2–20.7°, after crystallization from diethyl ether (5 ml. per g.) at −70°. For Grignard use a benzene solution was dried over sodium and distilled, finally at 87–88° (0.01 mm.), d_4^{20} 1.033, n_D^{20} 1.4378, $[\alpha]_D^{20}$ +12.69 ± 0.02°. The compound is chromatographically homogeneous.

Anal. Calc'd for $C_{12}H_{26}O_6$: OCH_3, 69.92. Found: 69.85.

1-Methoxy-2-methylbutane (prepared by G. A. Dauphinee). A suspension of 7.4 g. (0.3 mole) of sodium hydride in 600 ml. of dry xylene (b.p. 138–139°) and 26.4 g. (0.3 mole) of 2-methyl-1-butanol, $[\alpha]_D^{2.2}$ −5.60 ± 0.06, was stirred under nitrogen for twelve hours, then refluxed with 20 ml. of *tert*-butyl alcohol for four hours. The *tert*-butyl alcohol was distilled off under 20 mm. and the residual solution was stirred while 74.5 g. (0.4 mole) of methyl *p*-toluenesulfonate was added under nitrogen. After ten hours the system was drowned with 250 ml. of water. The nonaqueous phase was dried with calcium chloride and 175 ml. was distilled from it. The remainder was distilled *in toto* under reduced pressure, then refluxed under nitrogen with 4 g. of sodium hydride until a positive sodium benzophenone ketyl test was obtained. Distillation (90–93°, 750 mm.) gave 13.5 g. (45%), d_4^{20} 0.753, n_D^{20} 1.385, $[\alpha]_D^{21}$ +0.61 ± 0.04°.

2,3-Diphenylpropanoylanilide. The 1,2-diphenylchloroethane was washed at 4° with cold 75% aqueous sulfuric acid, then was separated, diluted with 2 vol. of benzene and treated with aqueous potassium carbonate. The solu-

(15) G. F. Zellhoefer, M. J. Copley, and C. S. Marvel, *J. Am. Chem. Soc.*, **60**, 1337 (1938).

(16) R. N. Lewis and J. R. Wright, *J. Am. Chem. Soc.*, **74**, 1253 (1952).

(17) Melting points have been corrected against reliable standards.

(18) S. Abbey, *Anal. Chem.*, **20**, 630 (1948).

(19) E. S. West and R. F. Holden, *J. Am. Chem. Soc.*, **56**, 930 (1934).

(20) M. L. Wolfrom, W. W. Binkley, W. L. Shelley, and H. W. Hilton, *J. Am. Chem. Soc.*, **73**, 3553 (1951).

tion was then dried over potassium carbonate and distilled in the presence of dry potassium carbonate, finally at 0.001 mm., b.p. 92–95°, d_4^{20} 1.096, n_D^{20} 1.5823.

To 4.1 g. (0.17 g. atom) of magnesium in a flamed, nitrogen-swept, conical three-necked flask[21] equipped with a sharp-blade 1300 r.p.m. stirrer were added a few ml. of a solution of 3.68 g. (0.017 mole) of purified halide and 2.49 g. (0.02 mole) of (+)2,3-dimethoxybutane in 30 ml. of benzene. After 10 min. at 20°, heat was evolved and a positive Gilman test was obtained. After 2 hr. of subsequent addition and 30 min. more at 25°, titration indicated 94% of Grignard reagent.

To this reagent was added during 30 min. 1.82 g. (0.015 mole) of phenyl isocyanate in 10 ml. of benzene. Hydrolysis in 50 ml. of cold 10% hydrochloric acid gave 1.94 g., m.p. 163.5–165°, augmented by 0.47 g., m.p. 164–167°, by benzene crystallization (3 ml. per g.) of the residue from evaporation of the benzene layer. The first 1.94 g. of this 50% yield was crystallized from 33 ml. of 95% ethanol; 69% recovered, m.p. 167–168°, $[\alpha]_D^{27}$ +0.90 ± 0.11° (7% solution in 2,5-dioxahexane). After recrystallization from benzene (10 ml. per g., 80% recovery, m.p. unchanged) rotation was $[\alpha]_D^{26}$ +0.30 ± 0.11°.

2,3-Diphenylpropanoic acid. Both pure and impure portions of the anilide were recombined and refluxed for twelve hours with 30 ml. of 1:1 (by volume) of water–sulfuric acid, then diluted to 200 ml. with water and extracted wih 115 ml. of ether. One half of the solution was extracted with two 20-ml. portions of 5% aqueous sodium carbonate. The alkaline extract was washed with chloroform, acidified with dilute sulfuric acid, then extracted with 60 ml. of chloroform. This solution dried by sodium sulfate was evaporated *in vacuo* leaving 0.45 g. (26% on the phenyl isocyanate basis) of yellowish product, m.p. 78–79.5°, $[\alpha]_D^{23}$ +3.31 ± 0.10° (16% in acetic acid).

Of this product, 0.40 g. was dissolved in 0.8 ml. of ethyl acetate and 8 ml. of hexane. This was applied to a partition chromatographic column of 2.5 cm. i.d. and was developed with hexane equilibrated with water-methanol–sulfuric acid.[22] The first six 25-ml. fractions contained only traces of the acid but subsequent fractions gave: 7, 0.036 g., m.p. 81–84°; 8, 0.154 g., m.p. 95–96°; 9, 0.136 g., m.p. 81–84°; 10, 0.027 g., m.p. 81–84° or 89% of the original acid. The racemic acid may melt at 82°, 88–89° or 95–96°[23] and the enantiomers are reported to melt at 83–89°.[14] When fraction 8 was dissolved in diethyl ether and was seeded with a crystal from fraction 9 it melted at 81–84°. Rotation of an 11% solution of fractions 8 and 9 in acetic acid was $[\alpha]_D^{25}$ +3.16 ± 0.10°.

2-Phenyl-2-butanol from ethyl halides in (+)dimethoxybutane. The formation of Grignard reagent from 1.25 g. (0.051 g. atom) of magnesium, 5.45 g. (0.05 mole) of ethyl bromide and 6.0 g. (0.05 mole) of (+)2,3-dimethoxybutane and 40 ml. of benzene under circumstances outlined above commenced within 5 min. Addition was complete within an hour and titration showed 76% of basic magnesium. The chilled reagent was treated with 4.20 g. (0.035 mole) of acetophenone in 15 ml. of benzene during 1 hr. at 4°. After 3 hr. more stirring at 4–25° (Gilman test negative) the system was poured into 50 ml. of saturated aqueous ammonium chloride and ice. The aqueous phase was twice extracted with 50 ml. total of benzene which was combined with the benzene phase of the hydrolysate and washed with two 20-ml. portions of saturated aqueous sodium chloride. The solvents were then removed under reduced pressure, and recovered by a dry-ice trap in order that the dimethoxybutane could be purified for re-use.

After removal of the solvents, the remainder was distilled at 42–50° (0.15 mm., bath at 60–80°) leaving 1.50 g. of residue (36% of the weight of acetophenone). The 2.81 g. of distillate was refluxed one hour with a mixture of 20 g. of Girard's "P",[24] 2.5 g. of acetic acid and 22.5 ml. of absolute ethanol, then poured into a solution of 1.98 g. of sodium carbonate in 100 ml. of water plus ice. The cold mixture was extracted rapidly with four 25-ml. portions of chloroform; this extract was dried with sodium sulfate and distilled, 2.21 g. (79% of crude distillate, 45% of theoretical), b.p. 52° (0.11 mm., bath at 70°), inert toward dinitrophenylhydrazone reagent, n_D^{20} 1.5192, d_4^{20} 0.977, $[\alpha]_D^{26}$ +0.60 ± 0.01° (neat). This product was twice crystallized by solution in 10 volumes of hexane in a flat-bottomed tube through the side arm of which passed nitrogen. Upon cooling to −70° and scratching or seeding, the crystals formed after two hours were freed from solvent by a close-fitting "filter stick." After drying under 10 mm. with calcium chloride and paraffin wax, the product (recovery 77%) had a fusion point −13° to −8°, $[\alpha]_D^{21}$ +0.62 ± 0.04°, n_D^{20} 1.5185. The ultraviolet spectrum (0.16 g./l. in absolute ethanol) showed the characteristics (λ, mμ, E)—Maxima: 266.5, 99; 263, 154; 257, 215; 251.5, 189; 247.5, 151. Shoulder: 241.5, 115. Minima: 262, 123; 255, 160; 228, 48. These physical constants are essentially unchanged by further purification except for fusion point, −11° to −8°.

The aqueous phase from Girard treatment was made 0.5*N* in sulfuric acid and thrice extracted with chloroform. The 60 ml. of extract was dried with sodium sulfate and evaporated at 50° under 300 mm. The residue was dissolved in 3 ml. of absolute ethanol and treated with 50 ml. of methanolic dinitrophenylhydrazine–hydrogen chloride reagent: 0.82 g. of acetophenone dinitrophenylhydrazone, m.p. 235°. A similar control mixture of acetophenone and 2-phenyl-2-butanol gave an 80% yield of the dinitrophenylhydrazone, m.p. 235°, so the derivative is equivalent to 0.41 g. (10%) of the acetophenone originally added to the Grignard reagent. This value is accounted in calculation of the 2-phenyl-2-butanol yield. Both dinitrophenylhydrazones on crystallization from benzene (100 ml. per g.) melted at 243–244°.

In a duplicate experiment the values were: 80% RMg*X*, 8% recovered acetophenone, 35% of high boiling material and 50% of 2-phenylbutanol, $[\alpha]_D^{25}$ +0.55 ± 0.02° (not crystallized). In a third experiment where the excess magnesium was removed from the reagent the acetophenone recovery was 15%, high boiling material 25%, 2-phenylbutanol 40%, $[\alpha]_D^{24}$ +0.61 ± 0.04°. In one experiment 9.2 g. (0.05 mole) of anhydrous magnesium bromide[25] was added to a filtered reagent but little of it dissolved.

Comparable experiments with ethyl iodide (light-protected) Grignard reagents were not amenable to reagent titration (10% yield in supernatant) because of precipitation in the system. Yields and properties shown in Table I were obtained by procedures identical with those described above. Recovery of acetophenone was 10%; high boiling material was 36% of the weight of original acetophenone.

The preparation of the ethyl chloride reagent differed only because a large excess (5 g., 0.2 g. atom) of magnesium was used. Initiation of Grignard reaction required 25 min. No acetophenone could be recovered and only 10% of the weight of original acetophenone was isolated as high-boiling by-product.

All samples of 2-phenyl-2-butanol could be converted by treatment for 16 days with phenyl isocyanate to a magma from which, by extraction with boiling hexane, 75–82% of the same crude urethane could be obtained. Crystallized from hot hexane (7 ml. per g.), the urethane of 2-phenyl-2-butanol melted[26] at 89–90° (45–62% recovery).

2-Phenyl-2-butanol from ethyl halides in polyethers. When mannitol hexamethyl ether was used with ethyl bromide

(21) G. F Wright, *J. Org. Chem.*, 1, 457 (1936).

(22) P. M. Bhargova and C. Heidelberger, *J. Am. Chem. Soc.*, 77, 166 (1955).

(23) W. von Miller and G. Rhode, *Ber.*, 25, 2017 (1892).

(24) A. Girard and G. Sandulesco, *Helv. Chim. Acta*, 19, 1095 (1936).

(25) O. Lerch, *J. prakt. Chem.*, 28, 338 (1883).

(26) E. G. E. Hawkins, *J. Chem. Soc.*, 2076 (1949).

under the standardized conditions outlined above, initiation of Grignard reagent formation required 15 min. Acetophenone equivalent to the 50% Grignard yield was added with standard processing except that the portion of mannitol hexamethyl ether which codistilled with the product had first to be removed by six 400-ml. water washings of the distillate dissolved in 25 ml. of benzene. Recovery of acetophenone (as its 2,4-dinitrophenylhydrazone) was 9%. A portion (0.220 g.) of the 17% yield of slightly impure 2-phenyl-2-butanol, $[\alpha]_D^{24}$ $-1.70 \pm 0.10°$, n_D^{20} 1.5174, was diluted with 0.280 g. of the inactive carbinol and twice crystallized from hexane at $-70°$. The 63% recovery had n_D^{20} 1.5183, $[\alpha]_D^{21}$ $-0.88 \pm 0.06°$, indicating the minimum rotation of the reaction product as $[\alpha]_D^{21}$ $-2.00 \pm 0.14°$.

Titration showed 33% of Grignard reagent from ethyl bromide in benzene-arabitol pentamethyl ether. An equivalent amount of acetophenone gave a product yielding 4% of recovered acetophenone and 14% of 2-phenyl-2-butanol, $[\alpha]_D^{21}$ -0.98 ± 0.08, which was purified by the dilution method described above to give an estimated $[\alpha]_D^{20}$ $-1.15 \pm 0.07°$ for the pure reaction product.

The reaction of ethyl chloride with magnesium in benzene-mannitol hexamethyl ether required strong heating for initiation, though a 66% yield of reagent was obtained. In this instance the polyether was washed by water from the benzene solution after treatment with acetophenone. The usual technique yielded 2% of recovered acetophenone and 17% of 2-phenyl-2-butanol, $[\alpha]_D^{25}$ $-0.63 \pm 0.06°$, n_D^{20} 1.5179; purified by dilution technique final estimation was $[\alpha]_D^{21}$ $-0.42 \pm 0.15°$.

2-Phenyl-2-butanol from bromobenzene. (a). In benzene and (+)2,3-dimethoxybutane. When the Grignard reagent from bromobenzene was prepared as described above a two-phase system was obtained—yellowish upper layer of 40 ml. (containing a 20% yield of Grignard reagent by titration) and a brown lower phase (8 ml.) containing brown gelatinous precipitate. Subsequent treatment with 2-butanone showed by negative Gilman test that less than 75% of reagent was present. The yield of 2-phenyl-2-butanol indicated about 30% of Grignard reagent yield but only 3% of the possible biphenyl was isolated.

The preparation was repeated in a Waring Blendor adapted like a gas-tight three-necked flask, the stirrer seal being packed with silicone grease. After adding 50 ml. of benzene and 15 ml. of a solution of 7.85 g. (0.05 mole) of bromobenzene and 6.1 g. (0.05 mole) of (+)2,3-dimethoxybutane in 50 ml. of benzene, stirring was begun at 8000–10,000 r.p.m. When reflux occurred after several minutes, the addition was continued for 30 min. with spontaneous reflux. The reagent, siphoned into a standard three-necked flask, was amber, slightly turbid, and almost homogeneous; titration showed 56% conversion to Grignard reagent.

An equivalent amount (2.0 g., 0.028 mole) of 2-butanone in 15 ml. of benzene was added and the system was processed as is described above, b.p. 53–56° (0.45 mm.), 3.35 g. (80%), n_D^{20} 1.5182, $[\alpha]_D^{21}$ $+2.05 \pm 0.02°$, inert toward dinitrophenylhydrazine reagent. This crude 2-phenyl-2-butanol was dissolved in 33 ml. of hexane, cooled to $-70°$, and filtered "by the stick" leaving 0.40 g. of biphenyl, m.p. 69–70° (10%). The filtrate, evaporated to 20 ml. gave crystals at $-70°$ which were recrystallized in the same way (recovery 50%, $[\alpha]_D^{20}$ $+2.90 \pm 0.06°$) and then crystallized a third time at $-70°$, recovery 86%, $[\alpha]_D^{20}$ $+3.04 \pm 0.06°$. The change in rotation indicated that the material before crystallization contained 67% of 2-phenyl-2-butanol; the yield was thus 54% on the basis of the ketone used in the reaction.

(b). In benzene and (+)-1-methoxy-2-methylbutane. The Grignard reagent from 7.4 g. (0.047 mole) of bromobenzene and 1.20 g. (0.049 g.-atom) of magnesium in 4.8 g. (0.047 mole) of 1-methoxy-2-methylbutane and 40 ml. of benzene required 15 min. at 20° for initiation. After 2 hr. of addition, stirring was continued for 10 hr. The system then was comprised of 34 ml. deep red-brown upper phase (30% basic Mg) and 12 ml. of a light-red lower phase (14% basic Mg). Upon treatment with 1.36 g. (0.0188 mole) of 2-butanone and with standardized processing the system gave a 5.5% yield of biphenyl and a 55% yield (ketone basis) of 2-phenyl-2-butanol, $[\alpha]_D^{21}$ $0.00 \pm 0.06°$, as well as 1.69 g. of high-boiling material.

(c). In benzene and mannitol hexamethyl ether. To 3 g. (0.12 g.-atom) of magnesium was added during one hour a solution of 4.71 g. (0.03 mole) of bromobenzene in 7.99 g. (0.03 mole) of manno-hexamethoxyhexane; initiation was induced by first heating to 80°. Stirring was continued at 20° for 8 hr. after completion of addition (basic Mg, 16%) and then for 3 hr. more at 65° (basic Mg, 47%). After 3 more hr. at 65° the titer did not change. The system was homogeneous.

After treatment with 0.95 g. (0.0132 mole) of 2-butanone the system was processed as described above (a benzene solution of the initial distillate being washed with 300 ml. of water to remove the polyether) to give 0.283 g. of crude 2-phenyl-2-butanol. This product was developed from a 1.6 × 16 cm. column of 4:1 Baker and Adamson silicic acid–Celite (dried at 90° after washing with acetone and water) by means of 1.5:98.5 ethanol-chloroform (V:V). The intermediate fractions contained 0.21 g. which was diluted with 0.305 g. of inactive 2-butanol and crystallized from 10 volumes of hexane at $-70°$, 61% recovery, n_D^{20} 1.5184, $[\alpha]_D^{20}$ $-0.29 \pm 0.04°$ (neat), expected spectrum, so that the 2-phenyl-2-butanol before dilution had at least $[\alpha]_D^{20}$ $-0.75 \pm 0.10°$.

(d). In benzene and arabitol pentamethyl ether. Since preliminary experiments showed that this Grignard reagent was difficult to prepare, a "semimicro" Waring Blendor unit (Central Scientific Co. 4282F) was modified by brazing on a water jacket around the fluted portion and by replacing the monel lid by a tight-fitting Teflon lid which was machined for the interchangeable joints of condenser and dropping funnel. After oven drying and displacement of air by nitrogen, the reagent was prepared from 2.0 g. (0.08 g.-atom) of magnesium (which had been heated under nitrogen in a separate container), 4.71 g. (0.03 mole) of bromobenzene, and 6.66 g. (0.03 mole) of arabo-pentamethoxypentane by maintaining the system at reflux temperature (steam in jacket) during 30 min. at 10,000 r.p.m. Subsequently the heated system (basic magnesium 14%) was stirred for 11 hr. at 65° (basic magnesium 24%). Treatment with 1.16 g. (0.016 mole) of 2-butanone and with processing described in the preceding experiment gave a 7% yield of 2-phenyl-2-butanol the rotation of which was essentially zero.

TORONTO 5
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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF MICHIGAN]

9,10-Dihydro-9,10-methanoanthracene and Its Perhydro Derivatives

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Received Aug. 6, 1956

The synthesis of 9,10-dihydro-9,10-methanoanthracene (dibenzobicyclo[2,2,1]heptadiene), I, is described. The preparations of a number of potential as well as actual intermediates containing the same tetracyclic system are described, and the conversion of two of these to two stereoisomeric perhydro derivatives, XVI and XX, is discussed. Ultraviolet spectra of I and related compounds are considered to afford evidence for interaction of nonadjacent (nonconjugated) chromophores.

In a preliminary communication[3] we have reported the synthesis of 9,10-dihydro-9,10-methanoanthracene (I), which despite a number of earlier claims for preparation of various of its derivatives, must be considered the parent and unique member of a new system of compounds. Our interest in this system stems from a suggestion[4] that the lactone produced by the action of 48% hydrobromic acid on 2-hydroxy-3-methyldibenzobicyclo[2,2,2]octadiene-*trans*-2,3-dicarboxylic acid[5] might be derived from I. Subsequent degradation[6] showed this hypothesis to be in error but thereby raised intriguing questions as to what might be the chemical nature of methylene substituted derivatives of I.

Discounting such reports of derivatives of I as have appeared in experimental literature[7,8,9] on the basis of subsequent disproofs[10,11] of all but one,[8] there remained the positive statement[12] that I was known and that oxidation removed the methylene bridge to give anthraquinone. Certain preliminary studies appeared to confirm the nature of the oxidation of the system in question (as stated in ref. 6, p. 1749), but, as will appear in the sequel, there is no basis for such a statement when I is subjected to oxidation.

Two potential routes to the synthesis of I were considered and investigated, one of which was completely unsuccessful but yielded new information on the benzilic acid rearrangement, wherein an attempt was made to contract the ethylene bridge of dibenzobicyclo[2,2,2]octadiene-2,3-dione. This will be reported elsewhere. The other route involved construction of the system about a preformed bicyclo[2,2,1]heptane system by means of the Diels-Alder reaction. A number of possibilities were considered, and two independent approaches were undertaken and are reported herewith.

The initial and less equivocal synthesis is outlined in Chart I and is patterned after the elegant synthesis of triptycene by Bartlett, Ryan, and Cohen.[13]

The starting material (II) for this series of reactions was readily prepared from 1,4-benzoquinone and cyclopentadiene,[14] and its conversion to III was effected at room temperature in order to avoid the difficulties encountered by others who were unable to bring about effective aromatization.[14,15] The structure of III was related to the quinone, obtained in poor yield by Diels and Alder[15] from II with ferric chloride in hydrobromic-acetic acid mixture, by reductive acetylation of the quinone to give III.

The desired ring system was completed by conversion of III to IV with butadiene, and aromatization was then attempted without success. Consequently IV was hydrolyzed to V and smoothly oxidized to VI which was oximated to VII. Conversion of VII to VIII was effected, but the latter proved to be extremely unstable, and the projected conversion to IX was not achieved. Instead, VII was catalytically reduced to X which was then deaminated to give XI, which unfortunately resisted aromatization. This route was then abandoned, with XI being reserved for comparison with products accessible by the successful alternative but more equivocal route outlined in Chart II.

The availability of XII[16] made this approach especially attractive, since the dienophilic character of the double bond in bicyclo[2,2,1]heptene has been established.[17] However, the *bis*-adduct of XII

(1) Abstracted from the Ph.D. dissertation of Masao Yoshimine, University of Michigan, 1955.

(2) Edgar C. Britton Fellow in Organic Chemistry, 1954–1955.

(3) W. R. Vaughan and M. Yoshimine, *J. Org. Chem.*, **21**, 263 (1956).

(4) K. M. Milton, Dissertation, University of Michigan, 1951.

(5) W. R. Vaughan and K. M. Milton, *J. Am. Chem. Soc.*, **74**, 5623 (1952).

(6) W. R. Vaughan, M. V. Andersen, Jr., and R. Q. Little, Jr., *J. Am. Chem. Soc.*, **76**, 1748 (1954).

(7) E. B. Barnett, J. W. Cook, and M. A. Matthews, *Ber.*, **60**, 2353 (1927).

(8) C. Dufraisse and L. Enderlin, *Bull. soc. chim.*, [5] **1**, 267 (1934).

(9) A. Muller, *J. Org. Chem.*, **12**, 815 (1947).

(10) J. W. Cook, *Ber.*, **60**, 2366 (1927); *J. Chem. Soc.*, 2798 (1928).

(11) W. E. Doering and J. A. Berson, *J. Am. Chem. Soc.*, **72**, 1118 (1950).

(12) F. C. Whitmore, *Organic Chemistry*, 1st ed., D. Van Nostrand Co., Inc., New York, N. Y., 1937, p. 867.

(13) P. D. Bartlett, M. J. Ryan, and S. G. Cohen, *J. Am. Chem. Soc.*, **64**, 2649 (1942).

(14) W. Albrecht, *Ann.*, **348**, 31 (1906).

(15) O. Diels and K. Alder, *Ber.*, **62**, 2337 (1929).

(16) A generous supply of this substance was kindly donated by the Shell Development Company, Emeryville, Calif.

(17) K. Alder and G. Stein, *Ann.*, **496**, 204 (1932).

CHART I

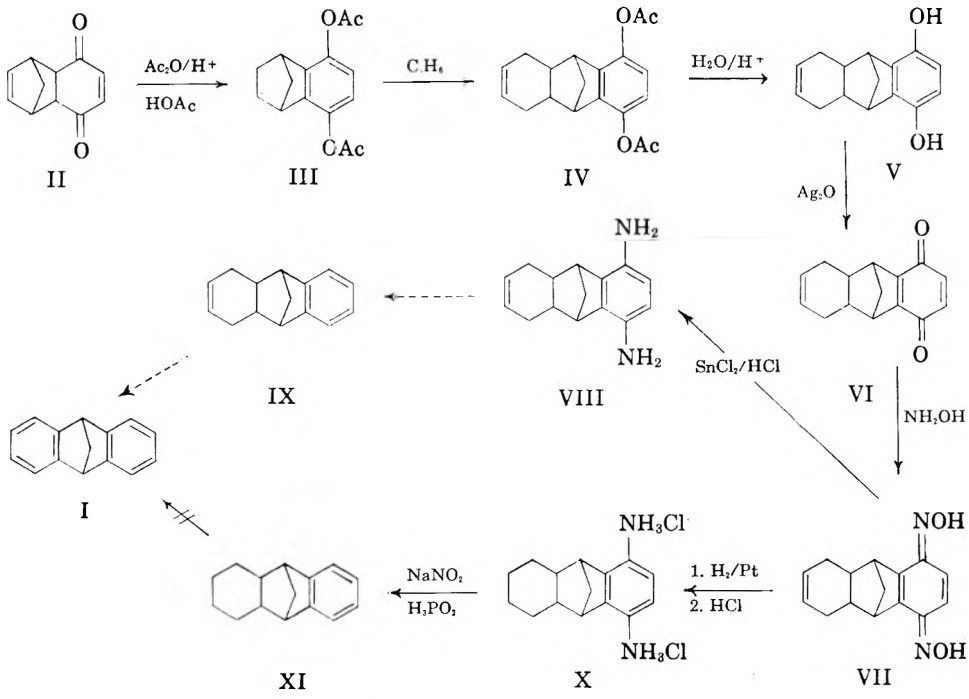
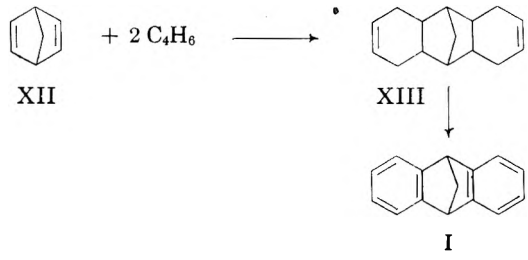
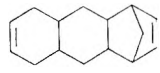


CHART II

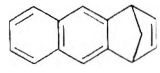


with butadiene (XIV), isomeric with XIII, must be considered and would lead to an equivocal structure (XV) for the dehydrogenation product.



XIV

Nevertheless, the reaction between XII and excess butadiene was carried out, and a product with an



XV

appropriate analysis for XIII (or XIV) was obtained in 9.4% yield. It seemed improbable that the second molecule of butadiene would add to the monoadduct at the cyclohexene double bond as long as there remained the intrinsically more reactive bicyclic double bond, and support for this hypothesis was obtained upon examination of the infrared spectrum of the product wherein there appears but one absorption band in the double bond region—and that at 1640 cm.$^{-1}$ corresponding to a normal unconjugated double bond. On the other hand, XII shows a weak absorption at 1550 cm.$^{-1}$, which is close to the Raman assignment[18] of 1568 cm.$^{-1}$ for the bicyclic double bond of dicyclopentadiene. With this encouragement aromatization of XIII was investigated.

Several attempts to dehydrogenate XIII with sulfur, with and without solvent, afforded only unidentifiable high-melting material. Next catalytic dehydrogenation over palladium charcoal in refluxing cymene was attempted, but only starting material and a trace of perhydrogenated XIII, m.p. 76.5–77.8° (XVI) were isolable. Thus, it seemed desirable to provide a hydrogen acceptor for the catalytic reaction, and the procedure of Adkins, Richards and Davis,[19] using 5% palladium on charcoal in benzene at 230°, with an initial nitrogen pressure of 450 p.s.i., was employed. Under these conditions there was isolated a 19% yield of material corresponding in analysis to I (or XV). The substance melted at 154.5–155.5°, which eliminated the isomeric methylanthracenes from consideration, as did the ultraviolet spectrum (Table I) and the failure to produce even a trace of anthraquinone on vigorous oxidation.

The correctness of assigning to the dehydrogenation product the desired structure I rather than XV is established by the dissimilarity of the ultraviolet spectrum to that of naphthalenic systems (no absorption maxima above 300 mμ) and its formal resemblance to that of 9,10-ethano-9,10-dihydroanthracene (XVII), (Table I) and by the high resolu-

(18) K. W. F. Kohlrausch and R. Seka, *Ber.*, **69**, 729 (1936).

(19) H. Adkins, L. M. Richards, and J. W. Davis, *J. Am. Chem. Soc.*, **63**, 1320 (1941).

TABLE I

ULTRAVIOLET ABSORPTION MAXIMA

Compound	Max. (mμ)	Log ε	Max. (mμ)	Log ε	Max. (mμ)	Log ε
I[a]	264[b]	3.07	272	3.30	278	3.41
XI[a]	259	2.89	265	3.06	272	3.10
XVII[a]	259[b]	2.93	265	3.18	272	3.30
XVIII[a,c]	266[b]	3.03	272	3.34	279	3.58
XIX[d]			264	3.06	272	3.00
Triptycene[e]	263[b]	3.25	271	3.66	278	3.56

[a] 95% ethanol: Cary Quartz Recording Spectrophotometer, Model II. [b] Shoulder. [c] Sample kindly supplied by A. C. Schoenthaler. [d] D. D. Phillips and J. Cason, *J. Am. Chem. Soc.*, 74, 2934 (1952). [e] P. D. Bartlett and E. S. Lewis, *J. Am. Chem. Soc.*, 72, 1005 (1950).

tion NMR spectra[20] of I and XVII: Only aromatic, methine, and methylene (no ethylenic) protons are detectable, and there is no mutual C—H and CH_2 splitting, confirming similar rigid structures possessing no ethylenic double bonds. Furthermore there are equal numbers of methine and methylene protons in I and twice as many methylene as methine hydrogens in XVII.

It is interesting to note that while chromic anhydride attacks both I and XVII, no trace of anthraquinone can be detected whereas 9,10-ethano-9,10-dihydroanthracene[21] (XVIII) readily affords anthraquinone under similar conditions. No attempt was made to characterize the oxidation products of I and XVII, but the implied preferential susceptibility to oxidation of the aromatic rings is reminiscent of triptycene[13] which affords anthraquinone on mild chromic anhydride oxidation. In triptycene this has been attributed to a possible Mills-Nixon effect[13,22] and in the present compounds an analogous situation would seem to obtain. The chemical shifts (δ) for the aromatic protons in I and XVII are greater than for toluene (−1.58), indicating fewer electrons per proton than in toluene, which is consistent with their structures; and while the line at $\delta = -2.6$ (XVII) is very sharp, indicating complete equivalence of all aromatic protons, that at $\delta = -2.1$ (I) shows evidence of unresolved structure and hence nonequivalence of the aromatic protons. This is indicative of increased disortion in I, which is to be expected, and is consistent with an increased susceptibility to oxidation and with a true Mills-Nixon effect.

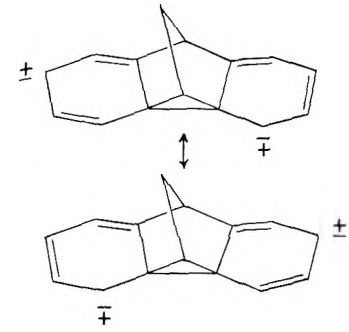
ULTRAVIOLET SPECTRA

The resemblance of I to triptycene is observable in their ultraviolet spectra, and for purposes of discussion, the principal absorption bands of several of the dihydroanthracenes mentioned above, as well as those for XI and 9,10-dimethyl-9,10-dihydroanthracene (XIX) are presented in Table I.

If XIX is considered a model compound for the 9,10-dihydroanthracene system, it will be noted that XI and XVII have spectra which resemble that of XIX closely, except for a generally increased intensity for XVII. Thus, the methano bridge in XI and the ethano bridge in XVII do not appear to influence the absorption characteristics of the adjacent aromatic ring(s). On the other hand, I, XVIII, and triptycene show more intense absorption by a factor of 2 to 3, and their maxima occur at from 4 to 7 mμ longer wave lengths than their apparent equivalents in XIX, XI, and XVII.

The wave lengths of the absorption maxima as well as the intensities of absorption for hydroaromatic compounds such as XIX are greater than for benzene, and this may be attributed to hyperconjugation, as for alkylbenzenes.[23] However, XI and XVII, which like triptycene (Table I, ref. *e*), are probably incapable of hyperconjugation on stereochemical grounds, spectroscopically resemble XIX. Friedel and Orchin[24] have suggested that the spatial overlap of two methyl groups in 4,5-dimethylphenanthrene and 4,5-dimethylchrysene introduces strain in the aromatic nucleus, causing an increased absorption maximum and intensity. Since there is undoubtedly strain imposed on the aromatic nuclei of XI and XVII by the 9,10-bridges (*cf.* NMR shifts for I and XVII aromatic protons, above), it is reasonable to attribute the resemblance of their spectra to that of XIX to this strain phenomenon.

While there is no other obvious phenomenon to account for the "abnormal" spectrum of XI, all of the remaining compounds (except the model, XIX) are capable of increased conjugation by interaction between nonadjacent chromophores as suggested by Bartlett and Lewis (Table I, ref. *e*) for triptycene and considered by Cram and Steinberg for the paracyclophanes[25]: *e.g.*,



(20) Kindly obtained by Dr. E. B. Baker of the Physical Research Laboratory, Dow Chemical Company, Midland, Mich.

(21) S. J. Cristol and N. L. Hause, *J. Am. Chem. Soc.*, 74, 2193 (1952); A. C. Schoenthaler, Dissertation, University of Michigan, 1955.

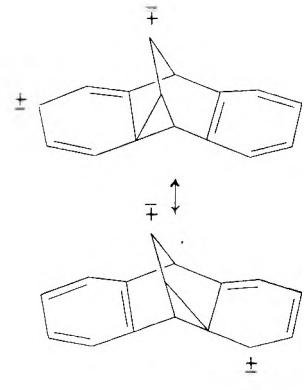
(22) *Cf.* G. W. Wheland, *Resonance in Organic Chemistry*, John Wiley & Sons, Inc., New York, N. Y., 1955, p. 497 f.

(23) F. A. Matsen, W. W. Robertson, and R. L. Chuoke, *Chem. Revs.*, 41, 273 (1947).

(24) R. A. Friedel and M. Orchin, *Ultraviolet Spectra of Aromatic Compounds*, John Wiley and Sons, Inc., New York, N. Y., 1951, pp. 23, 25.

(25) D. J. Cram and H. Steinberg, *J. Am. Chem. Soc.*, 73, 5691 (1951).

However, all of these systems also contain highly strained structures, and consequently the strain and nonadjacent chromophores interaction effects cannot be separated. One might expect the increase in strain in I over that in XVIII (bicyclo[2,2,1]heptane *vs.* bicyclo[2,2,2]octane)[26] to produce the increasing wavelength and intensity order, triptycene < XVIII < I. But the observed order is triptycene < I < XVIII, and therefore it is possible that in addition to interaction between the aromatic rings, there is interaction between the rings and the etheno or vinylene bridge: *e.g.*,



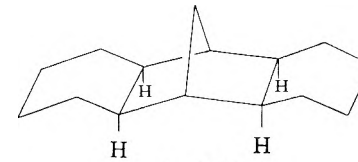
STERIC RELATIONSHIPS

It was originally thought that the skeletal structure of I might be established by relating the perhydro derivative of XI (XX) to the perhydro compound (XVI) derived from XIII. Accordingly, a sample of XVI, m.p. 76.5–77.8° (*vide supra*), was prepared by hydrogenation of XIII (Adams' catalyst), and XI was similarly reduced to give XX, m.p. 47.3–48.3°. Obviously, isomers rather than identical substances were produced. The mode of synthesis leaves no room to doubt the structure of XX, and the arguments advanced concerning the structure of I, above, establish by implication an identical structure for XVI; thus, stereoisomers are at hand. Of the numerous possibilities all but three can be eliminated by invoking the principles of *cis* addition in the Diels-Alder reaction and of one-side hydrogenation advanced by Linstead[27]: those remaining have exclusively *cis* ring junctions and may be represented as (*A*), *exo: exo;* (*B*), *exo: endo;* and (*C*), *endo: endo*, all configurations with respect to the methylene bridge. A consideration of Courtauld models[28] indicated clearly that spatial requirements prohibit two *endo* cyclohexane rings attached to the bicyclo[2,2,1]heptane system, and thus the existence of configuration *C* is rendered improbable. Consequently it is reasonable to assume that the two stereoisomers XVI and XX represent the remaining configurations *A* and *B*.

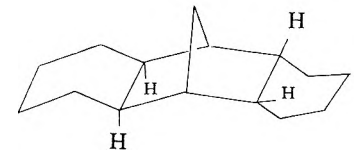
If one disregards for the moment the configuration produced by the synthesis of XI (*i.e.*, III → IV, Chart I) and considers only the hydrogenation of XI to XX, there is ample precedent for preferential *exo* hydrogenation.[29,30,31] This, then, will lead to *endo* ring junction for the new hydroaromatic ring, and XX will possess the *exo: endo* configuration, since the *endo: endo* configuration (*C*) has been eliminated on steric grounds.

Now if the initial Diels-Alder reaction had produced an *endo* ring junction, either the improbable *endo: endo* system would result from *exo* hydrogenation of the aromatic ring, or the hydrogenation would have had to be *endo*. The latter would be as improbable as the existence of the *endo: endo* system, since the original *endo* cyclohexane ring would effectively exclude the necessary quasiplanar contact of the aromatic ring with the catalytic surface (*cf.* ref. 27).

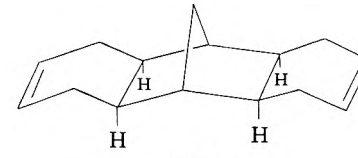
These arguments lead to the conclusions that the initial Diels-Alder reaction (III → IV, Chart I) must have produced an *exo* ring junction and that the reaction of XII with two molecules of butadiene must have produced two *exo* ring junctions (Chart



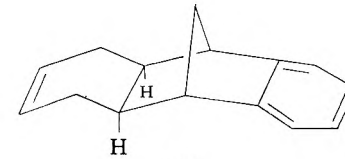
A: XVI



B: XX



XIII



XI

(26) P. D. Bartlett and F. D. Greene, *J. Am. Chem. Soc.*, **76**, 1088 (1954).

(27) R. P. Linstead, W. E. Doering, S. B. Davis, P. Levine and R. R. Whetstone, *J. Am. Chem. Soc.*, **64**, 1985 (1942).

(28) G. S. Hartley and C. Robinson, *Trans. Faraday Soc.*, **48**, 847 (1952).

(29) K. Alder and G. Stein, *Ann.*, **525**, 183 (1936).

(30) R. B. Woodward and H. Baer, *J. Am. Chem. Soc.*, **70**, 1161 (1948).

(31) K. Alder and W. Roth, *Ber.*, **87**, 161 (1954).

(32) G. Stork, E. E. van Tamelen, L. J. Friedman and A. W. Burgsthaler, *J. Am. Chem. Soc.*, **75**, 384 (1953).

II). In both Diels-Alder reactions, then, butadiene has added to a bicyclo [2,2,1]heptene (or heptadiene) system in the *exo* manner, for which there is again ample precedent.[29,31,32] Accordingly, XIII, and therefore XVI, have the *exo: exo* configuration (*A*) and XI, and therefore XX, have the *exo: endo* configuration (*B*).

It remains to comment upon the hydrogenation of XIII as it bears upon its structure as compared with XIV. The uptake of hydrogen plotted as a function of time gives a smooth curve, no break being observed. Taken by itself this fact is only suggestive of two sterically identical double bonds; but taken in concert with the infrared spectrum of the compound, which, as stated above shows but one double bond absorption—and that in the normal rather than bicyclic double bond region—it constitutes presumptive support for the assigned structure (XIII) and the assigned configuration.

EXPERIMENTAL

All melting points are uncorrected. Infrared spectra were obtained from Nujol mulls, unless otherwise noted, by means of a Perkin-Elmer Infrared Spectrophotometer, Model 21. Microanalyses were run by Goji Kodama (K) and Anna Griffin (G) University of Michigan, Department of Chemistry and Spang Microanalytical Laboratory, Ann Arbor, Mich. (S).

5,8-Diacetoxy-1,4-dihydro-1,4-methanonaphthalene (III). To a solution of 50.0 g. (0.287 mole) of 1,4,4a,8a-tetrahydro-1,4-methanonaphthalene-5,8-dione (II)[14] in 88.0 g. (0.862 mole) of acetic anhydride and 50 ml. of glacial acetic acid was added, with stirring, 4 ml. of concentrated hydrochloric acid. A slight temperature rise and darkening of the reaction mixture was noted. After standing overnight at room temperature the mixture was cooled, several ml. of water was added, and the sides of the flask were scratched to induce crystallization. White crystals were collected and washed with a small portion of water. The diluted filtrate was cooled and a second crop of white crystals was collected and washed with water. The two crops were combined and dried in a vacuum desiccator to give 47.5 g. (64%) of white crystals, m.p. 102–105°. Three recrystallizations from petroleum ether (b.p. 60–75°) yielded white crystals, m.p. 105–106°.

Anal. Calc'd for $C_{15}H_{14}O_4$: C, 69.75; H, 5.49. Found (K): C, 69.47; H, 5.49.

Reductive acetylation of 1,4-dihydro-1,4-methanonaphthalene-5,8-dione.[15] To a suspension of 0.0140 g. (0.0000804 mole) of 1,4-dihydro-1,4-methanonaphthalene-5,8-dione[15] in ten drops of acetic anhydride were added 0.05 g. of zinc dust and 0.02 mg. of sodium acetate and the mixture was heated to 70° for 10 min., thereby discharging the initial yellowish color.[33] One milliliter of glacial acetic acid was added and the hot solution was filtered from the zinc and zinc acetate. The filtrate was boiled and water was added to destroy the excess acetic anhydride, forming a slightly turbid mixture. After cooling the mixture in the refrigerator for an hour, 0.0030 g. (14%) of white crystals, m.p. 102.5–104.0°, was collected. A mixed m.p. with 5,8-diacetoxy-1,4-dihydro-1,4-methanonaphthalene, III, showed no depression.

1,4-Diacetoxy-5,8,8a,9,10,10a-hexahydro-9,10-methanoanthracene (IV). To 5.2 g. (0.096 mole) of butadiene condensed in a borosilicate glass combustion tube was added 2.50 g. (0.00968 mole) of III and 10 ml. of sodium dried benzene. The sealed tube was heated for 14 hr. at 205°, yielding a tan reaction mixture which was concentrated under an air jet to a tan gummy mass. The crude product was sublimed at 125° at 0.04 mm. for 4 hr., giving 2.34 g. of white crystalline material, m.p. 80–115°. The continued sublimation of the residue for 12 hr. yielded 0.40 g. of a white powder, m.p. 108–117°. The combined sublimates were crystallized from petroleum ether (b.p. 40–60°) to obtain 1.65 g. (54%) of white glistening plates, m.p. 116.5–119.0°. Several recrystallizations from petroleum ether (b.p. 40–60°) afforded white glistening plates, m.p. 119–120°.

Anal. Calc'd for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45. Found (K): C, 72.89; H, 6.77.

5,8,8a,9,10,10a-Hexahydro-1,4-dihydroxy-9,10-methanoanthracene (V). A solution of 0.190 g. (0.000608 mole) of IV in a mixture of 25 ml. of 5% hydrochloric acid and 150 ml. of 95% ethanol was heated under reflux for 2 hr. After one half of the solvent was stripped off at water pump pressure in a nitrogen atmosphere, the reaction mixture was cooled, and 0.125 g. (90%) of white glistening plates, m.p. 213–215° *d.*, was collected. The analytical sample, white glistening plates, m.p. 215.0–215.5° *d.*, was obtained after two recrystallizations from benzene.

Anal. Calc'd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found (G): C, 78.94; H, 6.86.

5,8,8a,9,10,10a-Hexahydro-9,10-methano-1,4-anthraquinone (VI). To a solution of 2.40 g. (0.0105 mole) of V in 150 ml. of absolute ether were added 5.40 g. (0.0244 mole) of freshly prepared silver oxide and 5.40 g. of anhydrous magnesium sulfate. This mixture was shaken for 45 min. and then was filtered. The filtrate was concentrated under an air jet, yielding 2.40 g. of deep yellow crystals, m.p. 119.0–123.5°. One crystallization from petroleum ether (b.p. 40–60°) gave 1.80 g. (75%) of fine yellow needles, m.p. 123–124°. The analytical sample was prepared by several recrystallizations from petroleum ether (b.p. 40–60°), yielding fine yellow needles, m.p. 125.0–125.5°.

Anal. Calc'd for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found (K): C, 79.32; H, 6.27.

5,8,8a,9,10,10a-Hexahydro-9,10-methano-1,4-anthraquinone dioxime (VII). A solution of 2.08 g. (0.00920 mole) of VI and 6.39 g. (0.00920 mole) of hydroxylamine hydrochloride in 75 ml. of ethanol was refluxed for ten hours and then was poured into 800 ml. of water. After 12 hr., a brownish precipitate was collected by filtration and dried. The dioxime, 1.95 g. (79%) of light brown powder, was obtained after two washings with benzene. The dioxime darkened at 195° and decomposed completely at 208°. The decomposition temperature was dependent on the rate of heating. Two recrystallizations from benzene yielded a light yellow powder. The melting point capillary was placed in the bath at 195° and heated at the rate of 10° per minute. The dioxime darkened at 205° and decomposed instantaneously at 211°.

Anal. Calc'd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found (S): C, 70.33; H, 6.21; N, 10.77.

1,4-Diamino-5,8,8a,9,10,10a-hexahydro-9,10-methanoanthracene (VIII). To a solution of 0.200 g. (0.000760 mole) of VII in 4 ml. of ethanol was added a solution of 0.65 g. of stannous chloride dihydrate in 4.7 ml. of concentrated hydrochloric acid. The reddish reaction mixture was heated at 80° for 5 min., discharging the color. From the cooled reaction mixture, white crystalline material was collected by filtration, washed with an ethanol–hydrochloric acid mixture and with ether. A sample of the product was burned leaving a white residue; therefore, to a solution of the crystals in water was added several drops of 5% sodium hydroxide, producing a white turbid mixture. Upon cooling and scratching the sides of the flask, a white precipitate was obtained which was quickly filtered, washed with boiled water, and dried. Nearly white crystals, 0.050 g. (29%), m.p. 103–108° d. were obtained. All attempts to purify the diamine further were unsuccessful.

(33) L. F. Fieser, *Experiments in Organic Chemistry*, 2nd ed., D. C. Heath and Company, New York, N. Y., 1941, p. 399.

Anal. Calc'd for $C_{15}H_{18}N_2$: C, 79.60; H, 8.02; N, 12.38. Found (S): C, 79.29; H, 8.15; N, 12.28.

1,4-Diamino-5,6,7,8,8a,9,10,10a-octahydro-9,10-methanoanthracene dihydrochloride (X). To a suspension of 0.04 g. of platinum oxide reduced in 10 ml. of absolute ethanol was added a solution of 0.500 g. (0.00195 mole) of VII in absolute ethanol. The theoretical volume of hydrogen was absorbed in 30 min. The platinum residue was filtered off and the filtrate was dried over Drierite, treated with Norit, and filtered. The brownish filtrate was saturated with dry hydrogen chloride and then 400 ml. of sodium dried ether was added, precipitating a tan material. The mixture was cooled. The resulting precipitate was collected by filtration and was dried in a vacuum desiccator. The reduction yielded 0.561 g. (95%) of tan crystals, m.p. 288–293° d. with previous darkening. No attempts to purify diamine hydrochloride were made.

Anal. Calc'd for $C_{15}H_{22}Cl_2N_2$: C, 59.79; H, 7.36; N, 7.30. Found (G): C, 59.52; H, 7.12; N, 7.43.

1,2,3,4,4a,9,9a,10-Octahydro-9,10-methanoanthracene (XI). This compound was prepared by the deamination procedure of Bartlett and Greene.[26] A solution of 1.00 g. (0.00320 mole) of X in 50 ml. of 50% hypophosphorous acid was added dropwise, with stirring, to a solution of 1.375 g. of sodium nitrite in 100 ml. of 50% hypophosphorous acid cooled to below −15°. In 5 min. a frothing of the yellow reaction mixture began. The addition required 1.5 hr., and the mixture was stirred for an additional hour at −15°. The reaction mixture was placed in the cold room at −5° for 5 hr., causing the formation of an orange precipitate. After adding 100 g. of ice to the reaction mixture, it was allowed to stand in the cold room for an additional 10 hr. The reaction mixture was then extracted with several portions of ether, totaling 300 ml. The combined ethereal extracts were washed with 5% sodium hydroxide, 5% hydrochloric acid, and water. The resulting orange ethereal solution was dried over anhydrous magnesium sulfate, filtered, and the ether blown off under an air jet to give a dark red sticky oil. The crude mixture was sublimed at 0.5 mm., at 50–55° for 10 hr., yielding 0.352 g. (55%) of white crystals, m.p. 59.5–61.0°. Crystallization from methanol gave 0.281 g. (44%) of fine white needles, m.p. 60.5–61.5°.

Anal. Calc'd for $C_{15}H_{18}$: C, 90.85; H, 9.15. Found (G): C, 90.62; H, 8.88.

1,4,4a,5,8,8a,9,9a,10,10a-Decahydro-9,10-methanoanthracene (XIII). To 41.0 g. (0.760 mole) of c.p. butadiene condensed in a stainless steel bomb was added a mixture of 5.00 g. (0.0530 mole) of bicyclo[2,2,1]hepta-2,5-diene (XII)[16,34] and a trace of hydroquinone in 50 ml. of benzene. The sealed bomb was heated for 24 hr. at 200–205°. After cooling, the light brown reaction mixture was concentrated on the steam bath under an air jet to give a yellowish brown gummy oil. The crude mixture was placed in a short path distillation apparatus and was heated at 100° under water pump pressures for one hour to remove low boiling components. The resulting gummy residue was heated between 105–120° at 0.05 mm. to give a colorless oil. The distillate was dissolved in ethanol and cooled to 0° in the refrigerator overnight. Long white plates, 1.02 g. (9.4%), m.p. 50–53°, were collected by filtration. The analytical sample, m.p. 54.0–55.5°, was prepared by two recrystallizations from ethanol.

Anal. Calc'd for $C_{15}H_{20}$: C, 89.94; H, 10.06. Found (K): C, 89.68; H, 10.10.

Molecular weight (bromination[35]) Calc'd: 200. Found: 197.

The infrared spectrum has medium bands at 3030 cm.$^{-1}$ and 1640 cm.$^{-1}$.

9,10-Dihydro-9,10-methanoanthracene I. The method of Adkins, Richards and Davies[19] was used to dehydrogenate XIII. To a solution of 0.500 g. (0.00200 mole) of XIII in 10 ml. of benzene in a glass lined stainless steel bomb was added 0.50 g. of 5% palladium-charcoal catalyst. The bomb was flushed with nitrogen, then put under an initial pressure of 450 p.s.i. of nitrogen, and heated at 230° for 14 hr. with shaking. The catalyst was filtered off and washed with 70 ml. benzene and 100 ml. of acetone. The solvent was stripped from the filtrate at water pump pressure at 40–50°, leaving a white oily mass. The crude product was crystallized from ethanol to yield 0.075 g. (19%) of white crystals, m.p. 151.5–153.0°. Two crystallizations from ethanol gave the analytical sample glistening white plates, m.p. 154.5–155.5°.

Anal. Calc'd for $C_{15}H_{12}$: C, 93.71; H, 6.29. Found (S): C, 93.54; H, 6.27.

Partial oxidation of 9,10-dihydro-9,10-methanoanthracene I. To a solution of 0.020 g. (0.00010 mole) of 9,10-dihydro-9,10-methanoanthracene, I, in 5 ml. of glacial acetic acid was added 0.040 g. (0.00040 mole) of chromic anhydride which was heated on a steam bath for 1 hr., giving a clear green solution. The cooled reaction mixture was poured into 25 ml. of water, forming a white precipitate which was filtered off, washed with water, and dried. The white crystals, 0.013 g., m.p. 151–153°, gave no anthraquinone vat test.[36] A sample crystallized from ethanol gave no m.p. depression with starting material. No attempt was made to isolate the oxidation products.

Oxidation of 9,10-dihydro-9,10-methanoanthracene I. To a solution of 0.20 g. (0.00010 mole) of 9,10-dihydro-9,10-methanoanthracene, I, in 5 ml. of glacial acetic acid was added 0.100 g. (0.00010 mole) of chromic anhydride which was heated on a steam bath for 24 hr. resulting in a clear green solution. The reaction mixture was poured into 50 ml. of water and cooled in a refrigerator for two weeks. No precipitate was formed. No attempt was made to identify the oxidation products and no anthraquinone could be detected.[36]

Oxidation of 9,10-dihydro-9,10-ethanoanthracene (XVII). To a solution of 0.050 g. (0.00024 mole) of XVII[21] was added 0.113 g. (0.00113 mole) of chromic anhydride in 10 ml. of glacial acetic acid; the mixture was heated for 2 hr., resulting in a clear green solution. The reaction mixture was poured into 50 ml. of water forming a white precipitate which was filtered off, washed with water, and dried. The white crystals, 0.0036 g., m.p. 138.0–140.5°, gave no anthraquinone vat test.[36] A sample recrystallized from ethanol gave no m.p. depression with starting material.

Perhydro-9,10-methanoanthracene (XVI). To a suspension of 0.20 g. of platinum oxide reduced in 10 ml. of glacial acetic acid was added a solution of 0.0902 g. (0.000451 mole) of XIII in 10 ml. of glacial acetic acid. The theoretical volume of hydrogen was absorbed in 15 min. and no break in the curve of hydrogen uptake *vs.* time was observed. The platinum residue was filtered off, and the filtrate was poured into 20 ml. of water to form a turbid mixture. After a week in the refrigerator, 0.0710 g. (77%) of white crystals, m.p. 75–77°, was collected by filtration and dried. Crystallization from ethanol yielded 0.0413 g. (45%) of long white needles, m.p. 76.5–77.8°.

Anal. Calc'd for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found (G): C, 88.14; H, 11.77.

Perhydro-9,10-methanoanthracene (XX). To a suspension of 0.05 g. of platinum oxide reduced in 10 ml. of glacial acetic acid was added a solution of 0.100 g. (0.000505 mole) of 1,2,3,4,4a,9,9a,10-octahydro-9,10-methanoanthracene (XI) in 5 ml. of glacial acetic acid. The theoretical volume of hydrogen was absorbed in 4 hr. The platinum residue was filtered from the reduction mixture and the solvent was stripped off at 40–50° under water pump pressure, yielding 0.087 g. (84%) of white crystals, m.p. 45–48°. Crystalliza-

(34) Julius Hyman and Co., Belg. pat. 498,176, Jan. 15, 1951; *C. A.*, 49, 372 (1955).

(35) S. Siggia, *Quantitative Organic Analysis Via Functional Groups*, 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1954, p. 69.

(36) Ref. 33, p. 190.

tion from methanol afforded 0.55 g. (53%) of white needles, m.p. 46.8–48.0°. The analytical sample was obtained by one further recrystallization from methanol yielding white needles, m.p. 47.3–48.3°.

Anal. Calc'd for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found (G): C, 88.02; H, 11.73.

ANN ARBOR, MICH.

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

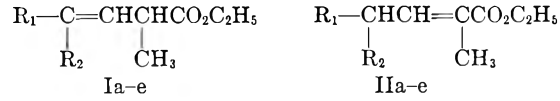
Olefinic Stability and Tautomeric Equilibria. I. Branched-Chain Unsaturated Esters[1]

KENNETH L. RINEHART, JR. AND LLOYD J. DOLBY

Received Aug. 6, 1956

The equilibria between conjugated and unconjugated isomers in two highly branched γ-alkyl unsaturated ester systems have been investigated. The proportion of unconjugated olefin has been shown to decrease with increasing branching in the γ-substituent. These results have been correlated with a number of earlier data and evidence has been presented supporting an interpretation in terms of steric interactions.

It was recently reported that the alkoxide-catalyzed isomerization of ethyl 4-ethyl-2-methyl-3-octenoate (Ib) leads to an equilibrium mixture containing approximately one third of this ester (or its glycol analog) and two thirds of the corresponding conjugated ester, ethyl 4-ethyl-2-methyl-2-octenoate (IIb).[2] The substitution of other *n*-alkyl groups for ethyl or *n*-butyl in the γ-position exerted little effect on the position of equilibrium in this system (Ic–IIc). However, when ethyl was replaced by methyl, the proportion of unconjugated isomer (Ia) in the equilibrated mixture with IIa was reported to be 56%.



Ia–e IIa–e

Ia, IIa: R_1 = *n*-$C_{10}H_{21}$, R_2 = CH_3
Ib, IIb: R_1 = *n*-C_4H_9, R_2 = C_2H_5
Ic, IIc: R_1 = *n*-C_7H_{15}, R_2 = *n*-C_7H_{15}
Id, IId: R_1 = *n*-C_4H_9, R_2 = *iso*-C_3H_7
Ie, IIe: R_1 = *n*-C_4H_9, R_2 = *tert*-C_4H_9

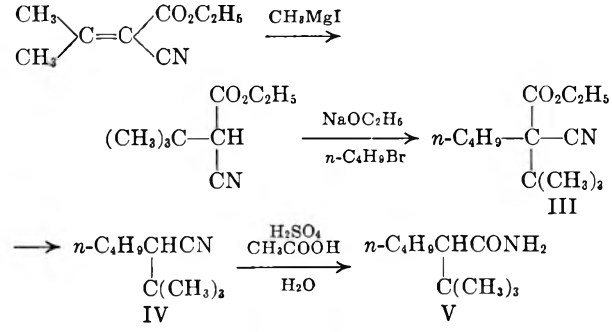
Enhanced hyperconjugative stabilization of the β,γ-double bond by the methyl group and reduced strain of the *cis*-type about the β,γ-double bond were considered as alternative explanations of the higher proportion of unconjugated isomer found in the equilibrated γ-methyl compounds. To examine these alternatives in systems containing more highly branched substituents, the corresponding esters with γ-isopropyl and γ-*tert*-butyl substituents (Id–IId and Ie–IIe, respectively) have been synthesized and the equilibrium mixtures of the two isomers determined after isomerization.[3]

(1) Presented in part at the 130th National Meeting of the AMERICAN CHEMICAL SOCIETY, Atlantic City, Sept. 16–21, 1956.

(2) J. Cason and K. L. Rinehart, Jr., *J. Org. Chem.*, 20, 1591 (1955).

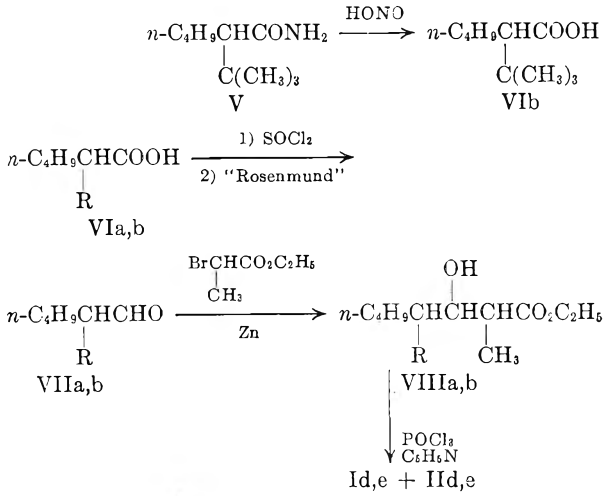
SYNTHESIS

Unsaturated esters required for these studies were prepared by dehydration of the β-hydroxy esters (VIIIa, VIIIb) formed in the Reformatsky reaction of the corresponding α-alkyl aldehydes (VIIa, VIIb) with ethyl α-bromopropionate. The aldehydes were obtained by Rosenmund reduction of the corresponding acid chlorides. Branched acids were prepared *via* modifications of the malonic ester synthesis. Thus, the synthesis of 2-*tert*-butylhexanoic acid (VIb) *via* ethyl isopropylidenecyanoacetate, ethyl *tert*-butylcyanoacetate and the dialkylcyanoacetate (III) is shown in the series of equations below. The corresponding 2-isopropylhexanoic acid (VIa) was prepared by a reaction sequence which is not shown, but which involved successive alkylations of malonic ester with isopropyl bromide and *n*-butyl bromide, followed by alkaline hydrolysis, acidification and decarboxylation.



III IV V

(3) The α-methyl substituent has been retained both as a point of reference throughout the series and to prevent thermal equilibration of the two isomers during distillation of the isomerized mixtures. Such equilibration is known to occur in the absence of an α-alkyl group [J. Cason, N. L. Allinger, and C. F. Allen, *J. Org. Chem.*, 18, 857 (1953)]. The α,γ-dialkyl system is further convenient in that no addition of alkoxide to the double bond has been found to occur for these compounds [*cf.* R. P. Linstead and E. G. Noble, *J. Chem. Soc.*, 610 (1934); R. P. Linstead, *J. Chem. Soc.*, 2498 (1929)].



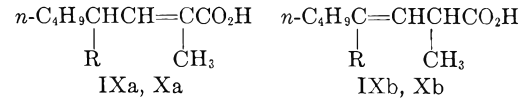
VI–VIIIa: R = *iso*-C_3H_7
VI–VIIIb: R = *tert*-C_4H_9

Alkylation of ethyl *tert*-butylcyanoacetate proceeded smoothly with sodium ethoxide as base (in contrast to the alkylation of isopropylmalonic ester, which required the stronger base potassium *tert*-butoxide). The ease of alkylation of the former compound despite the bulky *tert*-butyl group is explained by the stronger activation of the *alpha* hydrogen by the adjacent nitrile group. Hydrolysis of the α-*tert*-butyl nitrile (IV) gave the amide (V), which resisted further hydrolysis during 48 hours in a refluxing mixture of sulfuric acid, acetic acid, and water. Steric inhibition of amide hydrolysis has been observed previously[4a–d] and is to be expected with the bulky *tert*-butyl group in the position adjacent to the amide.[5] Treatment of the amide with nitrous acid,[4c, 4d, 4e] however, gave the desired acid (VIb) in 80% yield.

Over-all yields from aldehyde (VII) to the mixed unsaturated esters (I, II) were about 65%. Dehydration, effected with phosphorus oxychloride and pyridine, gave approximately equal quantities of conjugated and unconjugated esters (Id and IId) in the isopropyl series, but only 25% of the conjugated ester (IIe) and a preponderant amount of the β,γ-unsaturated isomer (Ie) in the γ-*tert*-butyl series, as estimated from refractive indices of distillation fractions containing the two isomers. From spectral and distillation data given previously it may be estimated that the corresponding dehydration mixtures of unsaturated esters obtained for the γ-methyl, γ-ethyl and γ-heptyl series (Ia and IIa, Ib and IIb, Ic and IIc) contained approximately 56%, 42%, and 53% of the conjugated esters, respectively.[2] There is, then, no observable trend in the proportion of α,β-unsaturated ester obtained in these dehydration mixtures as the γ-alkyl group is varied progressively from methyl (56%) to ethyl (42%) to isopropyl (50%) to *tert*-butyl (25%). While these relative percentages of the two isomers are, unfortunately, not highly accurate and are based on differing physical methods of analysis, they are presumed correct to within 10%. Within this accuracy it may be noted that the only mixture differing significantly in composition from one containing about 50% of each isomer is that obtained with the *tert*-butyl compounds, where the β,γ-unsaturated isomer was obtained in a ratio of 3:1.

Preferential formation of the unconjugated isomer in the dehydration of the γ-*tert*-butyl-β-hydroxy ester contrasts markedly with its lack of stability in the isomerizations described in the next section. It is also surprising in light of the recent work of Brown, Moritani, and Nakagawa, who have shown that both E_1 elimination[6] and E_2 elimination[7] proceed to give an increasing proportion of the isomeric olefin with the double bond further removed from the bulky group as the size of the group is increased. Factors influencing the dehydration, a rate-controlled process, have not been investigated for the present compounds and the mechanism of dehydration is in doubt, although at least a portion of the dehydration has been shown to occur *via* a β-alkyl phosphate.[8]

The isomeric unsaturated esters in each series were first purified by careful fractional distillation. The best samples of conjugated ester obtained from distillation were then further refined by saponification and partial re-esterification, which eliminated small quantities of the more readily esterified unconjugated acid.[2,8a] Similarly, partial esterification of the best distillation samples of unconjugated acids gave highly pure β,γ-unsaturated esters, which could be readily separated from the unesterified α,β-unsaturated acids. By this proce-



IXa,b: R = *iso*-C_3H_7
Xa,b: R = *tert*-C_4H_9

(4) (*a*) J. Cason and H. J. Wolfhagen, *J. Org. Chem.*, **14**, 153 (1949); (*b*) J. Cason, C. Gastaldo, D. L. Glusker, J. Allinger, and L. B. Ash, *J. Org. Chem.*, **18**, 1129 (1953); (*c*) N. Sperber, D. Papa, and E. Schwenk, *J. Am. Chem. Soc.*, **70**, 3091 (1948); (*d*) F. C. B. Marshall, *J. Chem. Soc.*, 2754 (1930); (*e*) W. E. Parham, W. N. Moulton and A. Zuckerbraun, *J. Org. Chem.*, **21**, 72 (1956).

(5) It may be noted that the empirical "rule of six" proposed by Newman [M. S. Newman, *J. Am. Chem. Soc.*, **72**, 4783 (1950); M. S. Newman, *Steric Effects in Organic Chemistry*, John Wiley and Sons, New York, 1956, pp. 206, 227] correlates amide hydrolysis and other carbonyl addition reactions with the degree of branching in aliphatic acids and their derivatives.

(6) (*a*) H. C. Brown and I. Moritani, *J. Am. Chem. Soc.*, **77**, 3607 (1955); (*b*) H. C. Brown and M. Nakagawa, *J. Am. Chem. Soc.*, **77**, 3610 (1955); (c) H. C. Brown and M. Nakagawa, *J. Am. Chem. Soc.*, **77**, 3614 (1955); (*d*) H. C. Brown and I. Moritani, *J. Am. Chem. Soc.*, **77**, 3623 (1955).

(7) (*a*) H. C. Brown, I. Moritani, and M. Nakagawa, *J. Am. Chem. Soc.*, **78**, 2190 (1956); (*b*) H. C. Brown and I. Moritani, *J. Am. Chem. Soc.*, **78**, 2203 (1956).

(8) K. L. Rinehart, Jr., Ph.D. dissertation, University of California, Berkeley, June, 1954, p. 42.

(8a) J. J. Sudborough and E. R. Thomas, *J. Chem. Soc.*, **99**, 2307 (1911).

TABLE I

PHYSICAL PROPERTIES OF 2,4-DIALKYLOCTENOIC ACIDS AND ESTERS

Compound	B.P., °C./Mm.	n_D^{25}	ϵ (mμ)
4-Isopropyl-2-methyl-2-octenoic acid	121–122/1.4	1.4639	13,900 (220)[a]
4-Isopropyl-2-methyl-3-octenoic acid	107–108/0.9	1.4507	2120 (220)
Ethyl 4-isopropyl-2-methyl-2-octenoate	95–96/2.5	1.4488	13,200 (218)[a]
Ethyl 4-isopropyl-2-methyl-3-octenoate	85–85.5/2.6	1.4368	1950 (218)
4-*tert*-Butyl-2-methyl-2-octenoic acid	128–130/1.4	M.p. 74–75°	13,800 (220)[a]
4-*tert*-Butyl-2-methyl-3-octenoic acid	110–111/0.9	1.4541	1925 (220)
Ethyl 4-*tert*-butyl-2-methyl-2-octenoate[b]	101–102/2.4	1.4513	12,860 (218)[a]
Ethyl 4-*tert*-butyl-2-methyl-3-octenoate	88–90/2.6	1.4395	2040 (218)

[a] Maximum. [b] Estimated to contain *ca.* 3% of saturated lactone (*cf.* Experimental).

dure, both the isomeric esters (Id and IId, Ie and IIe) and acids (IXa,b and Xa,b) were obtained for each homolog; physical properties are summarized in Table I.

Ultraviolet absorption spectra and refractive indices are seen to be quite different for the isomeric compounds. Refractive indices were employed in estimating the composition of the dehydration mixtures described above, while the ultraviolet absorption spectra of the isomeric acids IXa and IXb, Xa and Xb (*cf.* Fig. 1) were used for the calculation of the composition of isomerization mixtures, described in the next section. The conjugated isomer has a strong maximum near 220 mμ, in agreement with earlier observations for acids of this type.[2] The unconjugated acid has no strong absorption in this region. The spectra obtained for the unconjugated isomers in the present study have somewhat lower absorption than those described earlier, which indicates the higher state of purity achieved by the partial esterification procedure. While Fig. 1 gives the spectra of the isopropyl compounds IXa and IXb only, those of the *tert*-butyl compounds are nearly identical with these. The corresponding conjugated and unconjugated esters show similar spectral properties (*cf.* Table I).

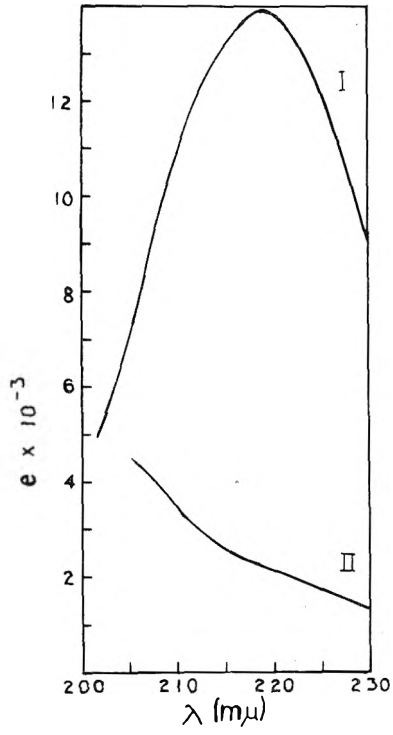


FIG. 1.—ULTRAVIOLET ABSORPTION SPECTRA OF ISOMERIC UNSATURATED ACIDS. I. 4-Isopropyl-2-methyl-2-octenoic acid. II. 4-Isopropyl-2-methyl-3-octenoic acid.

RESULTS OF EQUILIBRATIONS

The unsaturated esters were isomerized, employing sodium glycolate in refluxing ethylene glycol. Previous studies on the γ-ethyl analogs had shown that 27 hr. is a sufficient period to insure complete equilibration in esters of this type[2]; however, a somewhat longer time (36–41 hr.) was employed in the present studies to allow for the more highly branched substituents.

The work-up procedure after isomerization gives a mixture of isomeric unsaturated acids and the spectra of pertinent acids have been given in Fig. 1. From the absorption of the mixed acids isolated, compositions of the equilibrated mixtures have been calculated, as explained in the Experimental section.[9]

Two runs were made with the γ-isopropyl compounds to insure complete equilibration; the equilibrated mixtures were identical from the two runs and were calculated to contain 77% of the α,β-unsaturated isomer. The ultraviolet spectra of the equilibrated mixed γ-isopropyl acids IXa,b are given in Fig. 2, together with a theoretical spectrum calculated for a mixture of 77% conjugated isomer and 23% of the unconjugated compound; the three spectra are very nearly identical. The product from the γ-*tert*-butyl isomers contained 86% of α,β-unsaturated acid. Pertinent data are presented in Table II.

In order to insure that contamination of the

(9) The present ultraviolet method of analysis is similar to that employed by Bateman and Cunneen[10] and is more convenient and reliable than the iodine or bromine addition procedures employed by earlier investigators of tautomeric unsaturated acids and esters [R. P. Linstead and J. T. W. Mann, *J. Chem. Soc.*, 723 (1931); G. A. R. Kon, R. P. Linstead and J. M. Wright, *J. Chem. Soc.*, 599 (1934)].

(10) L. Bateman and J. I. Cunneen, *J. Chem. Soc.*, 2283 (1951).

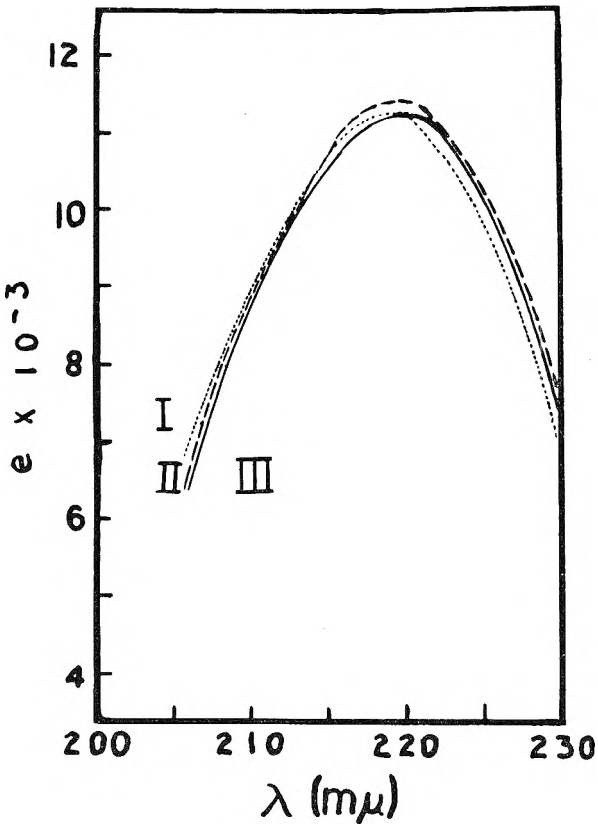


FIG. 2.—ULTRAVIOLET SPECTRA OF MIXTURES OF 4-ISOPROPYL-2-METHYL-2 (AND -3)-OCTENOIC ACIDS. I. Theoretical curve for a mixture containing 77% of the conjugated acid. II. Mixed acids isolated after 36 hours of equilibration by 3.4 N sodium glycolate in refluxing ethylene glycol (Run I). III. Mixed acids isolated after 39 hours of equilibration by 3.4 N sodium glycolate in refluxing ethylene glycol (Run II).

TABLE II

RESULTS OF EQUILIBRATIONS OF UNSATURATED ESTERS

Compound	Reflux Time, Hr.[a]	Per Cent of Conjugated Isomer Before equilibration	Per Cent of Conjugated Isomer After equilibration
4-Isopropyl-2-methyl-octenoates			
Run I	36	27	78
Run II	39	67	77
4-*tert*-Butyl-2-methyl-octenoates	41	16	86

[a] All equilibrations were performed with 3.4*N* sodium glycolate in refluxing ethylene glycol.

isomerization mixtures by nonequilibrating material was absent, the infrared spectra of the equilibrated γ-isopropyl acids (77% conjugated isomer) were examined and shown to be nearly identical with that of pure 4-ethyl-2-methyl-2-octenoic acid (IXa) except for minor differences in those regions where strong bands are shown by the corresponding 3-octenoic acid.

The equilibrium constant, K_{obs}, has been calculated for each of the isomerizations from the relative proportions of conjugated and unconjugated isomers measured by the spectral determinations. These are given in Table III, together with the corresponding constants for the γ-methyl and γ-ethyl compounds studied previously.

TABLE III

EQUILIBRIUM CONSTANTS AND FREE ENERGY DIFFERENCES FOR ISOMERIC UNSATURATED ESTERS

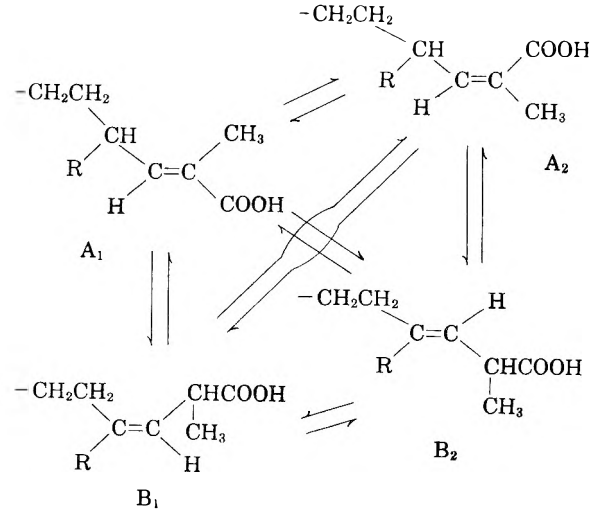
$$-CH_2CH_2-C(R)=CH-C(CH_3)-CO_2C_2H_5$$

R	Conjugated Isomer, %	K_{obs}[a]	K_{corr}[b]	$-\Delta F$,[c] Kcal.
CH_3	45	0.82	1.9–*2.7*	0.60–*0.93*
C_2H_5	68	2.1	4.2	1.33
iso-C_3H_7	78	3.5	*4.9*–6.1	*1.48*–1.68
tert-C_4H_9	86	6.1	6.1	1.68

[a] $K_{obs} = \frac{A_1 + A_2}{B_1 + B_2}$; A_1 and A_2 are *trans* and *cis* α,β-unsaturated isomers, respectively. B_1 and B_2 are *trans* and *cis* β,γ-unsaturated isomers, respectively. [b] $K_{corr} = \frac{A_1}{B_1}$. [c] $\Delta F = -RT \ln K_{corr}$; T = 468°K.

It is apparent that the observed equilibrium constants are in reality a measure and summation of six distinct and separate equilibria, since both α,β- and β,γ-unsaturated forms exist as *trans* and *cis* isomers, A_1 and A_2, B_1 and B_2, respectively, and each can isomerize *via* an enolate ion to any of the others. Thus,

$$K_{obs} = \frac{A_1 + A_2}{B_1 + B_2}$$



R = CH_3, C_2H_5, *iso*-C_3H_7, *tert*-C_4H_9

In order to compare the effect of the methyl, ethyl, isopropyl, and *tert*-butyl substituents in a single series of compounds it is desirable to isolate a single equilibrium from the six above. For each of the pairs of *trans* isomers A_1 and B_1 there has been

calculated a corrected equilibrium constant, $K_{corr} = A_1/B_1$, and from these constants the free energy differences between the pairs of *trans* isomers.[11] The results of these calculations are also given in Table III.

In calculating K_{corr} from K_{obs} it has been assumed that none of the *cis* conjugated isomer A_2 is present. The pure conjugated acids in the present series have physical constants nearly identical to those of the *trans* isomers described by Cason and Kalm, who studied both *cis*- and *trans*-2-methyl-2-alkenoic acids.[12] In particular, the ultraviolet absorption spectra of the *trans* compounds of these authors showed maxima at 217 mμ, ϵ_{max} 13,600 (in good agreement with the present spectral data in Table I), while the *cis* isomers had λ_{max} 218 mμ, ϵ_{max} 8,800. After isomerization of the present compounds the absorption maxima (11,300 for the γ-isopropyl mixtures, 12,200 for the γ-*tert*-butyl) remained considerably above that of the *cis* compounds (8800) and, as indicated above, the spectra were nearly identical in shape with that calculated for a mixture of *trans* conjugated and mixed unconjugated isomers. Further, as indicated above, the infrared spectrum of the isomerized γ-isopropyl acids agrees well with that of the pure conjugated acid, and it in turn with that of the *trans* isomer of Cason and Kalm, which is different from the spectrum of the *cis* isomer, particularly in the regions 1475–1425 cm.$^{-1}$ and 1300–1265 cm.$^{-1}$ Then

$$K_{obs} = \frac{A_1}{B_1 + B_2} = \frac{K_{corr}}{1 + K'}, \text{ where } K' = \frac{B_2}{B_1}$$

The value of K' differs for each of the systems studied and can only be approximately estimated since pure *cis* and *trans* isomers of this type have not been obtained and would be expected to be not only difficultly separable, but very similar in properties. However, two limiting cases are apparent among the present isomerides. For the γ-*tert*-butyl compounds, K' may be taken as zero and $K_{obs} = K_{corr}$, since in the *cis*-isomer B_2 the bulky *tert*-butyl group would exhibit very large steric interactions with the propionate group. That this approximation is reasonable is shown by molecular models (Stuart-Briegleb), from which the *cis*-isomer cannot be made. It may also be noted that Brown and Nakagawa obtained an 83:1 *trans*:*cis* ratio of the isomeric 4,4-dimethyl-2-pentenes (*sym*-*tert*-butylmethylethylenes) from the solvolytic elimination of 2-(4,4-dimethylpentyl)-*p*-bromobenzenesulfonate (*cf.* Table IV).[6c]

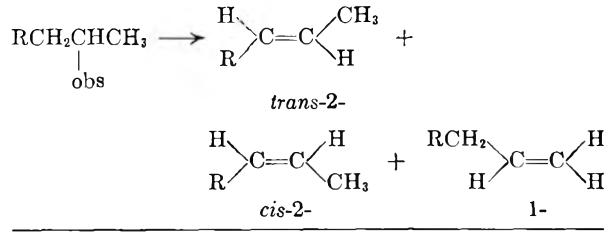
The other limiting case is that of the γ-ethyl compounds, where the two β,γ-unsaturated isomers should be formed in equivalent amounts, as the effect of *n*-alkyl substitution is nearly identical to that of ethyl.[2] Here $K' = 1$ and $K_{corr} = 2\,K_{obs}$.

For the γ-methyl and γ-isopropyl esters, estimation of K' is more difficult, although K' is certainly greater than unity for the methyl compounds and less than unity for the isopropyl isomers. Brown and Nakagawa have determined the relative amounts of *cis* and *trans* olefins formed in E_1 eliminations and from these data an estimate may be obtained of the relative effects of varying alkyl groups on olefin stability (Table IV).[6c] It may be seen that r = *trans*/*cis* is 1.39 for *sym*-methylethylethylene, 1.08 for *sym*-dimethylethylene and 1.94 for *sym*-isopropylmethylethylene. While these values may not involve equilibrium mixtures the relative effects for the various isomers undoubtedly parallel the equilibria involved. Thus, to compare the relative interaction of isopropyl and ethyl, $r_{ethyl}/r_{isopropyl} = 1.39/1.94$ is taken as a first approximation to K', and $K_{corr} = 1.71\,K_{obs}$. Since the α-propionate group attached to the double bond (β-carbon) in the present compounds is larger than the methyl group of the compounds investigated by Brown and Nakagawa, the *cis* interaction in the esters under consideration would be considerably larger. To correct for this effect a second approximation may be introduced, $r_{methyl}/r_{isopropyl} = 1.08/1.94$, where the bulk of an isopropyl group has been assumed to approximate that of the α-propionate group of the esters investigated. Then, to this second approximation,

$$K_{obs} = \frac{K_{corr}}{1 + (1.39/1.94)(1.08/1.94)}; \quad K_{corr} = 1.40\,K_{obs}$$

TABLE IV

COMPOSITION OF OLEFINS FORMED IN SOLVOLYSIS OF ALKYL BROSYLATES[a]



R	Per Cent of Total Olefin *trans*-2, %	*cis*-2, %	1-	r^c	1-/2-
CH_3[b]	46.5	43.5	10.3	1.08	0.11
C_2H_5	48.8	35.5	15.7	1.39	0.19
iso-C_3H_7	53.0	27.3	19.7	1.94	0.25
tert-C_4H_9	74.8	0.9	24.3	83	0.32

[a] Data of Brown and Nakagawa.[6c] Solvolysis in anhydrous acetic acid at 70°. [b] Tosylate. [c] r = *trans*-2/*cis*-2.

Similarly, for the γ-methyl compounds $r_{ethyl}/r_{methyl} = 1.39/1.08$ and $K_{corr} = 2.29\,K_{obs}$ (first approximation) and $K_{corr} = 3.32\,K_{obs}$ (second approximation). Both the first and second (underlined) ap-

(11) The trans α,β-unsaturated isomer is that with the β-alkyl group *trans* to the carboxyl. In the present discussions we have taken the *trans* β,γ-unsaturated isomer to be that with the varied alkyl group (methyl, ethyl, isopropyl, *tert*-butyl) *trans* to the propionate residue.

(12) J. Cason and M. J. Kalm, *J. Org. Chem.*, 19, 1947 (1954).

proximations of the equilibrium constants and free energy differences in the two series are given in Table III.

DISCUSSION

From the data presented in Table III it is apparent that the stability of an olefinic system depends upon the nature of the alkyl substituents at the double bond. The relative stabilizing effect of an alkyl group decreases from methyl through *tert*-butyl and may be summarized methyl > ethyl > isopropyl > *tert*-butyl. The over-all effect is rather large and the summation of the various equilibria involved (K_{obs}) shifts from an equilibrium slightly favoring the unconjugated isomer (γ-methyl substituent) to one in which the unconjugated compound is present in only small amount (γ-*tert*-butyl substituent).

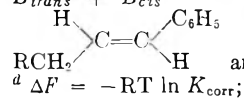
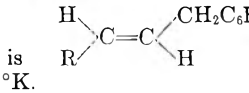
In evaluating the equilibrium constant $K_{obs} = (A_1 + A_2)/(B_1 + B_2)$ the amount of A_2, the *cis* conjugated isomer, has, as indicated above, been assumed to be negligible. The value of K_{obs} depends then on the concentrations of the *trans* conjugated isomer A_1 and of the two unconjugated isomers B_1 and B_2, and thus on the relative stabilities of these three species. A major portion of the change in K_{obs} in this series as the γ-alkyl substituent is made progressively more branched is due to a sharp decrease in the amount of B_2. In this *cis* unconjugated isomer (B_2) a bulky group (as *tert*-butyl) on the same side of the double bond as the α-propionate residue gives rise to strong steric repulsions. Interaction of this type between *cis* alkyl groups has long been recognized to lead to olefin destabilization[6c, 13, 26] and was earlier suggested as the predominant reason for the higher proportion of conjugated isomer found at equilibrium in the γ-ethyl substituted system compared to γ-methyl.[2]

On the other hand, the equilibrium constant $K_{corr} = A_1/B_1$ attempts to estimate the variation in the relative stabilities of the various *trans* unconjugated isomers, as distinct from the recognized increasing instability of the *cis* unconjugated isomers. From these calculations, equilibria between the *trans* isomers A_1 and B_1 are seen to favor the conjugated compound (A_1) in every case. Variations in K_{corr} for the various γ-alkyl unsaturated systems are not large; the equilibrium constant varies from 2.7 to 6.1 and there is a free energy difference of less than 0.8 kcal. between the methyl substituted compound and the *tert*-butyl.[14] These differences, though small, are, however, real and may be interpreted in varying ways.[15]

Bateman and Cunneen, who investigated equilibrations in γ-alkyl-phenylpropenes, observed a similar shift in equilibrium from the unconjugated isomer as the size of the γ-alkyl group was increased.[10] Pertinent data from this work, together with corrections based on relative amounts of *cis* and *trans* isomers similar to those described above, are presented in Table V.[16] These and other authors[17–20] have attributed the decreased stability of the olefins substituted with larger alkyl groups to a loss of carbon-hydrogen (C—H) hyperconjugation in progressing from methyl (with three α-hydrogens) to ethyl (two) to isopropyl (one) to *tert*-butyl (no α-hydrogens), and have assigned a value of 0.2–0.3 kcal. to each possible C—H hyperconjugation structure.[21] Changes in free energy with alteration of the alkyl substituent in the present series are seen to be of the same order of magnitude as those observed by Bateman and Cunneen, and C—H hyperconjugation remains a useful tool for the prediction of relative olefin stability.

TABLE V
EQUILIBRIUM COMPOSITIONS IN SYSTEMS[a]
$RCH{=}CH{-}CHC_6H_5$

R	% Conjugated Isomer[a]	K_{obs}[b]	K_{corr}[c]	$-\Delta F$,[d] Kcal.
CH_3	82	4.56	4.90	1.38
iso-C_3H_7	89	8.10	8.10	1.82
tert-C_4H_9	91	10.12	9.16	1.93

[a] Data of Bateman and Cunneen.[10] Isomerization in 20% methanolic potassium hydroxide at 165°. [b] $K_{obs} = \frac{A_{trans} + A_{cis}}{B_{trans} + B_{cis}}$. [c] $K_{corr} = A_{trans}/B_{trans}$, where A_{trans} is  and B_{trans} is  . [d] $\Delta F = -RT \ln K_{corr}$; $T = 438°K$.

(13) A value may be assigned to the *cis*-interaction of two methyl groups, based on heat of hydrogenation data for *cis*- and *trans*-2-butenes, where the difference between the two isomers is 1.0 kcal. [G. B. Kistiakowsky, J. R. Ruhoff, H. A. Smith, and W. E. Vaughan, *J. Am. Chem. Soc.*, 57, 876 (1935)] (Table VI, D and E).

(14) Although a good bit of approximation has been employed in the estimation of the methyl and isopropyl equilibria, the ethyl and *tert*-butyl figures rest on firmer support. Since K_{corr} and ΔF vary in a direct qualitative fashion throughout the series, discussion may be extended without serious inaccuracy from a comparison of ethyl and *tert*-butyl to the whole series.

(15) It has been assumed that the stability of the conjugated isomer A_1 remains constant throughout the present series. Thus, both conjugation with the carboxyl group and hyperconjugation, the latter treated in detail for the β,γ-unsaturated isomers, do not vary for the α,β-unsaturated isomers. Further, steric interaction, judged from models, does not differ significantly for the variously substituted esters.

(16) The first indication of the lessened stabilizing effect of higher alkyl substituents relative to methyl is to be found in the work of Linstead [A. A. Goldberg and R. P. Linstead, *J. Chem. Soc.*, 2343 (1928)] (Table VII, B, C, and D).

(17) (*a*) C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, Cornell University Press, Ithaca, New York, 1953, p. 564. (*b*) P. B. D. de la Mare, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 22 (1948).

(18) F. Becker, *Fortschr. chem. Forsch.*, 3, 187 (1955).

(19) J. W. Baker, *Hyperconjugation*, Oxford University Press, London, 1952, p. 64.

(20) E. R. Alexander, *Principles of Ionic Organic Reactions*, John Wiley and Sons, New York, 1950, p. 283.

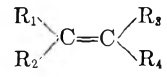
(21) Bateman and Cunneen attributed 0.3 kcal. to each C—H hyperconjugation structure in their phenyl-propenes, but only 0.2 kcal. to each structure in unsaturated esters, nitriles and acids.

There are certain theoretical considerations, however, which lead one to question seriously the validity of C—H hyperconjugation as the true reason for the enhanced stability of methyl over *tert*-butyl substituted olefins. There seems little doubt that alkyl substitution generally enhances the stability of a double bond. Thus, the studies of Kistiakowsky (*cf.* Table VI) have shown that the heat of hydrogenation of *trans*-2-butene, with two alkyl substituents, is 2.7 kcal. more than that of 1-butene, with one substituent (Table VI, E and C, respectively). Further, in progressing from ethene to 1-propene to *trans*-2-butene (Table VI, A, B, and E), the heat of hydrogenation is progressively reduced by about 2.6 kcal. per additional alkyl substituent and additional, somewhat smaller effects are observed with further methyl substitution (Table VI, F and G).

Similarly, the position of equilibrium in isomerized unsaturated acids was early shown to depend on the degree of substitution at each of the centers of unsaturation and while the equilibrium mixture of butenoic acids (no *alpha* or *gamma* substituents—Table VII, A) contained 98% of the conjugated

TABLE VI

HEATS OF HYDROGENATION OF OLEFINS[a]

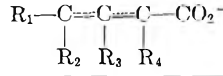


Compound	R_1	R_2	R_3	R_4	Heat of Hydrogenation,[a] Kcal.
A Ethene	H	H	H	H	32.8[b]
B Propene	CH_3	H	H	H	30.1[c]
C 1-Butene	C_2H_5	H	H	H	30.3[c]
D *cis*-2-Butene	CH_3	H	CH_3	H	28.6[c]
E *trans*-2-Butene	CH_3	H	H	CH_3	27.5[c]
F 2-Methyl-2-butene	CH_3	CH_3	CH_3	H	26.9[d]
G 2,3-Dimethyl-2-butene	CH_3	CH_3	CH_3	CH_3	26.6[d]
H 3-Methyl-1-butene	*iso*-C_3H_7	H	H	H	30.3[e]
I 3,3-Dimethyl-1-butene	*tert*-C_4H_9	H	H	H	30.3[e]
J 2-Methyl-1-butene	C_2H_5	CH_3	H	H	28.5[d]
K 2,4,4-Trimethyl-2-pentene	*tert*-C_4H_9	H	CH_3	CH_3	28.4[e]
L 2,4,4-Trimethyl-1-pentene	*neo*-C_5H_{11}	CH_3	H	H	27.2[e]

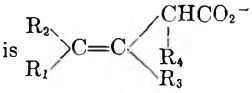
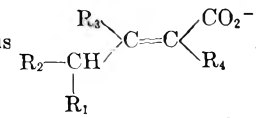
[a] Data of Kistiakowsky *et al.* Heats of hydrogenation are for gaseous reactants and products at 1 atmosphere and 82°C. [b] G. B. Kistiakowsky, H. Romeyn, Jr., J. R. Ruhoff, H. A. Smith, and W. E. Vaughan, *J. Am. Chem. Soc.*, **57**, 65 (1935). [c] G. B. Kistiakowsky, J. R. Ruhoff, H. A. Smith and W. E. Vaughan, *J. Am. Chem. Soc.*, **57**, 876 (1935). [d] G. B. Kistiakowsky, J. R. Ruhoff, H. A. Smith and W. E. Vaughan, *J. Am. Chem. Soc.*, **58**, 137 (1936). [e] M. A. Dolliver, T. L. Gresham, G. B. Kistiakowsky and W. E. Vaughan, *J. Am. Chem. Soc.*, **59**, 831 (1937).

TABLE VII

EQUILIBRIUM COMPOSITIONS IN UNSATURATED SYSTEMS[a]



Item	R_1	R_2	R_3	R_4	% α,β[a]	K_{obs}[b]	K_{corr}[c]	$-\Delta F$,[d] Kcal.
A	H	H	H	H	98	49	98.0	3.40
B	CH_3	H	H	H	68	2.12	2.55	0.70
C	C_2H_5	H	H	H	74	2.85	3.30	0.89
D	*iso*-C_3H_7	H	H	H	82[e]	4.56	5.07	1.21
E	CH_3	CH_3	H	H	6[f]	0.064	0.128	1.48
F	CH_3	H	H	CH_3	81[f]	4.26	4.88	1.17
G	CH_3	H	C_2H_5	H	21[g]	0.266	0.532	0.47
H	C_2H_5	H	*n*-C_3H_7	H	34[h]	0.515	1.03	0.02
I	*iso*-C_3H_7	H	*iso*-C_4H_9	H	49[f]	0.96	1.92	0.50

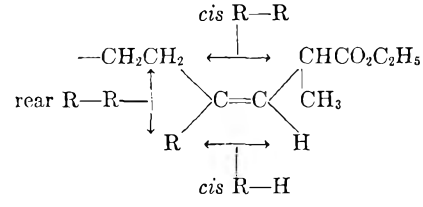
[a] From data of Kon, Linstead *et al.* Isomerizations conducted in aqueous potassium hydroxide (10 equivalents) at 100°C. [*cf.* R. P. Linstead and E. G. Noble, *J. Chem. Soc.*, 614 (1934)]. [b] $K_{obs} = \frac{\text{total, } \alpha,\beta\text{-unsaturated isomers}}{\text{total, } \beta,\gamma\text{-unsaturated isomers}}$. [c] $K_{corr} = \frac{A_1}{B_1}$, where A_1 is  and B_1 is  . [d] $\Delta F = -RT \ln K_{corr}$; $T = 373°K$. [e] R. Fittig, *Ann.*, **283**, 47 (1894). Cited in Ref. (16) in text. [f] Ref. (16) in text. [g] G. A. R. Kon, E. Leton, R. P. Linstead and L. G. B. Parsons, *J. Chem. Soc.*, 1411 (1931). [h] Ref. (9) in text.

isomer, the pentenoic acids (one *gamma* substituent) contained 68% and the 4-methylpentenoic acids (two *gamma* substituents) only 6% (Table VII, B and E, respectively). Conversely, *alpha* substitution, as in 2-methylpentenoic acids (Table VII, F) gave a shift to higher percentages of conjugated isomer (81%).

While it may then be agreed that alkyl substitution on a double bond in general increases the stability of the olefin, the degree to which a particular alkyl group stabilizes the olefin varies. Hyperconjugation of the C—H type has been invoked in this regard as indicated above. Recently, however, C—H hyperconjugation as the most important mode of alkyl electron release in substituted benzenes has been criticized by several authors[22-24] and these criticisms are equally valid in application to the present studies. Schubert and Sweeney have pointed out that in many of those properties which depend least on solvent effect the influence of methyl, ethyl, isopropyl, and *tert*-butyl substituents is very similar and is in the opposite direction to that predicted from C—H hyperconjugation. In particular, the *E*-bands in the ultraviolet spectra of *p*-alkyl nitrobenzenes, acetophenones and benzoic acids, and especially of their conjugated acids and of the triphenylmethylcarbonium ions, showed shifts in wave length and extinction coefficient more in keeping with a greater electron release by *tert*-butyl than methyl. Although these authors did not attempt to distinguish between C—C hyperconjugation and other modes of electron release as the predominating alkyl effect, it is clear that C—H hyperconjugation is not the only variable to be considered.[25] In the present compounds solvent effects should be relatively small since the two isomeric olefins are uncharged; hence by the above reasoning C—H hyperconjugation as a dominant effect is not to be expected. Further evidence against C—H hyperconjugation as the predominating influence may be seen in the heats of hydrogenation of methyl, ethyl, isopropyl, and *tert*-butyl ethylenes (Table VI, B, C, H, and I, respectively), which, within experimental error, are identical.

An alternative explanation of the present observations exists in steric interactions. These have, as indicated above, been recognized as important when involving alkyl-alkyl (R—R) interaction *cis* about a double bond. The magnitude of these effects is often large, as may be assessed by comparing the heats of hydrogenation of the isomeric 2-methyl-2 (and -1)-butenes and the 2,4,4-trimethyl-2(and -1)-pentenes (Table VI, F-J and K-J). In the former pair the 2-isomer is more stable by 1.6 kcal., while in the latter pair the 1-isomer is favored by 1.2 kcal., even though the double bond is less highly substituted. From these data, if methyl-methyl interaction involves about 1.0 kcal. of hindrance,[13] then methyl-*tert*-butyl R-R interaction may be estimated at *ca.* 3.8 kcal.[26]

In the present compounds interaction of the *cis* R-R type remains nearly constant in the β,γ-unsaturated isomer, involving interaction of a *n*-alkyl group with the α-propionate residue. There is, however, an increasing amount of steric repulsion between the β-hydrogen and the γ-alkyl substituent (methyl < ethyl < isopropyl < *tert*-butyl) in the series (*cis* R-H interaction). That such interaction is small is shown by the small increment in ΔF between the variously substituted compounds (0.2–0.4 kcal.). However, interference is not negligible and may be observed in molecular models of the unsaturated esters.



Such models suggest that the influence of branched substituents is somewhat more complex than that of simple R—H repulsion mentioned above. In particular, interaction between the two *gamma* substituents becomes serious with the larger substituents (rear R—R interaction).[26a] The methyl-substituted compound is the only one in which there is no compression of the *n*-alkyl group by the second γ-substituent. In all others there is restriction of rotation of the *n*-alkyl when the second alkyl substituent is in such a conformation as to minimize its interaction with the β-hydrogen (rear R—R repulsion) and there is repulsion by the β-hydrogen when the γ-alkyl substituent is in such a conformation as to minimize its interaction with the *n*-alkyl substituent (*cis* R—H interaction). In the γ-*tert*-butyl compound the total effect reaches a maximum and the compound is effectively locked in one con-

(22) W. M. Schubert and W. A. Sweeney, *J. Org. Chem.*, 21, 119 (1956).

(23) A. Burawoy and E. Spinner, *J. Chem. Soc.*, 3752 (1954).

(24) V. J. Shiner, Jr., *J. Am. Chem. Soc.*, **76**, 1603 (1954).

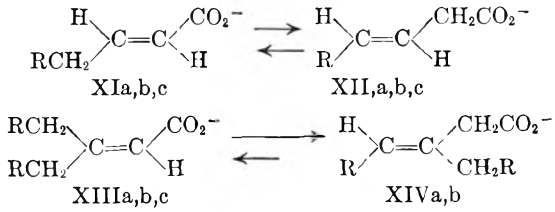
(25) Bateman and Cunneen[10] assigned a value 0.03 kcal. to each C—C hyperconjugation structure and assumed these could be neglected.

(26) Brown has recently assigned a value of 6.0 kcal. to this *cis* methyl-*tert*-butyl strain.[6b]

(26a) Steric compression of a similar nature ("B-strain") has been employed by Brown [for a review, *cf.* H. C. Brown, *J. Chem. Soc.*, 1248 (1956)] to explain the relative basicities of primary, secondary, and tertiary amines and the enhanced solvolytic rates of highly branched tertiary halides. The results in both of these systems were considered to be dut to a relief of strain in going from a tetrahedral to a trigonal state. The present "rear R—R" interaction makes no attempt to evaluate the relative stabilities of the tetrahedral and trigonal states, but is considered as a contributing part of the general steric rigidity about the double bond.

formation, in which there is repulsion of the *tert*-butyl group by both the β-hydrogen and the *n*-butyl group and also an enhanced *n*-butyl-α-propionate (*cis* R—R) interaction. From these considerations it may be been that the steric interactions are quite complex, and involve both primary and secondary effects.

A primary advantage of the steric approach in describing the results of isomerizations of unsaturated systems is that steric interactions are quite useful in explaining a number of anomalies unresolved by the hyperconjugation treatment. Thus, β-alkyl (or phenyl) substitution in an unsaturated ester system has been shown to increase the proportion of unconjugated isomer present at equilibrium (*cf.* Table VII, B *vs.* G, C *vs.* H, D *vs.* I) and this cannot be easily explained by C—H hyperconjugation since the β-substituent can hyperconjugate equally with either an α,β- or a β,γ-double bond.[17,19] A portion of this effect may be ascribed to the presence of a greater number of β,γ-unsaturated isomers present in the mixture, but even after correction for this statistical effect (Table VII) there is a definite shift toward the unconjugated isomer with β-substitution. The equilibria measured by K_{corr} are given below (XI–XII and XIII–XIV), where it may be seen that the introduction of a β-alkyl substituent introduces a *cis* opposition between β-alkyl and carboxylate in the conjugated isomer (XIII) and a *cis* opposition between β-alkyl and γ-alkyl in the unconjugated isomer (XIV).

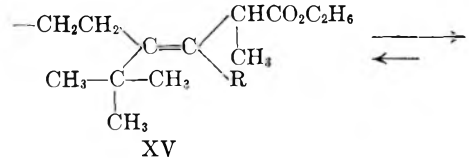


XIa,b,c XII,a,b,c

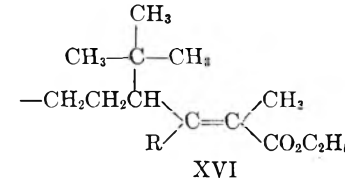
XIIIa,b,c XIVa,b

XIa, XIIa, XIIIa, XIVa: R = CH_3
XIb, XIIb, XIIIb, XIVb: R = C_2H_5
XIc, XIIc, XIIIc, XIVc: R = *iso*-C_3H_7

The results of isomerizations of β-substituted systems are readily interpreted if it is assumed that a carboxylate anion exerts a higher degree of repulsion on a *cis*-alkyl group than the repulsion exerted by another alkyl group.[27] If this be the case, then the *relative* effect of carboxylate *vs.* alkyl should decrease in the series methyl > ethyl > isopropyl. That this is indeed so is seen from the data of Table VII. By comparing appropriate systems it is seen that the difference in the free energy between the conjugated and unconjugated isomers without β-substituent and the free energy between the conjugated and unconjugated isomers with β-substituent ($\Delta F_{unsub} - \Delta F_{\beta\text{-sub}}$) is greatest in the case of the γ-methyl systems B and G (Table VII), where this difference is *ca.* 1.2 kcal. In the γ-ethyl systems (Table VII, C and H) the difference amounts to *ca.* 0.9 kcal., while in the γ-isopropyl systems (Table VII, D and I) it is about 0.7 kcal. Thus, in agreement with the above prediction, the order of repulsive effect is $-CO_2^- > iso\text{-}C_3H_7 > C_2H_5 > CH_3$. On the basis of this explanation it may be predicted that equilibration of a system similar to the present ones with γ-*tert*-butyl group but with a β-alkyl substituent (XV, XVI) would probably lead to a higher proportion of conjugated isomer (XVI) than the present systems without such β-substitution. We hope to report on results in such β-substituted compounds in a future communication.



XV

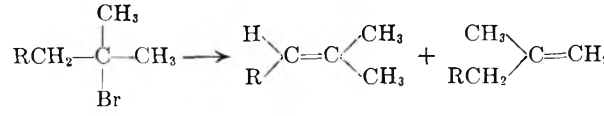


XVI

The present study deals with equilibrium or thermodynamically controlled processes and no attempt has been made to correlate these data with the numerous literature references concerning rate or kinetically controlled processes. It may be noted, however, that the recent work of Brown has shown that an increasing proportion of the less substituted isomer is formed in elimination reactions (both E_1 and E_2) as the size of the alkyl group R to be substituted on the olefin is increased.[6,7] Further, the influence of the branched alkyl in effecting this shift is more pronounced in the second series involving the elimination from a tertiary center (*cf.* Table VIII), than in the series dealing with elimi-

TABLE VIII

COMPOSITION OF OLEFINS FORMED IN SOLVOLYSIS OF ALKYL BROMIDES[a]



R	Per Cent of Total Olefin 2-, %	1-, %	1-/2-
CH_3	79	21	0.27
C_2H_5	71	29	0.41
iso-C_3H_7	59	41	0.70
tert-C_4H_9	19	81	4.26

[a] Data of Brown and Nakagawa.[6b] Solvolysis in *n*-Butyl Cellosolve at 25°C.

(27) Judged from bond radii and van der Waal's radii, the size of a carboxylate group is somewhat smaller than an isopropyl group, although the geometry is somewhat different, as the carboxylate is planar rather than tetrahedral. However, the full negative charge of the carboxylate anion might well repel other groups more strongly than the neutral alkyl residues.

nation from a secondary center (Table IV). This has been attributed by Brown to steric repulsion between alkyl R and methyl groups (*cis* R—R) in the former series,[6b] which should be considerably larger than the repulsion between alkyl and hydrogen (*cis* R—H) in the latter series.[6c]

In summary, then, the stability of substituted unsaturated esters is determined largely by the number of alkyl substituents on each isomeric olefin. A more highly branched substituent is generally less effective in stabilizing the double bond, and while this is in agreement with C—H hyperconjugation predictions, steric interactions are believed to offer a somewhat more satisfying explanation of the effect.

EXPERIMENTAL[28]

2-Isopropylhexanoic acid was prepared *via* two malonic ester syntheses. Diethyl isopropylmalonate,[31] obtained in 80% yield by a standard procedure,[32] had b.p. 212–214° (109–112°/21 mm.), n_D^{25} 1.4178 (lit.[32] b.p. 132–135°/44 mm.). The monoalkyl malonic ester was heated for one hour under reflux with potassium *tert*-butoxide[33] before the addition of *n*-butyl bromide. Diethyl *n*-butylisopropylmalonate,[31] which was obtained in 50% yield by this modified procedure, had b.p. 141–142°/28 mm., n_D^{25} 1.4310 (lit.[34] b.p. 136°/14 mm., n_D^{25} 1.4291). The disubstituted malonic ester (154.5 g.) was saponified with refluxing ethanolic potassium hydroxide to give the crude dibasic acid, which was decarboxylated by heating for two hours at 180°. Fractional distillation of the product gave 89.1 g. (74%) of 2-isopropylhexanoic acid, b.p. 121°/12 mm., n_D^{25} 1.4266 (lit.[35] b.p. 125°/10 mm., n_D^{25} 1.4270).

2-Isopropylhexanal was synthesized *via* the Rosenmund reduction of the corresponding acid chloride, prepared according to Bishop.[36] A mixture of 62 g. of 2-isopropylhexanoic acid and 125 g. of thionyl chloride was heated overnight under reflux and excess thionyl chloride was removed under aspirator pressure. Distillation through a short Vigreux column yielded 65 g. (94%) of 2-isopropylhexanoyl chloride, b.p. 75–78°/12 mm., n_D^{25} 1.4336 (lit.[37] b.p. 155–158°).

The procedure of Hershberg and Cason[38] was followed for reduction. In a run employing 65 g. of 2-isopropylhexanoyl chloride, 225 ml. of sodium-dried xylene, 11.2 g. of palladium-barium sulfate catalyst and 0.68 ml. of stock poison reaction had nearly ceased after 9 hrs., when 80% of the theoretical amount of hydrogen chloride had been evolved. The mixture was treated with Norit and filtered and the entire filtrate was fractionally distilled to give 34.6 g. (66%) of 2-isopropylhexanal, b.p. 85–86°/40 mm., n_D^{25} 1.4236. The aldehyde decomposed slowly on standing and gave unsatisfactory elemental analyses.

The *2,4-dinitrophenylhydrazone*[39] had m.p. 140.5–141° after two crystallizations from 95% ethanol.

Anal. Calc'd for $C_{15}H_{22}N_4O_4$: C, 55.88; H, 6.87; N, 17.38. Found: C, 55.82; H, 6.65; N, 17.14.

In a second run the yield of aldehyde was 58%.

Preparation and dehydration of ethyl 4-isopropyl-2-methyl-3-hydroxyoctanoate was effected by a procedure which has previously been described in detail.[2] A solution of 8.3 g. of 2-isopropylhexanal and 28.8 g. of ethyl α-bromopropionate in 83 ml. of sodium-dried benzene was added during one hour to 10.4 g. of zinc foil and 70 ml. of refluxing dry benzene. Refluxing was continued for two additional hours. Work up in the usual manner,[2] followed by fractional distillation, yielded 8.7 g. (61%) of ethyl 4-isopropyl-2-methyl-3-hydroxyoctanoate, b.p. 111°/2.3 mm., n_D^{25} 1.4455.

Anal. Calc'd for $C_{14}H_{28}O_3$: C, 68.41; H, 11.48. Found: C, 68.40; H, 11.23.

In a second run carried out in the same manner as the first, employing 34.6 g. of 2-isopropylhexanal, 120 g. of ethyl α-bromopropionate and 43.1 g. of zinc foil, the crude β-hydroxy ester was not distilled but was combined with the fractionated product from the first run and dehydrated directly to the mixed unsaturated esters, as described in the next paragraph.

The hydroxy ester obtained from the two runs above was dissolved in 312 g. of pyridine and cooled to *ca.* 0°. To the solution was added slowly with vigorous swirling 68 g. of phosphorus oxychloride. The mixture was allowed to stand 18 hours at room temperature, then was heated for 1½ hr. on the steam bath. Work-up in the usual manner, followed by fractional distillation, yielded 44.6 g. (65%, based on total starting aldehyde in the two Reformatsky runs) of mixed unsaturated esters contained in eighteen fractions. These included 5.1 g. of the β,γ-unsaturated ester (96% pure), b.p. 87–90°/2.8 mm., n_D^{25} 1.4372, 33.0 g. of intermediate fractions (containing *ca.* 50% of each isomer), b.p. 90–99°/2.8 mm., and 6.5 g. of the α,β-unsaturated isomer (98% pure), b.p. 97°/2.6 mm., n_D^{25} 1.4489. The composition of the above fractions was estimated from the refractive indices of the pure compounds (*cf.* below); the dehydration mixture thus contained approximately equal quantities of the two isomers.

Ethyl 4-isopropyl-2-methyl-3-octenoate. The best sample of β,γ-unsaturated ester from the fractional distillation in the preceding section (n_D^{25} 1.4372) was saponified with refluxing 2*N* ethanolic potassium hydroxide. The crude acid obtained was dissolved in 22.4 ml. of commercial absolute

(28) Melting points and boiling points are uncorrected. Unless otherwise noted, distillations were through a 4-ft. Podbielniak-type column.[29] Refractive indices are corrected to 25° using 0.0004/deg.[30] Ultraviolet spectra were determined, in duplicate, with a Beckman quartz spectrophotometer, Model DU; samples were prepared in specially purified heptane in concentrations such that the absorbances were in the range 0.3–0.6. Infrared spectra have been determined for all the compounds described and are on file in the Infrared Laboratory, Department of Chemistry and Chemical Engineering, University of Illinois. We are indebted to Mr. Jozsef Nemeth, Mrs. Maria Benassi and Mrs. Ruby Ju for microanalyses.

(29) J. Cason and H. Rapoport, *Laboratory Text in Organic Chemistry*, Prentice-Hall, Inc., New York, 1950, p. 237.

(30) J. Cason, N. L. Allinger, G. Sumrell, and D. E. Williams, *J. Org. Chem.*, **16**, 1173 (1951).

(31) We are indebted to Messrs. S. W. Blum, D. J. Casey, W. R. Hertler, T. C. Miller, and R. A. Mooney for assistance with the preparation of these compounds.

(32) C. S. Marvel and V. du Vigneaud, *Org. Syntheses*, **Coll. Vol. 2**, 94 (1943).

(33) Attempts to alkylate isopropylmalonic ester with *n*-butyl bromide employing sodium ethoxide as base were unsuccessful. Use of sodium *tert*-butoxide was previously employed for alkylation of isopropylmalonic ester by M. Kopp and B. Tchoubar, *Bull. soc. chim. France*, 30 (1951).

(34) H. A. Shonle and A. Moment, *J. Am. Chem. Soc.*, **45**, 248 (1933).

(35) E. L. Pelton and A. A. Holzschuh, U. S. Patent 2,517,708 [*Chem. Abstr.*, **45**, 2019i (1951)].

(36) W. S. Bishop, *Org. Syntheses*, **25**, 71 (1945).

(37) E. C. S. Jones and F. L. Pyman, *J. Chem. Soc.*, **127**, 2596 (1925).

(38) E. B. Hershberg and J. Cason, *Org. Syntheses*, **Coll. Vol. 3**, 627 (1955).

(39) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *The Systematic Identification of Organic Compounds*, 4th ed., John Wiley and Sons, New York, 1956, p. 219.

ethanol and 0.95 ml. of concentrated sulfuric acid was added. The solution was allowed to stand for 10 hr. at room temperature and was then diluted with water and extracted with hexane. The hexane extracts were washed with saturated sodium carbonate to remove any unreacted acid. Tbe solution was dried, solvent was removed, and the residue was fractionally distilled to give 3.1 g. of ethyl 4-isopropyl-2-methyl-3-octenoate. A center cut had b.p. 85–85.5°/2.6 mm., n_D^{25} 1.4368. The ultraviolet absorption spectrum has no maximum above 205 mμ and no inflection near 218 mμ (ϵ_{218} 1950).

Anal. Calc'd for $C_{14}H_{26}O_2$: C, 74.28; H, 11.58. Found: C, 73.65; H, 11.66.

4-Isopropyl-2-methyl-3-octenoic acid. A solution of 1.5 g. of pure ethyl 4-isopropyl-2-methyl-3-octenoate (n_D^{25} 1.4368) in 10 ml. of 2*N* ethanolic potassium hydroxide was allowed to stand for 12 hr. at room temperature and was then refluxed for one hour. The usual work-up procedure and fractional distillation yielded 0.8 g. of 4-isopropyl-2-methyl-3-octenoic acid, b.p. 107–108°/0.9 mm., n_D^{25} 1.4507. The ultraviolet absorption spectrum (Fig. 1, Curve II) shows no maximum above 205 mμ and only low absorption near 219 mμ (ϵ_{220} 2120).

Anal. Calc'd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18; eq. wt., 198. Found: C, 72.68; H, 11.53; eq. wt., 195.

4-Isopropyl-2-methyl-2-octenoic acid. A solution of 6.5 g. of the best sample of α,β-unsaturated ester from the fractional distillation above (n_D^{25} 1.4489) was refluxed for 7 hr. in 25 ml. of 2*N* ethanolic potassium hydroxide. The crude acid obtained was allowed to stand for 10 hr. at room temperature in a solution of 48 ml. of absolute ethanol and 2 ml. of concentrated sulfuric acid. The solution was diluted with water and extracted with hexane. The hexane solution was extracted exhaustively with saturated sodium carbonate and the sodium carbonate extracts in turn washed with hexane. Acidification of the sodium carbonate solution then precipitated the conjugated acid, which was worked up in the usual way to give 2.3 g. of 4-isopropyl-2-methyl-2-octenoic acid. A center cut had b.p. 121°/1.4 mm., n_D^{25} 1.4639. The ultraviolet absorption spectrum (Fig. 1, Curve I) has λ_{max} 219 mμ, ϵ_{max} 13,900.

Anal. Calc'd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18; eq. wt., 198. Found: C, 72.77; H, 11.41; eq. wt., 200.

Ethyl 4-isopropyl-2-methyl-2-octenoate was prepared by esterifying 1.5 g. of the acid (n_D^{25} 1.4539) in dilute refluxing ethanolic sulfuric acid. Fractional distillation yielded 1.4 g. of the conjugated ester, b.p. 95–96°/2.5 mm., n_D^{25} 1.4488. The ultraviolet absorption spectrum has λ_{max} 217 mμ (ϵ_{max} 13,200).

Anal. Calc'd for $C_{14}H_{26}O_2$: C, 74.28; H, 11.58. Found: C, 73.98; H, 11.68.

Ethyl tert-butylcyanoacetate[31] was prepared by the method of Alexander, McCollum, and Paul.[40] The intermediate ethyl isopropylidenecyanoacetate,[31] prepared according to Cope and Hancock,[41] was obtained in 37% yield, b.p. 117–119°/18 mm., m.p. 28° (lit.[42] m.p. 28°). A solution of 126.2 g. of ethyl isopropylidenecyanoacetate in ether was added to the Grignard reagent from 140 g. of methyl iodide and 24.3 g. of magnesium turnings. The mixture was stirred overnight at room temperature and then refluxed for one hour. The usual work-up procedure gave on fractional distillation 67.4 g. (49%) of ethyl *tert*-butylcyanoacetate, b.p. 87–89°/20 mm., n_D^{25} 1.4246 (lit.[40] b.p. 88°/5 mm., n_D^{25} 1.4258).

Ethyl n-butyl-tert-butylcyanoacetate[31] was prepared by the usual malonic ester alkylation procedure[43] from 99.5 g. of ethyl *tert*-butylcyanoacetate, 14 g. of sodium and 98.5 g. of *n*-butyl bromide. The sodium ethoxide–malonic ester solution was refluxed for one hour before the addition of the butyl bromide and for 9 hr. after the addition. Dilution with water and the usual work-up procedure and fractional distillation yielded 75 g. (56%) of ethyl *n*-butyl-*tert*-butylcyanoacetate, b.p. 121–123°/15 mm., n_D^{25} 1.4401.

Anal. Calc'd for $C_{13}H_{23}NO_2$: C, 69.28; H, 10.28; N, 6.22. Found: C, 69.20; H, 10.15; N, 6.65.

2-tert-Butylhexanenitrile. A solution of 117.2 g. of ethyl *n*-butyl-*tert*-butylcyanoacetate and 135 ml. of 5*N* ethanolic potassium hydroxide was refluxed for 2 hr. The reaction mixture was diluted with water and acidified to give an oily layer. The two phases were separated; when the organic layer was washed with water it solidified to white crystalline *n*-butyl-*tert*-butylcyanoacetic acid. The acid had m.p. 113–114° after recrystallization from hexane.

Anal. Calc'd for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10. Found: C, 67.04; H, 9.82; N, 7.29.

The aqueous phase was extracted with ether and the ether extracts were combined with the solid acid, then washed with water, and dried over sodium sulfate. Ether was removed by flash distillation and the cyano acid was decarboxylated by heating for two hours at 195°. The resulting 2-*tert*-butylhexanenitrile was distilled rapidly at atmospheric pressure, b.p. 202°, then fractionally re-distilled to yield 73.0 g. (92%) of nitrile, b.p. 99–100°/31 mm., n_D^{25} 1.4241.

Anal. Calc'd for $C_{10}H_{19}N$: C, 78.36; H, 12.50; N, 9.14. Found: C, 78.65; H, 12.48; N, 9.33.

2-tert-Butylhexanoic acid was prepared by the method of Parham.[4e] A solution composed of 30 g. of 2-*tert*-butylhexanenitrile, 30 g. of concentrated sulfuric acid, 120 g. of glacial acetic acid, and 60 g. of water was heated for 48 hr. under reflux. The cooled reaction mixture was poured over ice to give a white solid, which was extracted from the aqueous layer with ether. The ether extracts were extracted with saturated sodium carbonate; however, acidification of the carbonate extracts yielded no organic acid. Ether was removed by distillation to give 31.1 g. (93%) of 2-*tert*-butylhexanamide. A small sample was crystallized twice from acetone as long transparent needles, m.p. 102–103°.

Anal. Calc'd for $C_{10}H_{21}NO$: C, 70.12; H, 12.36; N, 8.17. Found: C, 69.97; H, 12.26; N, 8.37.

The amide obtained above (31.1 g.) was mixed with 165 ml. of concentrated sulfuric acid and 150 ml. of glacial acetic acid. The resulting mixture was cooled to 0° and a solution of 12.3 g. of sodium nitrite in the minimum amount of water was added with mechanical stirring. The reaction was allowed to warm to room temperature, and was then heated to 60°; evolution of nitrogen began at 36°. After gas evolution had ceased, the mixture was cooled to 0° and the diazotization procedure was repeated. The reaction mixture was then decanted slowly into 300 ml. of ice water. The oily layer which formed was extracted into hexane. Removal of solvent and fractional distillation yielded 25.4 g. (81%) of 2-*tert*-butylhexanoic acid, b.p. 120–124°/7 mm., n_D^{25} 1.4304.

Anal. Calc'd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.72. Found: C, 69.36; H, 11.93.

In a second run a solution of 35.2 g. of nitrile, 35 g. of concentrated sulfuric acid, 75 g. of acetic acid, and 35 g. of water was refluxed for three days. The intermediate amide was not isolated but was diazotized directly. To the crude reaction mixture was added 97 ml. of concentrated sulfuric acid. The resulting mixture was cooled to 0° and diazotized twice with 15.8 g. quantities of sodium nitrite solution, as above. Work-up as before and fractional distillation yielded 31 g. (78%) of 2-*tert*-butylhexanoic acid.

2-tert-Butylhexanal was prepared by Rosenmund reduc-

(40) E. R. Alexander, J. D. McCollum, and D. E. Paul, *J. Am. Chem. Soc.*, **72**, 4791 (1950).

(41) A. C. Cope and E. M. Hancock, *Org. Syntheses*, **Coll. Vol. 3**, 399 (1955). For an alternative procedure, *cf.* F. S. Prout, R. J. Hartman, E. P.-Y. Huang, C. J. Korpics, and G. R. Tichelaar, *Org. Syntheses*, **35**, 7 (1955); F. S. Prout, *J. Org. Chem.*, **18**, 928 (1953).

(42) G. Komppa, *Ber.*, **33**, 3530 (1900).

(43) C. S. Marvel, *Org. Syntheses*, **Coll. Vol. 3**, 495 (1955).

tion of the acid chloride, as described for 2-isopropylhexanal above. The intermediate 2-*tert*-butylhexanoyl chloride, from 56.4 g. of 2-*tert*-butylhexanoic acid and 117 g. of thionyl chloride, was obtained in 94% yield (59 g.) after distillation through a short Vigreux column, b.p. 95°/20 mm., n_D^{25} 1.4393. The acid chloride (59 g.) was converted to the aldehyde, employing 10.25 g. of palladium-barium sulfate and 0.62 ml. of sulfur-quinoline poison in 210 ml. of sodium-dried xylene. The reaction appeared complete after 8½ hr., when 79% of the theoretical amount of hydrogen chloride had been evolved. Work-up and fractional distillation of the entire solution yielded 28.6 g. (59%) of 2-*tert*-butylhexanal. A center cut had b.p. 85–86°/23 mm., n_D^{25} 1.4280.

The *2,4-dinitrophenylhydrazone* had m.p. 163–164° after two crystallizations from 95% ethanol.

Anal. Calc'd for $C_{16}H_{24}N_4O_4$: C, 57.12; H, 7.19; N, 16.66. Found: C, 57.38; H, 6.89; N, 16.71.

An unsuccessful attempt was made to prepare 2-*tert*-butylhexanal *via* lithium aluminum hydride reduction of 2-*tert*-butylhexanenitrile. A solution of 0.684 g. of lithium aluminum hydride in 100 ml. of ether was added at dry ice-temperature to 11.3 g. of the nitrile in 100 ml. of ether. After the mixture had been stirred for one hour at this temperature it was allowed to warm to room temperature. Hydrolysis at 0° and distillation of the product gave only recovered starting nitrile.

Preparation and dehydration of ethyl 4-tert-butyl-2-methyl-3-hydroxyoctanoate. This β-hydroxy ester was prepared by the Reformatsky reaction as described above for the preparation of ethyl 4-isopropyl-2-methyl-3-hydroxyoctanoate. The present sequence employed 28.0 g. of 2-*tert*-butylhexanal, 100 g. of ethyl α-bromopropionate and 35.8 g. of zinc foil. A small portion of the hydroxy ester was distilled through a 3-ft. modified Vigreux column,[44] b.p. 114°/2 mm., n_D^{25} 1.4482.

Anal. Calc'd for $C_{15}H_{30}O_3$: C, 69.72; H, 11.70. Found: C, 69.86; H, 11.57.

This material was combined with the undistilled crude hydroxy ester and dehydrated as described for the γ-isopropyl hydroxy ester. In this case 285 g. of pyridine and 62 g. of phosphorus oxychloride were employed. After the usual work-up procedure, the product was fractionally distilled to yield 26.5 g. (62%) of mixed unsaturated esters, obtained in 16 small fractions. The composition of each fraction was estimated from the refractive indices for the pure conjugated and unconjugated esters given below. Thus, there were obtained 16.6 g. of β,γ-unsaturated ester (96% pure) b.p. 89–92°/2.4 mm., n_D^{25} 1.4399, 4.5 g. of intermediate fractions (containing 28% of α,β-unsaturated ester), b.p. 89–94°/2.2 mm. and 5.4 g. of α,β-unsaturated ester (88% pure) b.p. 94–95°/2.2 mm., n_D^{25} 1.4502. From the composition of these fractions it was estimated that the dehydration gave a mixture containing only 25% of the conjugated isomer.

Ethyl 4-tert-butyl-2-methyl-3-octenoate was obtained in pure form by the partial esterification method described above for ethyl 4-isopropyl-2-methyl-3-octenoate. From 16.6 g. of β,γ-unsaturated ester (n_D^{25} 1.4399) there was obtained after saponification and partial esterification 12.9 g. of pure ethyl 4-*tert*-butyl-2-methyl-3-octenoate; the best sample had b.p. 88–90°/2.6 mm., n_D^{25} 1.4395. The ultraviolet absorption spectrum showed no maximum above 205 mμ and only low absorption at 218 mμ (ϵ_{218} 2040).

Anal. Calc'd for $C_{15}H_{28}O_2$: C, 74.92; H, 11.77. Found: C, 74.80; H, 11.66.

4-tert-Butyl-2-methyl-3-octenoic acid was prepared by saponification in ethanolic potassium hydroxide of 3.0 g. of ethyl 4-*tert*-butyl-2-methyl-3-octenoate (n_D^{25} 1.4395). The pure acid (1.2 g.) had b.p. 109–111°/0.9 mm., n_D^{25} 1.4541. The ultraviolet spectrum shows no inflection point above 205 mμ and only low absorption near 220 mμ (ϵ_{220} 2120).

Anal. Calc'd for $C_{13}H_{24}O_2$: C, 73.53; H, 11.39; eq. wt., 212. Found: C, 73.98; H, 11.35; eq. wt., 211.

4-tert-Butyl-2-methyl-2-octenoic acid was initially purified by partially esterifying the acid obtained on saponification of the high-boiling distillation fraction above (n_D^{25} 1.4502), as previously described for the isopropyl conjugated acid. The unsaturated acid obtained in this manner had b.p. 130°/1.5 mm., m.p. 68–70° and the ultraviolet absorption spectrum (λ_{max} 220 mμ, ϵ_{max} 11,800) showed it to be relatively impure.

The unconjugated isomer was accordingly removed by a procedure involving lactonization, as has been previously described.[2] A mixture of 7.5 g. of 4-*tert*-butyl-2-methyl-2-(and 3-) octenoic acids (consisting of 86% of the Δ^2 isomer), 35 ml. of ethylene glycol and 2.5 ml. of concentrated sulfuric acid was refluxed for 40 hr. The reaction mixture was poured into water and the mixture of conjugated glycol ester and lactone was isolated in the usual manner. Saponification of this mixture and fractional distillation yielded 1.5 g. of pure 4-*tert*-butyl-2-methyl-2-octenoic acid, b.p. 129–130°/1.3 mm., m.p. 74–75°. The ultraviolet spectrum of this sample had λ_{max} 220 mμ, ϵ_{max} 13,800.

Anal. Calc'd for $C_{13}H_{24}O_2$: C, 73.53; H, 11.39; eq. wt., 212. Found: C, 73.50; H, 11.63; eq. wt., 216.

Ethyl 4-tert-butyl-2-methyl-2-octenoate was obtained in somewhat impure form by esterification of the acid (m.p. 68–70°) obtained from the partial esterification technique above. From 1.0 g. of acid there was obtained 0.8 g. of ethyl 4-*tert*-butyl-2-methyl-2-octenoate, b.p. 101–102°/2.4 mm., n_D^{25} 1.4513. Although there were no bands in the infrared spectrum indicating presence of β,γ-unsaturated ester, a small shoulder at 1775 cm.$^{-1}$ is indicative of the presence of saturated γ-lactone.[2] The ultraviolet absorption spectrum (λ_{max} 218 mμ, ϵ_{max} 12,860) shows the sample to contain *ca.* 3% of unconjugated material.

Anal. Calc'd for $C_{15}H_{28}O_2$: C, 74.92; H, 11.77. Found: C, 74.73; H, 11.51.

Determination of the composition of mixtures of α,β- and β,γ-unsaturated acids and esters. A. Ultraviolet absorption spectra. In the isomerization experiments described below, mixtures of conjugated and unconjugated unsaturated acids were obtained. Ultraviolet spectra of these mixtures were determined and compared algebraically and graphically with the spectra of the pure isomeric acids given above. In the algebraic method the extinction coefficient of the mixture was determined at the wave length for which the two pure isomers show the maximum differential between their extinction coefficients. For both the isopropyl and *tert*-butyl acids this wave length is 220 mμ. The compositions of mixtures were then calculated from the following formula.[2]

For 4-isopropyl-2-methyl-2(and -3)-octenoic acids:

$$139X + 21.2(1 - X) = \epsilon'_{220}$$

For 4-*tert*-butyl-2(and -3)-octenoic acids:

$$138X + 19.2(1 - X) = \epsilon'_{220}$$

In each case X is the fraction of conjugated isomer, while $\epsilon'_{220} = \epsilon_{220} \times 10^{-2}$ for the mixture of acids.

For each mixture analyzed in this manner, a theoretical curve was prepared, based on the percentage calculated from the above formulas of the two isomers present in the mixture and the observed spectra of the pure isomers in the range of high absorption (205–230 mμ). In each case the theoretical curves so prepared were in excellent agreement with those obtained for the equilibration mixtures (*cf.* Fig. 2). Thus, the shapes of the curves[2] confirm the compositions calculated algebraically.

B. Refractive indices. For mixtures of unsaturated isomeric esters, obtained from fractional distillation of the dehydration products above, the composition was estimated algebraically from the refractive indices of the mixture and of

(44) Ref. (29), p. 245.

the two pure isomeric esters. A linear dependence of refractive index on composition was assumed. While this method is subject to distortion by small amounts of impurities and is not so accurate as that employing the ultraviolet spectra, it has the advantages of speed and simplicity and was also employed in roughly estimating the composition of the mixtures of unsaturated acids obtained from equilibrations.

Equilibrations of mixed esters were performed according to a previously described procedure.[2]

A. Ethyl 4-isopropyl-3-methyl-2(and -3)-octenoates. Run I. A solution of 3.4*N* sodium glycolate was prepared in a metal flask by dissolving 5.8 g. of sodium in 75 ml. of anhydrous ethylene glycol. This had been previously dried by distilling 150 ml. of glycol from over sodium into the metal flask and then redistilling half of this quantity to remove last traces of water. To the sodium glycolate solution was added 10 g. of a mixture of ethyl 4-isopropyl-2-methyl-2(and -3)-octenoates (n_D^{25} 1.4410) containing ca. 27% of the conjugated isomer. The resulting mixture was refluxed for 36 hours, cooled, and diluted with water, then refluxed an additional hour to saponify the glycol esters. The reaction mixture was poured into water, acidified, and worked up in the usual manner. The mixed acids, which were distilled rapidly, weighed 8.1 g. and had b.p. 115–124°/1 mm., n_D^{25} 1.4602. A small sample taken just prior to distillation had n_D^{25} 1.4605, showing that no separation of isomers had occurred during distillation. From the refractive index of the distilled mixture it was estimated to contain 72% of the conjugated isomer. The ultraviolet absorption spectrum (Fig. 2, Curve II) has ϵ_{220} 11,270, from which the mixture may be calculated to contain 78% of the α,β-unsaturated isomer.

Run 2. The second run was performed in the same manner as the first. A mixture of 10 g. of mixed γ-isopropyl unsaturated esters (n_D^{25} 1.4488), containing 67% of conjugated isomer, and 75 ml. of 3.4*N* sodium glycolate solution was heated for 39 hr. under reflux, then diluted with water and worked up as before. The mixed unsaturated acids obtained weighed 8.1 g. and had b.p. 114–130°/1 mm., n_D^{25} 1.4602. From the refractive index the mixture was estimated to contain 72% of the conjugated isomer. The ultraviolet absorption spectrum (Fig. 2, Curve III) has ϵ_{220} 11,170, from which it may be calculated that the mixture contains 77% of the α,β-unsaturated isomer.

B. Ethyl 4-tert-butyl-2-methyl-2(and -3)-octenoates. The same procedure was employed as that described above for the γ-isopropyl esters. A mixture of 10 g. of mixed γ-*tert*-butyl esters (n_D^{25} 1.4413), containing *ca.* 16% of the conjugated isomer, and 75 ml. of 3.4*N* sodium glycolate solution was heated for 41 hr. under reflux and worked up as above. The isomerized product was distilled to give 7.9 g. of a solid mixture of acids, b.p. 115–135°/0.9 mm. The ultraviolet spectrum had ϵ_{220} 12,200, from which the mixture may be calculated to contain 86% of the conjugated isomer. The shape of the absorption spectrum between 205 and 230 mμ also agrees well with that calculated for a hypothetical mixture containing 86% of the conjugated acid.

URBANA, ILL.

[CONTRIBUTION FROM KOPPERS CO., INC., MONOMER FELLOWSHIP AT MELLON INSTITUTE]

Isomerization Accompanying the Acetylation of *p-t*-Butyltoluene

W. J. HEINTZELMAN AND B. B. CORSON

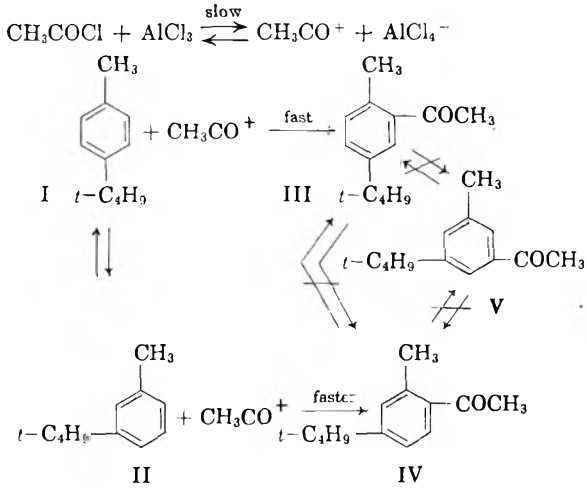
Received Aug. 6, 1956

By suitable choice of the order of addition of the reactants, the acetylation of *p-t*-butyltoluene can be directed to give either 2-methyl-4-*t*-butylacetophenone or 2-methyl-5-*t*-butylacetophenone.

There is considerable confusion in the literature concerning the orientation of the ketones resulting from the aluminum chloride catalyzed acetylation of certain *p*-dialkylbenzenes in which one or both of the alkyl groups are secondary or tertiary. It has been variously reported that the product is a 2,4-dialkylacetophenone,[1–5] a 2,5-dialkylacetophenone,[5,6] and a mixture of 2,4- and 2,5-dialkylacetophenones.[7] These conclusions were based on nonquantitative data—the isolation of ketone derivatives, often in small yield.

We have investigated the acetylation of *p-t*-butyltoluene under a variety of conditions and determined the composition of the acetylated products by means of infrared spectrometry. Our results support a mechanism in which the rate-determining step is the ionization of acetyl chloride and the rate of acetylation of *p-t*-butyltoluene is slower than the rate of acetylation of *m-t*-butyltoluene.

It was further shown that 2-methyl-4-*t*-butylacetophenone (IV) and 2-methyl-5-*t*-butylacetophe-



(1) Newton, *J. Am. Chem. Soc.*, **65**, 2444 (1943).
(2) Nightingale and Hucker, *J. Org. Chem.*, **18**, 1529 (1953).
(3) Pines and Shaw, *J. Org. Chem.*, **20**, 373 (1955).
(4) Royals and Prasad, *J. Am. Chem. Soc.*, **77**, 1696 (1955).
(5) Watts and Taylor, *J. Chem. Soc.*, 1123, 5054 (1952).
(6) Hennion and McLeese, *J. Am. Chem. Soc.*, **64**, 2421 (1942).
(7) Nightingale and Shackelford, *J. Am. Chem. Soc.*, **78**, 133 (1956).

TABLE I

ACETYLATION OF *p-t*-BUTYLTOLUENE

(CH_3COCl–$AlCl_3$/$C_4H_9C_6H_4CH_3$ mole ratio = 1.1/1)

Expt.	Hours: Addition	Hours: After addition	T°C.	Solvent	Methyl-*t*-butylacetophenone: % Yield	% Comp'n: 2,4-	% Comp'n: 2,5-
Procedure A: $C_4H_9C_6H_4CH_3$–CH_3COCl Mixture Added to $AlCl_3$							
1	1.5	6.0	25–30	CS_2	85	97	3
2	1.5	1.5	25–30	CCl_4	62	94	6
3	1.5	1.5	0–10	CS_2	70	74	26
4[a]	1.5	10.0	0–10	CS_2	45	45	55
5[b]	1.5	1.5	25–30	CCl_4	73	97	3
Procedure B: $C_4H_9C_6H_4CH_3$ Added to CH_3COCl–$AlCl_3$ Mixture							
6	1.5	1.5	25–30	CCl_4	56	51	49
7	0.3	1.5	0–10	CCl_4	67	36	64
8	1.5	1.5	0–10	CCl_4	75	29	71
9[c]	1.5	1.5	0–10	CCl_4	60	24	76
10	1.5	1.5	0–10	$C_6H_5NO_2$	28	13	87
11	1.5	1.5	0–10	$C_6H_5NO_2$	37	7	93
12[d]	1.5	1.5	0–10	CCl_4	61	9	91

[a] Ferric chloride was substituted for aluminum chloride. [b] *t*-Butyltoluene (*m-p* = 65–35) was substituted for *p-t*-butyltoluene. [c] Previous to addition of the *p-t*-butyltoluene, the acetyl chloride–aluminum chloride mixture was aged for 1 hour. [d] Aluminum chloride–acetyl chloride to *p-t*-butyltoluene mole ratio was 3.

none (III) result from the acetylation of the corresponding *t*-butyltoluenes and not from the rearrangement of an isomeric methyl-*t*-butylacetophenone since neither 2-methyl-4-*t*-butylacetophenone (IV) nor 2-methyl-5-*t*-butylacetophenone (III) nor 3-methyl-5-*t*-butylacetophenone (V) is isomerized under acetylation conditions. Presumably, the presence of the acetyl group deactivates the ring sufficiently to stabilize the positions of the alkyl groups.

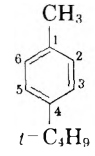
In accordance with this mechanism we can direct the acetylation reaction to give either 2-methyl-4-*t*-butylacetophenone (IV) or 2-methyl-5-*t*-butylacetophenone (III), depending upon the order of addition of the reactants.

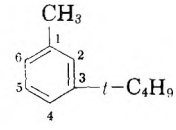
When the order of addition of reactants restricts the ionization of acetyl chloride and favors the isomerization of *p-t*-butyltoluene, the composition of the product depends upon the relative rates of acetylation of *m-* and *p-t*-butyltoluenes. In experiments 1 to 3 of Table I, mixtures of *p-t*-butyltoluene and acetyl chloride were added to suspensions of aluminum chloride in nonpolar solvents. The relatively slow ionization of acetyl chloride allowed the major portion of the *p-t*-butyltoluene to isomerize to *m-t*-butyltoluene prior to acetylation with the result that the ketone products contained 74% to 97% of 2-methyl-4-*t*-butylacetophenone.

Inasmuch as the equilibrium composition of *t*-butyltoluene is 67% *meta-* 33% *para-*,[8] it is evident that *m-t*-butyltoluene acetylates faster than *p-t*-butyltoluene. If it were not so, the acetylation of *p-t*-butyltoluene under isomerizing conditions could not produce a ketone mixture containing more than 67% of 2-methyl-4-*t*-butylacetophenone.

(8) Schlatter and Clark, *J. Am. Chem. Soc.*, 75, 361 (1953).

The greater reactivity of *m-t*-butyltoluene can be attributed to the combined effects of the hyperconjugation of the methyl group and the induction of the *t*-butyl group activating the 6-position. No position in *p-t*-butyltoluene is similarly activated; positions 2- and 4-of *m-t*-butyltoluene are similarly activated but are relatively sterically hindered.





When the order of addition of the reactants favors the ionization of acetyl chloride and restricts the isomerization of *p-t*-butyltoluene, the product is mainly 2-methyl-5-*t*-butylacetophenone. In experiments 6 to 9 of Table I, *p-t*-butyltoluene was added to a preformed mixture of acetyl chloride and aluminum chloride in a nonpolar solvent. Under these conditions of increased CH_3CO^+ concentration, the rate of acetylation was accelerated with respect to the isomerization of *p-t*-butyltoluene, with the result that the ketones produced contained 49% to 71% of 2-methyl-5-*t*-butylacetophenone.

Furthermore, when *p-t*-butyltoluene was added to mixtures of acetyl chloride and aluminum chloride in a polar solvent (experiments 10, 11 of Table I), the resulting ketone products contained 87% to 93% of 2-methyl-5-*t*-butylacetophenone. Thus, the polar solvent aided the ionization of acetyl chloride, thereby increasing the concentration of CH_3CO^+, with the result that the rate of acetylation was accelerated. Similarly (experiment 12 of Table I), increasing the CH_3CO^+ concentration by using a 2 molar excess of aluminum chloride–acetyl chloride

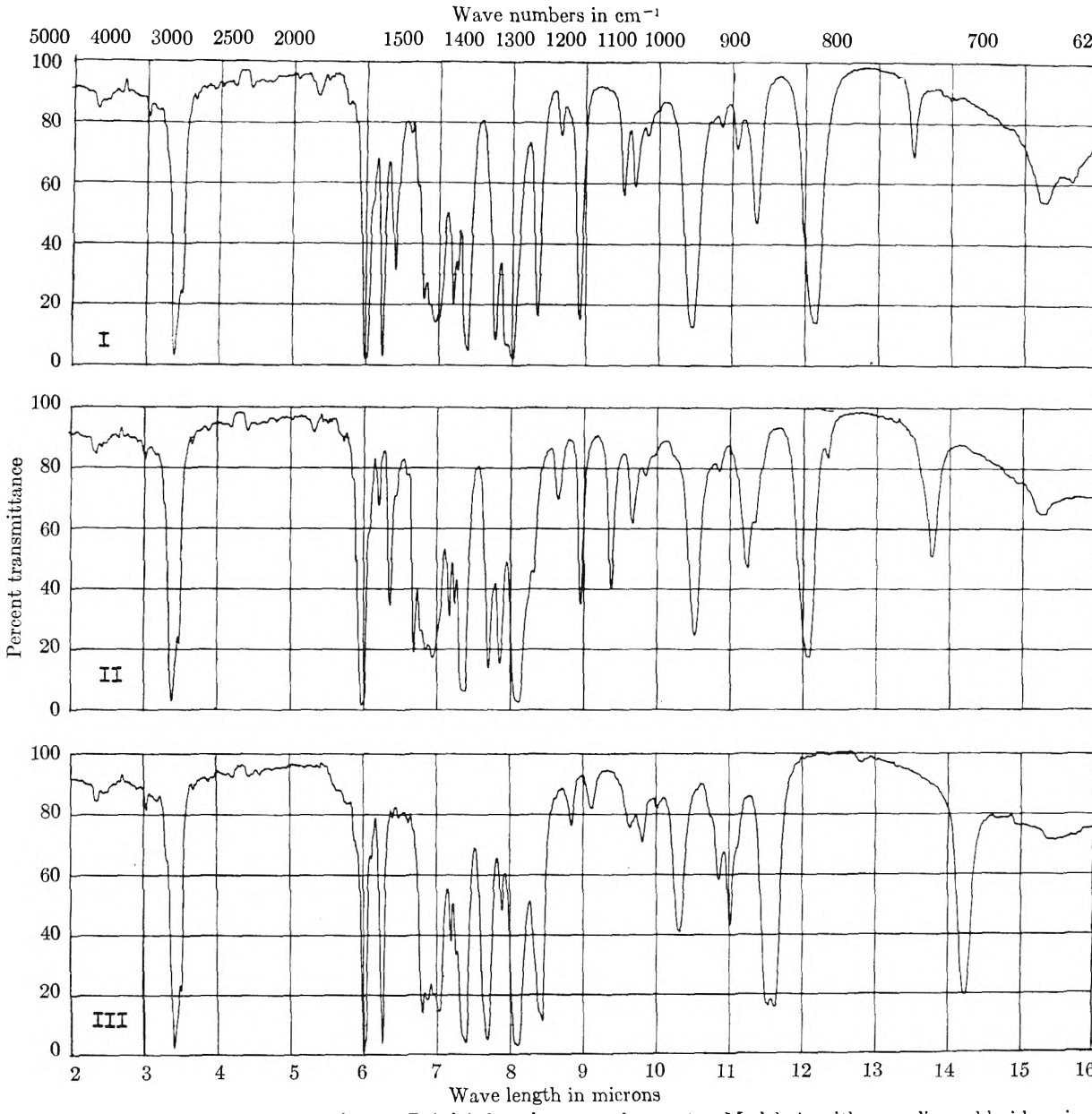
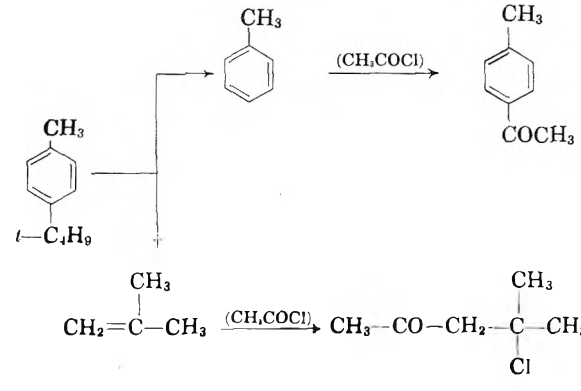


Fig. 1.—Infrared spectra measured on a Baird infrared spectrophotometer Model A with a sodium chloride prism, undiluted sample, 0.028 mm. cell thickness: I, 2-methyl-4-*t*-butylacetophenone; II, 2-methyl-5-*t*-butylacetophenone; III, 3-methyl-5-*t*-butylacetophenone.

gave a ketone mixture containing 91% of 2-methyl-5-*t*-butylacetophenone.

It is to be noted that whereas Nightingale and Shackelford[7] reported that the acetylation of *p*-cymene and *p-sec*-butyltoluene in the presence of ferric chloride as catalyst gave no 2,4-dialkylacetophenone, we obtained a ketone from *p-t*-butyltoluene under their conditions which contained 45% of 2-methyl-4-*t*-butylacetophenone (experiment 4 of Table I).

In all of the acetylation experiments there was obtained in addition to the methyl-*t*-butylacetophenones a certain amount of low boiling by-product which was shown (experiment 2 of Table I) to be a mixture of *p*-methylacetophenone, *t*-butyltoluene and mesityl oxide. Evidently a portion of the *t*-



butyltoluene is debutylated to toluene and isobutylene both of which then react with acetyl chloride

to give, respectively, *p*-methylacetophenone and 4-chloro-4-methyl-2-pentanone. The latter is subsequently dehydrohalogenated to mesityl oxide.[9]

EXPERIMENTAL

Melting points are corrected.

p-t-Butyltoluene. Isobutylene (560 g., 10 moles) was passed into a stirred, 0–10° mixture of 920 g. (10 moles) of toluene and 100 ml. of concentrated sulfuric acid during 3 hr. After stirring the mixture for an additional hour at 0–10°, the hydrocarbon layer was washed with water, refluxed for 1 hour with 300 ml. of 20% aqueous sodium hydroxide and washed again with water. The dried hydrocarbon was distilled through a 23-plate column at 5/1 reflux ratio to give 1129 g. (76% yield) of *t*-butyltoluene; b.p. 185–195°/750 mm., *o-m-p* ratio 0–7–93. Redistillation of this isomer mixture through a 45-plate column at 25/1 reflux ratio gave 740 g. of material which was recrystallized from ethanol 4 times and finally redistilled through a 23-plate column at 10/1 reflux ratio to give 420 g. of *p-t*-butyltoluene; b.p. 191.5°/740 mm., t_f[10] −52.69° (99.7 mole % pure), n_D^{25} 1.4896, d_4^{25} 0.8574. The reported constants[11] are: b.p. 192.76°/760 mm., t_f −52.515°, n_D^{25} 1.4895, d_4^{25} 0.8573. Its infrared spectrum was identical with that of an authentic sample.[12]

Acetylation procedure A. To a stirred mixture of 200 ml. of solvent and 51 g. (0.38 mole) of anhydrous aluminum chloride was added a mixture of 30 g. (0.38 mole) of acetyl chloride and 51 g. (0.35 mole) of *t*-butyltoluene. After stirring for an additional time, the product was poured into a mixture of 40 ml. of concentrated hydrochloric acid and 120 g. of crushed ice. The organic layer, combined with two carbon tetrachloride extracts of the aqueous layer, was washed successively with water, 5% aqueous sodium carbonate, and water. The solvent was stripped off and the residue was distilled through a 27-plate column at 20 mm. at 5/1 reflux ratio. The fraction distilling at 140–150°/20 mm., was taken for analysis.

Acetylation procedure B. To a stirred mixture of 200 ml. of solvent and 51 g. (0.38 mole) of anhydrous aluminum chloride was added 30 g. (0.38 mole) of acetyl chloride during 15 min. To this mixture was added 51 g. (0.35 mole) of *t*-butyltoluene; the mixture was stirred for an additional 1.5 hr. then worked up as in method *A*.

Composition of low boiling by-product. In order to obtain sufficient low boiling by-product to establish its composition, experiment 2 of Table I was repeated on a seven-fold scale. The crude product was steam distilled until practically no more organic material came over. The organic portion of the distillate was distilled through a 23-plate column at 10/1 reflux ratio until, when nearly all of the carbon tetrachloride had distilled, hydrogen chloride started to be evolved. The distillation was stopped and the residue was stirred and heated to 70° with 400 cc. of 5% alcoholic potassium hydroxide during 1 hr. The mixture was diluted with water, and the organic layer, after washing with water, was distilled through a 23-plate column at 10/1 reflux ratio to give four main fractions: (*a*) 14.3 g., b.p. 125–128°/740 mm., identified as mesityl oxide by its infrared spectrum and by the m.p. and mixture m.p. (both 197–198°) of its 2,4-dinitrophenylhydrazone[13]; (*b*) 16.2 g., 185–187°/740 mm., identified by its infrared spectrum as *p-t*-butyltoluene contaminated with a small amount of *m-t*-butyltoluene; (*c*) 17.3 g., b.p. 116–127°/20 mm., identified as *p*-methylacetophenone by its infrared spectrum and by the m.p. and mixture m.p. (both 259–260°) of its 2,4-dinitrophenylhydrazone[13]; (*d*) 79.3 g. of methyl-*t*-butylacetophenone, b.p. 141–148°/20 mm.

The organic residue from the steam distillation was stirred with 5% alcoholic potassium hydroxide at 70° and distilled as above to give an additional 122 g. of methyl-*t*-butylacetophenone.

2-Methyl-4-t-butylacetophenone (spectrometric standard). *t*-Butyltoluene (250 g., 1.7 moles, *o–m–p* ratio 0–7–93) was acetylated by procedure A to give 225 g. (70% yield) of crude 2-methyl-4-*t*-butylacetophenone, t_f 9.47° (88–94 mole % pure). Six crystallizations of this ketone from methanol at −25°, followed by distillation through a 23-plate column at 10/1 reflux ratio gave 146 g. of 2-methyl-4-*t*-butylacetophenone; b.p. 146.5°/20 mm., t_f 11.90° (99.0–99.4 mole % pure).

2-Methyl-5-t-butylacetophenone (spectrometric standard). *t*-Butyltoluene (157 g., 1.1 moles, *o–m–p* ratio 0–7–93) was acetylated by procedure B to give 142 g. (70% yield) of mixed ketones. After cooling overnight at −6°, the mixture was filtered and the solid was recrystallized 3 times from methanol at −6° and finally distilled through a 10-cm. Vigreux column to give 51 g. of 2-methyl-5-*t*-butylacetophenone; b.p. 146°/20 mm., t_f 30.72° (99.4–99.8 mole % pure).

3-Methyl-5-t-butylacetophenone (spectrometric standard). To a 0–10° mixture of 1179 g. (10 moles) of ethyltoluene (*o–m–p* ratio 0–70–30) and 71 g. (0.4 mole) of ferric chloride was added 555 g. (6.0 moles) of *t*-butyl chloride during 1 hr. After stirring for an additional hour the product was poured into a mixture of 150 ml. of concentrated hydrochloric acid and 900 g. of crushed ice and the mixture was steam distilled. The hydrocarbon distillate was redistilled through a 23-plate column at 5/1 reflux ratio to give 319 g. (30% yield) of 3-ethyl-5-*t*-butyltoluene; b.p. 214–216°/740 mm., t_f −33.14° (87–94 mole % pure).

The 3-ethyl-5-*t*-butyltoluene was oxidized as follows: Oxygen was bubbled through a stirred mixture of 142 g. (0.8 mole) of the hydrocarbon and 3.4 g. of 10% manganese naphthenate for 11 hr. at 120–125°. The mixture was cooled, filtered, washed with 10% aqueous sodium hydroxide, refiltered, washed with water, and dried. Distillation through a 27-plate column at 5/1 reflux ratio gave 64 g. of 3-ethyl-5-*t*-butyltoluene (b.p. 108–112°/20 mm.) plus 37 g. of a mixture of 3-methyl-5-*t*-butylacetophenone and the corresponding carbinol (b.p. 140–150°/20 mm.). This ketone-carbinol mixture was prepared to the amount of 120 g.

Anal. Calc'd for $C_{13}H_{18}O$: Carbonyl, 14.7. Found: Carbonyl, 9.9. Calc'd for $C_{13}H_{20}O$: Hydroxyl, 8.9. Found: Hydroxyl, 2.1.

The ketone-carbinol mixture was oxidized as follows: A solution of 60 g. (0.2 mole) of sodium dichromate, 50 ml. of concentrated sulfuric acid, and 300 ml. of water was added with stirring to 120 g. (0.63 mole) of the ketone-carbinol mixture during 1 hr. The temperature did not exceed 50°. The reaction mixture was stirred for an additional 0.3 hr., then extracted with ether. The extract, after washing with dilute sodium hydroxide solution, was stripped of ether and the residue was distilled through a 27-plate column at 5/1 reflux ratio to give 92 g. (77% yield) of crude 3-methyl-5-*t*-butylacetophenone (b.p. 141–150°/20 mm.).

Anal. Calc'd for $C_{13}H_{18}O$: Carbonyl, 14.7. Found: Carbonyl, 12.5.

(9) Konakoff, *J. Russ. Chem. Soc.*, **26**, 5 (1894); Krapivin, *Chem. Abstr.*, **5**, 1281 (1911).

(10) t_f = freezing temperature determined by extrapolation of freezing curve; temperatures measured by platinum resistance thermometer and G-2 Mueller bridge which had been certified by National Bureau of Standards and checked prior to use at the triple point of water and with a National Bureau of Standards benzoic cell.

(11) Rossini, *et al.*, *Selected Values of Physical Properties of Hydrocarbons*, Carnegie Press, Pittsburgh 13, Pa., 1953, p. 73.

(12) Authentic sample obtained from American Petroleum Institute, Carnegie Institute of Technology, Pittsburgh 13, Pa.

(13) Huntress and Mulliken, *Identification of Pure Organic Compounds, Order I*, John Wiley & Sons, N. Y., 1941.

TABLE II

PROPERTIES AND DERIVATIVES OF METHYL-*t*-BUTYLACETOPHENONES

Acetophenone	B.P., °C./20 Mm.[a]	T_f, °C.	Purity, Mole %	Semicarbazone, M.P., °C. Found	Semicarbazone, M.P., °C. Lit.	Derived Benzoic Acid M.P., °C. Found	Derived Benzoic Acid M.P., °C. Lit.	Derived Benzoic Acid Equiv. Wt. Found	Derived Benzoic Acid Equiv. Wt. Calc'd
2-Methyl-4-*t*-butyl-	146	11.90	99.0–99.4	195–196	197[b]	142–143	143–144[b]	192.6	192.3
2-Methyl-5-*t*-butyl-	146	30.72	99.4–99.8	180–181	183[4]	98–99	101[5]	192.7	192.3
3-Methyl-5-*t*-butyl-	148	46.14[b]	99.0–99.5	177–178	...	163–164	162[14]	192.0	192.3

[a] Uncorrected. [b] Reported m.p. 47°.[14]

A mixture of 90 g. (0.47 mole) of 3-methyl-5-*t*-butylacetophenone, 71 g. (0.64 mole) of semicarbazide hydrochloride, 95 g. (1.2 moles) of sodium acetate, 280 ml. of water, and 350 ml. of ethanol was refluxed for 1 hour. The solution was cooled to room temperature and filtered. The solid was crystallized 5 times from ethanol to give 50 g. (43% yield) of semicarbazone; m.p. 177–178°, white needles.

Anal. Calc'd for $C_{14}H_{21}N_3O$: N, 16.99. Found: N, 16.69.

The semicarbazone was hydrolyzed by refluxing for 1 hr. with 400 ml. of 20% hydrochloric acid, and the regenerated ketone was extracted with ether. Distillation of the concentrated ether extract through a 27-plate column at 5/1 reflux ratio gave 35 g. (91% yield) of 3-methyl-5-*t*-butylacetophenone; b.p. 148°/20 mm., t_f 46.14° (99.0–99.5 mole % pure).

Anal. Calc'd for $C_{13}H_{18}O$: C, 82.06; H, 9.54. Found: C, 81.94; H, 9.71.

Hydrobromite oxidation of dialkylacetophenones. The structures of the dialkylacetophenones (99+ mole % pure) were established by oxidation to known dialkylbenzoic acids. The general procedure follows: To a stirred, 0–10° mixture of 150 ml. of 5% aqueous sodium hydroxide and 10 g. (0.13 mole) of bromine was added 4.0 g. (0.02 mole) of dialkylacetophenone during 1 hr. The mixture was subsequently stirred for 9 hr. at 60°. The reaction mixture was cooled and extracted with ether to remove residual ketone. The aqueous layer was acidified and extracted with ether. The extract of the aqueous layer was concentrated and the solid residue was crystallized or sublimed to give about a 75% yield of methyl-*t*-butylbenzoic acid.

Nonisomerization of methyl-t-butylacetophenones. A mixture of 10 g. (0.05 mole) of 2-methyl-4-*t*-butylacetophenone (99.0–99.4 mole % pure), 10 g. (0.08 mole) of aluminum chloride and 100 ml. of carbon tetrachloride was stirred at 30° for 3 hr., then poured into an ice–hydrochloric acid mixture. The organic layer was washed successively with water, 5% aqueous sodium carbonate, and water. Carbon tetrachloride was stripped off, and the residue was distilled through a 10-cm. Vigreux column to give 7.9 g. (79% yield) of ketone whose infrared absorption spectrum was that of 2-methyl-4-*t*-butylacetophenone.

Similar treatment of 2-methyl-5-*t*-butylacetophenone (99.4–99.8 mole % pure) and 3-methyl-5-*t*-butylacetophenone (99.0–99.5 mole % pure) showed that these ketones also were not isomerized under the conditions employed, which were the conditions used in the acetylation of *p*-*t*-butyltoluene.

(14) Baur-Thurgau, *Ber.*, **31**, 1345 (1898).

PITTSBURGH 13, PA.

[CONTRIBUTION FROM THE COURTAULD INSTITUTE OF BIOCHEMISTRY]

Constant *Ortho* Effect with an Interacting Substituent

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Received Aug. 8, 1956

Infrared spectra of a number of substituted anthranilic acids were determined in chloroform and in potassium bromide disks. The extensive hydrogen bonding present in chloroform solution appears to involve both carboxyl and amino groups, but the infrared results suggest that in the solid state hydrogen bonding is confined to the carboxyl groups. No evidence exists for the presence of zwitter ion structures in these compounds. Carbonyl frequencies are linearly related to the σ values of the substituent groups. In spite of the broadening of the carbonyl bands produced by hydrogen bonding, the relation with σ values is readily appreciated from the solution data, but is less apparent from data obtained with solids. Comparison of the spectra of substituted benzoic and anthranilic acids shows that the amino group exerts a constant influence on the carbonyl stretching frequency.

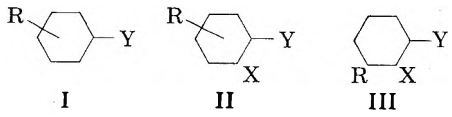
A second substituent R in a benzene ring produces an effect on the reactivity and other properties of the first substituent *Y* which is dependent on the nature and position of R. If the latter group is present in the *meta* or *para* position with respect to *Y*, its effect on *Y* is usually related to the σ value of the R group.[2,3] In multiple substitution, σ constants of the substituents are additive, since in any reaction series in which only the original substituent is modified, the entropy changes are presumably constant. Although σ values cannot be allocated to substituents in the *ortho* position to *Y*, this essential additivity property is likely to be preserved. Thus the presence of a further substituent *X* in the *ortho* position to group *Y* should produce a constant effect on the properties and reactivity of group *Y* in a series of substituted compounds.[3,4]

(1) British Empire Cancer Campaign Research Fellow.

(2) L. P. Hammett, *Physical Organic Chemistry*, McGraw-Hill, New York, 1940, p. 188.

(3) H. H. Jaffé, *Chem. Revs.*, **53**, 191 (1953).

(4) H. H. Jaffé, *Science*, **118**, 246 (1953).

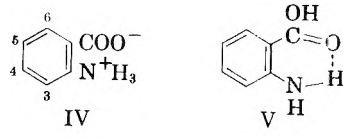


I II III

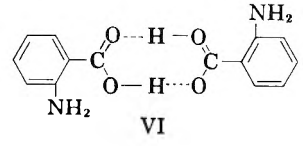
Differences in some measurable reactivity, or other property, of group Y in the corresponding structures I and II should therefore be independent of the particular R group selected. In structure III mutual interactions of groups R and X might be expected to complicate this relationship and possibly variable interactions, such as hydrogen bonding, occurring between groups X and Y could also give rise to discrepancies. It should clearly be possible to interchange the roles of substituents X and Y so that for suitable reactivities and properties of group X, the presence of substituent Y will exert a constant effect.

Substituted anthranilic acids were selected for study because of the interesting structural and hydrogen bonding possibilities of these compounds and in order to examine the constancy of the *ortho* effect in a series of compounds in which strong interaction is to be expected between the adjacent X and Y groups.

The structural possibilities for anthranilic acid and its derivatives include the zwitter ion IV and related forms produced by dipolar association, an intramolecularly bonded form V, and a variety of intermolecularly bonded structures of which VI possesses the associated carboxylic acid group and others possess the amino group of one molecule linked to the carboxyl group of an adjacent molecule.



IV V



VI

In addition to these, anthranilic acid exists in various polymorphic forms which might be related to the possible existence of different types of polymeric association.[5] Previous investigations have not fully elucidated the structural problems outlined above. X-ray studies[5,6,7,8] have given information on the crystal habit of anthranilic acid in its different modifications, but have shed little light on its molecular structure. Data on solubilities, molecular volumes, dissociation constants, heats of neutralization, dielectric constants and chemical reactivities[9,10] indicate that the nonpolar form is the main structure of anthranilic acid, even in aqueous solution, while the polar forms may be of greater significance in *m*- and *p*-aminobenzoic acids. This is also supported by the infrared spectrum of anthranilic acid. Three crystalline forms of anthranilic acid have been examined in Nujol mulls by infrared spectroscopy[5] and, although the main features were reproduced, sufficient minor variations occurred to permit Ebert and Gottlieb[5] to suggest the use of infrared spectroscopy as a tool in the study of polymorphism. Studies of the carbonyl stretching frequencies of methyl anthranilate and methyl salicylate have shown that intramolecular hydrogen bonding is present in these compounds.[11]

RESULTS AND DISCUSSION

The presence of two NH_2 and one CO stretching frequencies in their normal positions in solid anthranilic acids, together with the absence of any bands that can be definitely attributed to zwitter ion forms, indicate that further consideration of this type of structure is unnecessary. The very broad band between 3500 and 2800 cm.$^{-1}$ which appears in the spectrum of a few substituted anthranilic acids, examined in this region in chloroform solution, suggests the occurrence of both intra- and intermolecular hydrogen bonding. The infrared spectra of substituted anthranilic acids in potassium bromide disks possess the asymmetric and symmetric NH_2 bands of medium intensity near 3500 and 3400 cm.$^{-1}$, respectively. A broad band of about the same intensity is present in the 3100 to 2800 cm.$^{-1}$ region and a broad band of somewhat lower intensity, which forms a shoulder on the previous band and itself possesses several indistinct submaxima, is present between 2800 and 2500 cm.$^{-1}$ in all the compounds. This broad absorption is identical with that of benzoic acid and is in the frequency range characteristic of the associated carboxylic acid group. Absence of any indication of free hydroxyl absorption at 3650 cm.$^{-1}$ and of any maximum near 3300 to 3200 cm.$^{-1}$, which is to be associated with the NH . . . OC linkage, confirms the suggestion that in the solid state, association occurs through the carboxyl groups. Slight broadening of the carboxyl absorption at certain other wave numbers also supports structure VI as representing the association of anthranilic acid molecules in the solid state. Two compounds that exhibit variations from this scheme are 3- and 6-nitroanthranilic acids. The differences that appear in lower frequency absorptions of these acids suggest that the 3-nitro compound possesses intramolecular NO . . . HN bonding in addition to the intermolecular

(5) A. A. Ebert and H. B. Gottlieb, *J. Am. Chem. Soc.*, **74**, 2806 (1952).
(6) M. Prasad and M. R. Kapadia, *Indian J. Phys.*, **9**, 239 (1935).
(7) A. F. Wells, *Phil. Mag.*, **37**, 184 (1946).
(8) Armour Research Foundation, *Anal. Chem.*, **21**, 1016 (1949).
(9) P. Spinoglio and F. Brunello, *Gazz. chim. ital.*, **67**, 256 (1937).
(10) G. Denoto, *Gazz. chim. ital.*, **63**, 247 (1933).
(11) W. Gordy, *J. Chem. Phys.*, **8**, 516 (1940).

bonding already postulated. Considerable broadening of the NH_2 frequencies, so that they coalesce to give a single band, with the 6-nitro compound implies that the intermolecular bonding might involve the $NO_2 \ldots H_2N$ linkage as well as the associated carboxylic acid group.

Table I shows that a correlation exists between both the asymmetric and symmetric NH_2 stretching vibrations and the σ constants[2,3] of the substituent groups with reference to their positions relative to the NH_2 group. These values, being with reference to position 2 in the ring, are given the symbol σ_2. A similar correlation was observed by Flett[12] with substituted anilines in carbon tetrachloride. The data for the 6-nitro compound clearly cannot be considered for correlation purposes and methoxy compounds frequently possess anomalous behavior.[3] Equations of the regression lines for the remaining relevant data in Table I are $\nu = 3485 + 74.9\sigma_2$ and $\nu' = 3377 + 64.1\sigma_2$. Correlation coefficients[3] for the asymmetric and symmetric NH_2 frequencies are 0.817 and 0.770, respectively.

TABLE I

HAMMETT'S σ CONSTANTS AND ASYMMETRIC (ν) AND SYMMETRIC (ν') NH_2 FREQUENCIES[a] OF SUBSTITUTED ANTHRANILIC ACIDS

Substituent	σ_2	ν	ν'
5-Me	−0.170	3450	3335
4-Me	−0.069	3500	3395
None	0	3500	3395
4-MeO	0.115	3453	3355
5-Cl	0.227	3500	3385
4-I	0.352	3505	3405
4-Cl	0.373	3510	3400
4-Br	0.391	3517	3400
4-NO_2	0.710	3535	3415
6-NO_2	0.710	3460	3360[b]
3-I	...	3435	3325
3-Cl	...	3490	3375
3-NO_2	...	3480	3355

[a] All bands of medium intensity relative to the carbonyl absorption. [b] Broad band.

All the anthranilic acids show intense absorption in the 1670 cm.$^{-1}$ region, produced by the stretching vibrations of the C=O group. In all cases only one maximum is obtained but frequently, both in chloroform and as disks, this is broadened over about 6 wave numbers owing to hydrogen bonding.

Where the maxima are not absolutely sharp the central frequency is quoted. It can be seen from Table II that the carbonyl frequencies, both in chloroform and in disks, can be correlated with the σ values of the substituents considered in relation to the carbonyl group (σ_1). This correlation is better with solutions than with disks, but in view of the extensive hydrogen bonding that occurs it can be considered satisfactory even with the solids. Although the anthranilic acid used was crystallized from water and should therefore be the normal form, the results obtained using potassium bromide disks agree better with results given by Flett[13] for the high temperature form and therefore it seems likely that a transition occurred in the preparation of the disks.

In view of the uncertainty attached to the σ value of the *p*-nitro group,[3] 4-nitroanthranilic acid has been omitted from a quantitative consideration of the correlations. Regression lines for the data presented in Table II obey the equation $\nu_c = 1674 + 11.5\sigma_1$ and $\nu_d = 1666 + 11.9\sigma_1$ and the correlation coefficients for solutions and disks are 0.887 and 0.642, respectively.

TABLE II

σ VALUES AND CARBONYL FREQUENCIES OF ANTHRANILIC ACIDS

Substituent	σ_1	ν_c[a]	ν_d[b]
4-MeO	−0.268	[d]	1658
4-Me	−0.170	1673	1660
5-Me	−0.069	1674	1675
None	0	1673	1668
4-F	0.062	1675	[d]
4-Cl	0.227	1676	1667
4-Br	0.232	[d]	1667
4-I	0.276	[d]	1672
3-F	0.337	1678	[d]
5-F	0.337	1680	[d]
3-I	0.352	1676	1669
3-Cl	0.373	1680	1668
5-Cl	0.373	1679	1668
3-Br	0.391	1678	[d]
3-CF_3	0.415[c]	1680	[d]
3-NO_2	0.710	1683	1675
4-NO_2	1.27	1686	1675
6-NO_2	...	[d]	1672

[a] CO frequencies in chloroform. [b] CO frequencies in disks. [c] H. H. Jaffé, *Chem. Revs.*, **53**, 222 (1953). [d] Not measured.

An examination of the vibrational spectra of 60 assorted carboxylic acids enabled Flett[13] to suggest a range of frequencies characteristic of the carboxyl group. All these bands occur in a well defined form in the acids we have investigated. Frequencies near 2700 cm.$^{-1}$ and 1670 cm.$^{-1}$ have already been considered and the remaining carboxyl bands are collected in Table III. The band near 1430 cm.$^{-1}$ is probably a C—O— stretching vibration. In this series the bands near 1430 cm.$^{-1}$ and 1250 cm.$^{-1}$ are well defined, the latter in particular being intense and usually possessing a slightly broad maximum. These frequencies appear to increase with the σ value of the substituent. The absorption near 900 cm.$^{-1}$ is of a more variable character.

The relation between the carbonyl frequencies of substituted anthranilic acids in chloroform and the σ_1 values is approximately linear, the slope being similar to that found in both benzoic acid monomers

(12) M. St. C. Flett, *Trans. Faraday Soc.*, **44**, 767 (1948).

(13) M. St. C. Flett, *J. Chem. Soc.*, 962 (1951).

TABLE III

LOWER FREQUENCY COOH BANDS[a]

Substituent			
4-MeO	1428 m	1248 s	918 vw
4-Me	1430 m	1248 s	933 w
5-Me	1430 m	1250 s	918 w 904 w
None	1428 s	1253 s	924 s
4-Cl	1432 s	1253 s	921 s 900 m
4-Br	1435 s	1252 s	903 s
4-I	1433 m	1252 s	894 m
3-I	1447 m 1420 m	1266 m 1248 s	900 w
3-Cl	1425 s	1274 s 1258 s	922 vw 896 w
5-Cl	1430 m	1245 s	[b]
3-NO_2	1442 m	1258 s	884 w
4-NO_2	1433 m	1255 s	885 w
6-NO_2	1460 m 1428 w	1274 s 1217 s	888 vw

[a] Substituted anthranilic acids in potassium bromide disks. [b] Not measured.

and dimers.[12,14,15] This demonstrates the constancy of the effect of the amino group on the carbonyl group. Specific illustration of this feature is given in Table IV. A similar comparison of carbonyl frequencies for the solids, is given in Table V. The discrepancy in the case of 6-nitroanthranilic acid is not unexpected as the nitro group is adjacent to the carboxyl group. Constancy in the effect of an *ortho* substituent on carbonyl frequencies is also implicit in previous infrared data on substituted isatins.[16]

TABLE IV

EFFECT OF NH_2 GROUP ON CO FREQUENCIES OF ANTHRANILIC ACIDS IN SOLUTION

Substituent[a]	ν^b	$\nu_0{}^c$	$\nu - \nu_0$
4-Me	1673	1739	−66
None	1673	1743	−70
4-Cl	1676	1746	−70
3-Cl	1680	1746	−66
5-Cl	1679	1746	−67
3-NO_2	1683	1750	−67

[a] Numbering for substituents refers to anthranilic acid. [b] Frequencies for substituted anthranilic acids in chloroform. [c] Figures given by Flett[12] for the corresponding benzoic acid monomers in carbon tetrachloride.

TABLE V

EFFECT OF NH_2 GROUP ON CO FREQUENCIES OF SOLID ANTHRANILIC ACIDS

Substituent[a]	ν^b	$\nu_0{}^c$	$\nu - \nu_0$
None	1668	1685	−17
4-Cl	1667	1685	−18
3-NO_2	1675	1690	−15
4-NO_2	1675	1690	−15
6-NO_2	1672	1700	−28

[a] Numbering for substituents refers to anthranilic acid. [b] Frequencies for anthranilic acids in potassium bromide disks. [c] Figures given by Flett[13] for the corresponding benzoic acid dimers in Nujol mulls.

Interesting information was expected on the effect of the carboxyl group on the two amino stretching frequencies but, owing to the broad character of the NH_2 absorptions in aromatic amines in the solid state, data for comparison purposes could not be obtained.

EXPERIMENTAL

Spectra. Infrared data were obtained with a Perkin-Elmer 21 double-beam recording spectrometer fitted with a rock-salt prism.

Compounds. Substituted anthranilic acids were prepared by alkaline peroxide oxidation of the corresponding isatins using a method previously described.[17,18]

3-Trifluoromethylanthranilic acid was obtained as white needles from aqueous ethanol, m.p. 159°.

Anal. Calc'd for $C_8H_6F_3NO_2$: C, 46.8; H, 2.9. Found: C, 46.6; H, 3.0.

3-Fluoroanthranilic acid was obtained as white plates from aqueous ethanol and had m.p. 183°.

Anal. Calc'd for $C_7H_6FNO_2$: C, 54.2; H, 3.9. Found: C, 54.0; H, 3.8.

Acknowledgment. The authors thank Mr. A. Madle for his assistance with the measurements.

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(14) N. Fuson, M. L. Josien and E. M. Shelton, *J. Am. Chem. Soc.*, **76**, 2526 (1954).

(15) D. G. O'Sullivan and P. W. Sadler, *J. Org. Chem.* (in the press).

(16) D. G. O'Sullivan and P. W. Sadler, *J. Chem. Soc.*, 2202 (1956).

(17) P. W. Sadler, *J. Org. Chem.*, **21**, 169 (1956).

(18) P. W. Sadler, and R. L. Warren, *J. Am. Chem. Soc.*, **78**, 1251 (1956).

[CONTRIBUTION FROM THE LABORATORY OF CHEMICAL PHARMACOLOGY, NATIONAL CANCER INSTITUTE[1]]

Resolution and Rearrangement of α-Methylhydrocinnamic Acid and of Its 3,4-Dimethoxy Derivative

ANTHONY W. SCHRECKER

Received Aug. 13, 1956

(−)-α-Methylhydrocinnamic acid (I), prepared by resolution with (+)-α-methylbenzylamine, was converted to optically pure (−)-α-methylphenethylamine (II). An analogous series of reactions was carried out with the 3,4-dimethoxy derivative.

(+)-α-Methylhydrocinnamic acid, obtained by resolving the racemate with quinine[2] or menthylamine,[3] has been used extensively, especially by Wallis and his school, in studying the steric course of saturated nucleophilic rearrangements.[4] Thus the Curtius,[5] Hofmann,[6] Lossen,[7] Schmidt,[8] and Wolff[9] rearrangements were shown to proceed with retention of configuration.

It seems surprising that no method for preparing the optical isomer, (−)-I,[10] of this acid has been reported. Indeed, references to the *levo* isomer mention only partly racemic material, recovered from the mother liquors of the quinine salt of (+)-I.[5,9b]

The use of (−)- and (+)-α-methylbenzylamine (α-phenylethylamine) (III) in the resolution of atrolactic and mandelic acid[16] suggested its application to the resolution of I into both antipodes.

Treatment of racemic I with (−)-III and fractional crystallization of the diastereoisomeric salts from ethyl acetate provided, in 50% yield, (+)-I-(−)-III, from which (+)-I, $[\alpha]_D$ +23.5° (undiluted) was obtained. Resolving the impure *levo* acid from the mother liquors (or racemic I) with (+)-III similarly afforded (−)-I, $[\alpha]_D$ −24.6°. It may be mentioned that (+)-I, as obtained by resolution with quinine or menthylamine, had specific rotations not higher than 22.6°,[2,3] and in most reported instances considerably lower.[5,6,7,9]

Both the Curtius and the Schmidt rearrangement of (−)-I provided (−)-α-methylphenethylamine (*levo*-amphetamine) (II),[10] the hydrochloride of which in water had $[\alpha]_D$ −25.6° (*c* 4.8) (identical values in both rearrangements) and −24.6° (c 9.0). The latter value agrees with that reported by Leithe[17] for pure (+)-II hydrochloride[18] obtained by resolving racemic II. Essentially complete retention of asymmetry was to be expected, since the Curtius[19] and Schmidt[20] rearrangements of hydratropic acid also proceed with over 99% retention. The reported[5,8] rotations of (+)-II hydrochloride formed in the same rearrangements from (+)-I were, on the other hand, considerably lower,[18] a fact which can be explained only partly by the optical impurity of the acid used as the starting material.[5]

(−)-I: R = H
(−)-IV: R = OCH_3

(−)-II: R = H
(−)-V: R = OCH_3

Arylaliphatic acid azides generally have been prepared from the acid chlorides with sodium azide in anhydrous solvents ("dry method"[21]); this pro-

(1) The National Institutes of Health, Public Health Service, U. S. Department of Health, Education, and Welfare.

(2) F. S. Kipping and A. E. Hunter, *J. Chem. Soc.*, **83**, 1005 (1903).

(3) R. H. Pickard and J. Yates, *J. Chem. Soc.*, **95**, 1011 (1909).

(4) C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, Cornell Univ. Press., Ithaca, N. Y., 1953, p. 500.

(5) L. W. Jones and E. S. Wallis, *J. Am. Chem. Soc.*, **48**, 169 (1926).

(6) E. S. Wallis and S. C. Nagel, *J. Am. Chem. Soc.*, **53**, 2787 (1931).

(7) E. S. Wallis and R. D. Dripps, *J. Am. Chem. Soc.*, **55**, 1701 (1933).

(8) J. v. Braun and E. Friehmelt, *Ber.*, **66**, 684 (1933).

(9) (*a*) J. F. Lane, J. Willenz, A. Weissberger, and E. S. Wallis, *J. Org. Chem.*, **5**, 276 (1940); (*b*) K. B. Wiberg and T. W. Hutton, *J. Am. Chem. Soc.*, **78**, 1640 (1956).

(10) The absolute D-configuration of (−)-I and (−)-II, shown in the formulas,[11] follows from Karrer and Ehrhardt's[12] conversion of D-phenylalanine to L-(+)-II.[13] The D-configuration of (−)-IV and (−)-V has been demonstrated[14] by an analogous conversion of L-3,4-dihydroxyphenylalanine to *N*-tosyl-(−)-V, which was found to have the same negative rotation as the compound obtained by direct tosylation of (−)-V.

(11) *Cf.* W. Klyne, *Chemistry and Industry*, 1022 (1951).

(12) P. Karrer and K. Ehrhardt, *Helv. Chim. Acta*, **34**, 2202 (1951).

(13) The change from D to L in this conversion is due to the change in the chief function.

(14) A. W. Schrecker and J. L. Hartwell, to be published. This direct proof that (−)-I and (−)-IV belong to the same configurational series confirms the previously postulated[15] configuration of guaiaretic acid and related lignans.

(15) A. W. Schrecker and J. L. Hartwell, *J. Org. Chem.*, **21**, 381 (1956).

(16) L. Smith, *J. prakt. Chem.*, (2) **84**, 731 (1941).

(17) W. Leithe, *Ber.*, **65**, 660 (1932).

(18) The reported constants for (+)-II hydrochloride are: m.p. 147°,[5] 146°,[8] 156°[17]; $[\alpha]_D^{20}$ (in water) +16.6° (*c* 4.80),[5] +16.1° (*c* 4.163),[8] $[\alpha]_D^{15}$ +24.8° (*c* 9.00).[17]

(19) J. Kenyon and D. P. Young, *J. Chem. Soc.*, 263 (1941).

(20) A. Campbell and J. Kenyon, *J. Chem. Soc.*, 25 (1946).

(21) P. A. S. Smith, *Org. Reactions*, **3**, 373 (1946).

cedure was used in the Curtius rearrangements of (+)-I[5] and of hydratropic acid.[19] The "wet method"[21] has apparently not been employed for this class of compounds. However, its use in the present study yielded (without isolation of the various intermediates) over 90% of pure (−)-II hydrochloride.

Resolution of 3,4-dimethoxy-α-methylhydrocinnamic acid (IV), required for determining the absolute configuration of various lignans,[15] with quinine yielded (+)-IV, $[\alpha]_D$ +27.5° (chloroform). The impure (−)-IV, set free from the mother liquors, yielded a (−)-IV-(−)-III salt, slightly less soluble in ethyl acetate than its diastereoisomer (Table I),[22] from which (−)-IV,[10] $[\alpha]_D$ −28.1° (chloroform) was isolated. The Curtius rearrangement of the enantiomorphic acids yielded (+)- and (−)-3,4-dimethoxy-α-methylphenethylamine (V).[10]

TABLE I

PHYSICAL CONSTANTS OF α-METHYLBENZYLAMINE SALTS

Salt	M.p., °C	$[a]_D$[a]	Solubility[b]
(+)-I-(+)-III[c]	120–121	+22.7°	2.64
(−)-I-(+)-III	127.3–129.5	+1.4°	1.00
(+)-I-(−)-III	127–129.5	−1.5°	—
(+)-IV-(+)-III[c]	107–109	+22.3°	1.39
(−)-IV-(+)-III[c]	113.5–114.5	−2.1°	1.47
(−)-IV-(−)-III	107–109	−22.0°	—
(+)-IV-(±)-III[c,d]	110.4–111.4	+12.8°	—

[a] 2% solution in chloroform. [b] Determined in ethyl acetate at 23° and expressed as grams/100 g. of solution. [c] Prepared from the two pure components and crystallized from ethyl acetate. [d] Racemic III was recovered from this salt.

EXPERIMENTAL[23]

α-Methylcinnamic acid. A vigorously stirred suspension of 9.1 g. of sodium hydride in 125 ml. of methyl propionate was cooled in ice and treated with 0.45 ml. of absolute ethanol, then with 31.84 g. of benzaldehyde in 50 ml. of methyl propionate during 10 min. The ice bath was removed after one hour, replaced as soon as the vigorous reaction started, then removed again, and stirring was continued for another 2 hr. The organic layer was separated, after cautious addition of 28 ml. of acetic acid, then of 100 ml. of water, and the aqueous phase extracted with ethyl acetate. The combined ester solutions were washed with *N* hydrochloric acid and with sodium chloride solution, dried with sodium sulfate, and evaporated *in vacuo*. The residual ester was refluxed with 33.6 g. of potassium hydroxide in 60 ml. of water and 240 ml. of methanol for one hour. The solution was concentrated, diluted with water to *ca.* 500 ml., acidified with 6 *N* hydrochloric acid, chilled overnight, and the collected solid was washed with ice water; yield 35.67 g. (73%), m.p. 75–81°. The acid crystallized from hexane in colorless prisms, m.p. 80.5–81.0° (lit.[24] m.p. 81–82°).

3,4-Dimethoxy-α-methylcinnamic acid. The combined ester solutions, obtained from 18.53 g. of sodium hydride, 101.7 g. of veratraldehyde, and 356 ml. of methyl propionate, were washed with *N* hydrochloric acid, extracted with aqueous potassium carbonate, dried over potassium carbonate, concentrated, and passed through an alumina column which was then washed with chloroform. Evaporation of the eluates and crystallization from ether-hexane yielded 115.0 g. (80%) of the methyl ester as colorless prisms, m.p. 62.5–64.5° (lit.[25] m.p. 65–67°). The free acid was obtained in 99% yield by saponifying this ester with 2 molar equivalents of potassium hydroxide. It formed colorless needles, m.p. 142.8–143.8° (lit. m.p. 142–143°,[25] 144°[26]). Additional acid, isolated by acidifying the potassium carbonate extract and by saponifying the evaporated mother liquors of the recrystallized ester, was purified by crystallization from ethanol, raising the total yield from veratraldehyde to 86%.

DL-*α-Methylhydrocinnamic acid* (*I*) was prepared in 95% yield by treating 30 g. of α-methylcinnamic acid and 99.8 g. of sodium hydroxide in 900 ml. of water with 90 g. of Raney nickel-aluminum alloy at 90°.[27] The cooled filtrate and washings were stirred into 720 ml. of concd. hydrochloric acid and about 700 g. of ice and extracted with ether (600 + 300 + 300 ml.). The ether extracts were washed with 2 *N* hydrochloric acid and with sodium chloride solution, dried, and evaporated. The distilled acid (b.p. 148–149°/9 mm., 116.5°/0.5 mm.) solidified on chilling; m.p. 36–37°; yield 28.9 g. (95%). A sample crystallized from pentane in colorless prisms, m.p. 36.6–37.5° (lit.[28] m.p. 37°).

DL-*3,4-Dimethoxy-α-methylhydrocinnamic acid* (*IV*) was obtained in 94% yield as colorless hexagonal plates, m.p. 61.5–62.8° (lit.[29] m.p. 58–59°), after evaporating the ether extracts and recrystallizing the residue from ether-pentane.

Anal. Calc'd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.39; H, 7.44.

L-(+)-*α-Methylhydrocinnamic acid.*[10] A cold solution of 41.0 g. of racemic I in 350 ml. of ethyl acetate was treated with 30.25 g. of (−)-α-methylbenzylamine (III),[30] heated to dissolve the precipitate, and allowed to cool slowly. The solid was recrystallized six times from ethyl acetate to yield 16.1 g. of the (+)-I-(−)-III salt as long colorless needles, m.p. 127–129.5°, $[\alpha]_D^{20}$ −1.48° (c 2.00, chloroform). Systematic recrystallization of the second crops gave another 1.8 g. of pure salt, bringing the total yield to 50%.

Anal. Calc'd for $C_{18}H_{23}NO_2$: C, 75.75; H, 8.12; N, 4.91. Found: C, 75.69; H, 8.08; N, 4.90.

The free acid was obtained in 95% yield by shaking the salt with ether and excess 2 *N* sulfuric acid and extracting the aqueous phase[31] with additional ether. The extracts were washed four times each with 2 *N* sulfuric acid and with sodium chloride solution, dried, and evaporated. Distillation gave (+)-I, b.p. 112°/0.25 mm., d_4^{20} 1.0654, $[\alpha]_D^{20}$ +23.51° (*l* 1, undiluted) (lit.[3] +22.65°).

D-(−)-*α-Methylhydrocinnamic acid.*[10] The impure (−)-I,

(22) The small difference in solubilities would appear to make a direct resolution of racemic IV with III impractical. However, such a direct resolution could nevertheless be accomplished, apparently because the (−)-IV-(−)-III salt (and its antipode) crystallizes more rapidly than the diastereoisomeric salt. It is noteworthy that the solubility relationship is reversed in the case of the I-III salts.

(23) Melting points are corrected and were determined with the Hershberg apparatus. Boiling points are uncorrected.

(24) R. Stoermer and G. Voht, *Ann.*, **409**, 36 (1915).

(25) A. Müller, M. Mészáros, K. Körmendy, and A. Kuszman, *J. Org. Chem.*, **17**, 787 (1952).

(26) W. S. Ide and J. S. Buck, *J. Am. Chem. Soc.*, **62**, 425 (1940).

(27) E. Schwenk, D. Papa, B. Whitman, and H. F. Ginsberg, *J. Org. Chem.*, **9**, 175 (1944).

(28) M. Conrad and C. A. Bischoff, *Ann.*, **204**, 177 (1880).

(29) R. D. Haworth, C. R. Mavin, and G. Sheldrick, *J. Chem. Soc.*, 1423 (1934).

(30) A. W. Ingersoll, *Org. Syntheses*, Coll. Vol. 2, 506 (1943); W. Theilacker and H. G. Winkler, *Ber.*, **87**, 690 (1954). Both methods appear equally satisfactory.

(31) Pure (−)-III is recovered from the aqueous solution by treatment with alkali, ether extraction, and distillation.

recovered from the mother liquors of the (+)-I-(−)-III salt and treated with (+)-III,[30] yielded 51% of the (−)-I-(+)-III salt, m.p. 127.3–129.5°, $[\alpha]_D^{20}$ +1.36° (*c* 2.00, chloroform), which was also prepared from racemic I (after 10 recrystallizations: m.p. 128–130°, $[\alpha]_D^{20}$ +1.13°). The free acid had b.p. 111°/0.22 mm., n_D^{20} 1.5145, d_4^{22} 1.065, $[\alpha]_D^{22}$ −24.56° (*l* 1, undiluted).

L-(+)-*3,4-Dimethoxy-α-methylhydrocinnamic acid.*[10] The quinine salt was prepared from 96.7 g. of racemic IV and 140 g. of quinine in about 1800 ml. of ethanol and recrystallized thrice from the same solvent. It formed electrified needles, m.p. 163.7–164.3°, $[\alpha]_D^{20}$ −84.5° (*c* 1.98, chloroform). The yield, including pure material isolated from the mother liquors, was 90%.

Anal. Calc'd for $C_{12}H_{16}O_4 \cdot C_{20}H_{24}N_2O_2$: C, 70.05; H, 7.35; N, 5.11. Found: C, 69.71; H, 7.15; N, 5.00.

The free acid was isolated in the same way as (+)-I; evaporation of the ethereal solution gave a viscous oil which, dried in a high vacuum, was used directly for further reactions. A sample was distilled in a bulb tube: b.p. 130° (bath temperature)/0.01 mm., $[\alpha]_D^{21}$ +27.5° (*c* 4.01, chloroform).

Anal. Calc'd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 63.84; H, 7.16.

The acid chloride, prepared from 1 g. of the acid with 1.15 ml. of oxalyl chloride in 97% yield, had b.p. 90° (bath temperature)/0.015 mm. and $[\alpha]_D^{20}$ +20.5° (*c* 5.73, benzene).

The amide was obtained from the acid chloride with concd. aqueous ammonia; it crystallized from water in colorless needles, m.p. 121.5–122.5°, $[\alpha]_D^{21}$ +60.5° (*c* 0.99, chloroform).

Anal. Calc'd for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.68. Found: C, 64.44; H, 7.53.

D-(−)-*3,4-Dimethoxy-α-methylhydrocinnamic acid.*[10] Treating the impure (−)-IV, recovered from the quinine salt mother liquors, with (−)-III afforded the (−)-IV-(−)-III salt in 77% yield, based on the racemic IV used originally. The major portion was obtained pure after three recrystallizations from ethyl acetate; m.p. 107–109.3°, $[\alpha]_D^{20}$ −22.0° (*c* 2.01, chloroform).

Anal. Calc'd for $C_{12}H_{16}O_4 \cdot C_8H_{11}N$: C, 69.54; H, 7.88; N, 4.06. Found: C, 69.46; H, 7.68; N, 3.86.

The free acid had b.p. 120° (bath temperature)/0.005 mm., $[\alpha]_D^{21}$ −28.1° (*c* 4.16, chloroform).

Anal. Calc'd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 63.80; H, 7.32.

The acid chloride had b.p. 95° (bath temperature)/0.01 mm., $[\alpha]_D^{21}$ −21.3° (*c* 4.89, benzene).

Anal. Calc'd for $C_{12}H_{15}ClO_3$: Cl, 14.61. Found: Cl, 14.01.

D-(−)-*α-Methylphenethylamine (II).*[10] (*a*) *By the Curtius rearrangement.* (−)-I (5.35 g.) was refluxed with 8.4 ml. of oxalyl chloride for one hour, and the solution evaporated *in vacuo*[32] and re-evaporated twice after adding dry benzene. The acid chloride, dissolved in 22 ml. of dry acetone, was added rapidly at −10° to a magnetically stirred solution of 4.38 g. of sodium azide in 13 ml. of water. The mixture was stirred at 3° for 1 hr. and extracted twice with a total of 37 ml. of benzene; the extracts were washed with sodium chloride solution, dried rapidly with sodium sulfate, filtered, and the residue was washed with another 15 ml. of benzene. The filtrate was concentrated at room temperature *in vacuo*[32] to about 1/3 of its volume, brought to about its original volume with dry benzene, heated to 62° over 15 min. in the presence of a piece of Teflon (which seemed to promote nitrogen evolution), kept at this temperature for 1 hr., and evaporated *in vacuo*. The residue was warmed with 17.5 ml. of concd. hydrochloric acid at 45° for 5 min., diluted with water, and the solution extracted once with ether to remove a slight opalescence. It was then treated with excess 10 *N* sodium hydroxide and extracted twice with ether. The extracts were washed with 10 *N* sodium hydroxide, dried with powdered sodium hydroxide, filtered, treated with 8 ml. of 5 *N* ethanolic hydrogen chloride, and evaporated to dryness. The residual (−)-II hydrochloride was washed with ether and dried; yield 5.06 g. (90.5%), m.p. 155.7–156.7°, $[\alpha]_D^{21}$ −25.62° (*c* 4.80, water).[18] The neutral sulfate was obtained by treating the hydrochloride with 5 *N* sodium hydroxide, extracting the amine with benzene, and adding one equivalent of ethanolic sulfuric acid. It crystallized from water-ethanol-acetone in colorless leaflets, $[\alpha]_D^{20}$ −22.34° (*c* 8.00, water).[33]

(*b*) *By the Schmidt rearrangement.* A well-stirred solution of 7.02 g. of (−)-I in 50 ml. of chloroform was treated with 13 ml. of concd. sulfuric acid, then at 45° with 3.62 g. of sodium azide over 0.5 hr.[20] Stirring at 45° was continued during 0.5 hr., and the mixture was worked up as under (*a*). The hydrochloride (yield 6.18 g., 84%) crystallized from ethanol-ether in colorless prisms, m.p. 153–155°, $[\alpha]_D^{23}$ −25.62° (*c* 4.78, water), −24.60° (*c* 9.02).[18] The neutral sulfate had m.p. 328–329° (decompn. and darkening), $[\alpha]_D^{20}$ −24.57° (*c* 2.00, water), $[\alpha]_D^{21}$ −22.11° (*c* 8.00).[33]

D-(−)-*3,4-Dimethoxy-α-methylphenethylamine* (*V*)[10] was obtained from (−)-IV by the Curtius rearrangement, following the procedure used for preparing (−)-II. The dried ethereal extract was evaporated, and the residue distilled (b.p. 96°/0.08 mm.). The viscous oil (83% yield) solidified in the receiver; m.p. 37–40°. A sample crystallized from pentane in long colorless needles, m.p. 39–40°, $[\alpha]_D^{21}$ −31.9° (*c* 3.80, ethanol) (−32.1°, *c* 4.00 in a second run), −30.9° (*c* 4.13, chloroform).

Anal. Calc'd for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.45; H, 8.63; N, 7.04.

The neutral sulfate was prepared in 91% yield with the exact amount of ethanolic sulfuric acid. It crystallized from dilute ethanol in colorless shiny leaflets, m.p. 313–315° (decompn. and darkening), $[\alpha]_D^{21}$ −21.4° (*c* 2.00, water).

Anal. Calc'd for $2C_{11}H_{17}NO_2 \cdot H_2SO_4$: S, 6.56. Found: S, 6.58.

The hydrochloride was too deliquescent to be obtained pure.

L-(+)-*3,4-Dimethoxy-α-methylphenethylamine*, yield 92%, had m.p. 37–40°, $[\alpha]_D^{21}$ +32.1° (*c* 3.98, ethanol), and formed a neutral sulfate, m.p. 313° (decompn.), $[\alpha]_D^{20}$ +20.5° (*c* 2.00, water).

Solubilities of α-methylbenzylamine salts (Table I). The pure salts (1 g.) were stirred magnetically in a glass-stoppered Erlenmeyer flask at 35° for 18 hr., then at 23° for 1 hr., and the suspension was centrifuged. A 5-ml. aliquot of the supernatant was weighed in a stoppered weighing bottle and evaporated in an air current. The residue was weighed after drying in a vacuum desiccator.

Acknowledgment. The author is indebted to Miss Mary M. Trail for performing a large portion of the experiments. Analyses were performed by Dr. W. C. Alford and his associates.

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(32) A rotating evaporator (Rinco Instrument Co., Greenville, Ill.) was used.

(33) Reported $[\alpha]_D$ (in water) for (+)- and (−)-II sulfate (base resolved with tartaric acid): +24.3°, −26.2° (*c* 2)[34]; +21 to 22.7°, −22.70° (*c* 8).[35]

(34) F. M. Jaeger and J. A. van Dijk, *Proc. Acad. Sci. Amsterdam*, 44, 26 (1941).

(35) Personal communication by G. E. Ullyot.

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

Cyclohepta[*de*]naphthalene (Pleiadiene)

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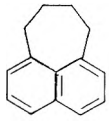
Received Aug. 13, 1956

A re-examination of the reaction between chloranil and 7,8,9,10-tetrahydrocyclohepta[*de*]naphthalene (I) has shown that low yields of cyclohepta[de]naphthalene are produced. A brief discussion of the resonance stabilization of such compounds is presented.

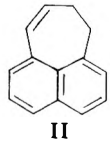
An investigation of certain nonbenzenoid "aromatic" compounds, initiated in 1949,[1] was concerned primarily with the attempted synthesis of cyclohepta[*de*]naphthalene (III). Although initial attempts to synthesize III were unsuccessful,[1] an inconclusive experiment conducted in the course of that investigation suggested that III may have been formed, although in low yield, by the dehydrogenation of 7,8,9,10-tetrahydrocyclohepta[*de*]naphthalene (I) using chloranil as the hydrogen acceptor.[2,3,4] The present report is concerned with a re-examination of that reaction.

Since this work was completed, the synthesis of III, by more conventional methods, has been reported, along with chemical evidence pertaining to the question of resonance stabilization in that substance.[5] These data[5] and the results of the chloranil reaction suggest that such stabilization is slight, if present at all.

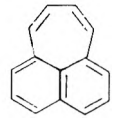
The conversion of I to olefin II by reaction with lead tetraacetate, although previously reported to be undependable, has proved to be entirely satisfactory. Further attempts to prepare III from II, however, have not been successful.



I



II



III

The synthesis of III was finally effected by the treatment of I with chloranil in refluxing xylene solution,[2] from which, I, II, and III were isolated by chromatography and fractional crystallization. The mobilities of these three substances on alumina were so similar that several chromatograms were required for effective separation. Based on unrecovered I (23% recovery), II was formed in 56% yield and III in 7.5% yield.

Pleiadiene (III) which appears to possess little resonance stabilization contains 14 π electrons. Acepleiadylene (IV), on the other hand, contains 16 π electrons and appears to possess significantly greater stabilization than III.[5] These facts would appear discordant with the Hückel requirement[6] of $4n + 2$ π electrons for resonance stability.[5] It is implied, however, in the model used by Platt[7] that in such systems peripheral electrons play a dominant role in resonance stabilization. Structures III and IV contain one and two "internal" carbon atoms, respectively. If the π electrons associated with "internal" carbon atoms be ignored and only peripheral p orbitals are considered to interact normally, then the peripheral system of III does not comply with the rule, while that of IV satisfies it. Superimposed on this is the interaction of "internal" p orbitals with the peripheral system.

III

IV

This secondary interaction is less easily described with regard to type and degree and, although it could be calculated on the basis of molecular orbital theory, assumptions inherent in such applications of the theory would render the results questionable.

EXPERIMENTAL[8]

7,8-Dihydrocyclohepta[de]naphthalene (II). A solution comprised of 6.85 g. (0.014 mole) of lead tetraacetate and 2.31 g. of I dissolved in 55 ml. of purified[9] acetic acid was heated, protected from atmospheric moisture, for 1.2 hr. The mixture was chilled, diluted with 300 ml. of water and extracted with several portions of ether. Washing with water and aqueous sodium hydrogen carbonate followed by

(1) Gardner and Horton, *J. Am. Chem. Soc.*, **74**, 657 (1952).

(2) Arnold, Collins, and Zenk, *J. Am. Chem. Soc.*, **62**, 983 (1940).

(3) Braude, Linstead, Mitchell, and Woolridge, *J. Chem. Soc.*, 3595 (1954).

(4) Treibs, Steinert, and Kirchhof, *Ann.*, **581**, 54 (1953).

(5) Boekelheide and Vick, *J. Am. Chem. Soc.*, **78**, 653 (1956).

(6) Hückel, *Z. Elektrochem.*, **43**, 752 (1937).

(7) Platt, *J. Chem. Phys.*, **22**, 1448 (1954). The relative importance of peripheral electrons in resonance considerations was first pointed out to us by a referee.

(8) Melting points are corrected.

(9) Purification by fractional distillation of a mixture of acetic acid and acetic anhydride from potassium permanganate.

drying and evaporation of solvent left the crude product as an oil. It was converted to the picric acid complex by dissolving it in 10 ml. of methanol containing 2.68 g. of picric acid. There was obtained 2.64 g. (51%) of red-brown complex, m.p. 129–132° (dec.) (lit.[1] 131–133°). Decomposition of a sample of the complex gave II, identified by m.p. and mixed m.p. Its ultraviolet absorption spectrum exhibited λ_{max} 229 mμ and 300 mμ, log ε 4.75 and 3.80, respectively (alcohol).

Cyclohepta[de]naphthalene. A suspension of 5.00 g. (0.0274 mole) of I and 13.52 g. (0.0548 mole) of recrystallized chloranil in 85 ml. of xylene was refluxed in a nitrogen atmosphere for 20 hr. The reaction mixture was transferred to a separatory funnel by repeated rinsing with petroleum ether (60–66°) and 10% aqueous sodium hydroxide and diluted with 700 ml. of water. After extracting the aqueous phase with several portions of ether, the combined organic solution was washed twice with dilute sodium hydroxide and then repeatedly with water. The dry (sodium sulfate) solution was distilled through a 2 ft. bead-packed column using a steam bath.

The residual oil was then dissolved in a minimum volume of petroleum ether (60–66°) and charged to a column of acid-washed alumina (1 × 18 in.). The first eluate, containing I and II, appeared colorless in white light and blue in ultraviolet light. The red band (black in ultraviolet) contained III. The red eluate was concentrated using the bead column and the chromatography repeated. A third chromatogram afforded 0.454 g. of red liquid which was then dissolved in 20 ml. of ethanol and treated with 20 ml. of saturated alcoholic picric acid solution. The mixture was warmed until homogeneous, cooled, and filtered to yield 0.64 g. of brown-black complex, m.p. 186° (dec.) (7.5% based on unrecovered I). Repeated recrystallization from ethanol gave pure picric acid complex of III, m.p. 206–208° (dec.).

Anal. Calc'd for $C_{20}H_{13}N_3O_7$: C, 58.96; H, 3.21. Found: C, 58.54; H, 3.09.

A sample (0.196 g.) of the complex was decomposed by washing an ethereal solution several times with aqueous sodium hydrogen carbonate. Isolation in the usual manner gave 0.084 g. of red solid (III), m.p. 88.5–90° (with sintering at 86°). The sample for analysis was prepared by sublimation at 0.3 mm.

Anal. Calc'd for $C_{14}H_{12}$: C, 94.34; H, 5.66. Found: C, 94.20; H, 5.62.

A mixed melting point with material prepared by the other route[5,10] was not depressed. Catalytic hydrogenation of a 2.8 mg. sample gave I. The ultraviolet absorption spectrum of III was virtually identical with that reported.[5]

The colorless eluates from all of the above chromatograms were combined and concentrated as before. To the residual oil thus obtained was added a solution of 5.0 g. of picric acid in 50 ml. of ethanol. Fractional crystallization gave a total of 4.82 g. (56% based on unrecovered I) of light red complex of II, m.p. 127–130° (dec.) (lit.[1] 131–133°). Further recrystallization gave material melting 130–132° (dec.). The bronze color previously reported for this complex was found to be due to a slight contamination by black solid. The pure hydrocarbon (II) was isolated and identified as described above, m.p. 44.5–46° (lit.[1] 43–45°).

The mother liquor of the above picric acid complex was concentrated and cooled whereupon 2.63 g. (23%) of orange complex of I crystallized, m.p. 113–114°, characterized in the usual way.

Acknowledgment. The authors are indebted to Dr. Carl Wulfman for most helpful discussion, to Professor V. Boekelheide for interesting and helpful correspondence, and to Research Corporation for the financial support of the work.

AUSTIN, TEX.

(10) Kindly provided by Prof. V. Boekelheide.

[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY OF THE UNIVERSITY OF CHICAGO]

Reactions of Atoms and Free Radicals in Solution. XXXIX. The Reaction of Diacetyl Peroxide with *sec*-Butyl Nitrite and 3-Amyl Nitrite

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Received Aug. 15, 1956

The thermal decomposition of diacetyl peroxide in *sec*-butyl nitrite and 3-amyl nitrite results in the formation of a white solid of empirical formula CH_3NO. Cryoscopic molecular weight determination in benzene indicates that the material is a "dimer" $(CH_3NO)_2$. The Rast method (in camphor) indicated a molecular weight of 55. Upon hydrogenation of the "dimer" $(CH_3NO)_2$ a quantitative yield of methylamine was obtained. The "dimer" $(CH_3NO)_2$ forms a hydrochloride of the empirical formula $(CH_3NO.HCl)$.

It was shown in previous publications that nitroso compounds[2] and nitrite esters[3] are excellent inhibitors in the free radical bromination of aliphatic hydrocarbons. In the hope of elucidating the mechanism whereby nitrite esters act as inhibitors, the reactions of diacetyl peroxide with 3-amyl nitrite and *sec*-butyl nitrite, respectively, were investigated.

When diacetyl peroxide, dissolved in *sec*-butyl nitrite, was slowly added to *sec*-butyl nitrite, maintained at 73°, a reaction resulted (as indicated by an evolution of gas). Upon cooling the reaction mixture, a white solid, *A*, separated, and no additional amounts of this material were found on concentrating the filtrate. It was also established by conventional chemical methods that the filtrate contained

(1) The material presented in this paper formed part of a dissertation submitted in 1948 by Theodore H. Meltzer to the Graduate School of the University of Chicago in partial fulfillment of the requirements for the Ph.D. degree.

(2) Kharasch, White, and Mayo, *J. Org. Chem.*, **3**, 33 (1938).

(3) Kharasch, Hered, and Mayo, *J. Org. Chem.*, 6, 818 (1941).

methyl ethyl ketone, *sec*-butyl alcohol, and methyl acetate.[4]

If we assume that the decomposition of diacetyl peroxide proceeds in part in the manner indicated below:

$$CH_3COOOCOCH_3 \xrightarrow{\Delta} CH_3. + CO_2 + CH_3COO.$$

$$\underset{\displaystyle ONO}{CH_3CH_2CHCH_3} + CH_3. \longrightarrow \underset{\displaystyle O.\;\; B}{CH_3CH_2CHCH_3} + (CH_3NO)$$

$$2(CH_3NO) \longrightarrow (CH_3NO)_2 \quad A$$

$$2B \longrightarrow \text{ketone} + \text{alcohol}$$

then the yield of the white solid *A* is about 45% of the amount calculated on this basis.

The analyses of the white solid *A* (m.p. 122°) indicated that it has the empirical formula CH_3NO. Cryoscopic molecular weight determination in benzene indicated that it was a "dimer" $(CH_3NO)_2$ in that solvent. Subsequent to completion of this work, Coe and Doumani[5] described the "preparation of nitrosomethane dimer (m.p. 122°) by the photochemical decomposition of *tert*-butyl nitrite in the vapor-phase at 25° and at pressures of about 50 mm. using a quartz mercury vapor lamp."[6]

Toward some reagents, the dimer $(CH_3NO)_2$ behaves in a manner similar to that of the "monomer" $(CH_2{=}NOH)$.[7] Toward other reagents its behavior is quite different. Thus, both the "monomer" $(CH_2{=}NOH)$ and the "dimer" $(CH_3NO)_2$ reduce Tollen's reagent and Fehling's solution. When heated in the presence of acetic acid, both give tests for formaldehyde. They differ, however, in that the "monomer" forms a crystalline acetyl (and benzoyl) derivative, whereas we have been unable to form an acetyl (or a benzoyl) derivative of the "dimer" $(CH_3NO)_2$. Furthermore, whereas the "monomer" $(CH_2{=}NOH)$ forms salts of the empirical formula $(CH_2{=}NOH)_3{\cdot}HCl$, the "dimer" $(CH_3NO)_2$ forms salts of the empirical formula[8] $(CH_3NO){\cdot}HCl$. Also, an aqueous solution of formaldoxime monomer shows continuous absorption in the ultraviolet, whereas an aqueous solution of the "dimer" exhibits a maximum at 276 mμ.

Hydrogenation of the "dimer" $(CH_3NO)_2$ in the presence of PtO_2 gave about 98% of the calculated amount of methylamine. Dunstan and Bossi[7] claim that when formaldoxime "monomer" is reduced by a metal and an acid or a metal in basic solution, all of the nitrogen appears as ammonia, but when the acetyl derivative is similarly reduced, two atoms of nitrogen appear as ammonia and the third as methylamine.

Many unsuccessful attempts were made by us to convert the "monomer" $(CH_2{=}NOH)$ to the "dimer" $(CH_3NO)_2$, and the "dimer" to the "monomer." It would appear that the "monomer" and the "dimer" are distinct entities, and that in some solvents at least they do not exist in a tautomeric equilibrium. The conclusion that nitrosoalkanes isomerization to oximes is not instantaneous has also been reached by Chilton and Gowenlock[9] and Müller and Metzger.[10]

EXPERIMENTAL

The diacetyl peroxide was prepared by the procedure previously described.[11] The *sec*-butyl and the 3-amyl nitrite were prepared by the procedure described in "Organic Syntheses."[12] The alcohols and the nitrite esters used in this study had the following physical constants: *sec*-butyl alcohol (b.p. 98–99°, n_D^{20} 1.3972); *sec*-butyl nitrite (b.p. 67–68°, n_D^{20} 1.3727); 3-amyl alcohol (b.p. 114–115°, n_D^{20} 1.4079); 3-amyl nitrite (97–98°, n_D^{20} 1.3867).

The apparatus and procedure used in the decomposition of diacetyl peroxide have been described in a previous publication.[11]

Decomposition of diacetyl peroxide in sec-butyl nitrite. Diacetyl peroxide (32.5 g. of 95% material = 0.26 mole), dissolved in *sec*-butyl nitrite, was slowly added to *sec*-butyl nitrite maintained at 73°. It took 2 hr. for the introduction of the peroxide (the ratio of nitrite to peroxide was 6:1). At the end of that time, the mixture was heated for an additional 10 hr. The gases (CO_2 and CH_4) were collected in the usual way.

The reaction mixture was then cooled to −80°, and the white solid *A* which separated (7 g.) was collected on a filter. Unsuccessful attempts were made to obtain additional amounts of the solid by removal of some of the nitrite ester at reduced pressure.

Crystallization of the white solid *A* (7 g.) from carbon tetrachloride gave a material (6.5 g.) which melted at 122°, and a material (0.5 g.) which was very little soluble in carbon

(4) At the time this work was done, no satisfactory methods for the quantitative estimation of the methyl ethyl ketone, *sec*-butyl alcohol, and methyl acetate in the *sec*-butyl nitrite (used as a solvent) were available, although there was no difficulty in demonstrating (qualitatively) the presence of these materials. The gases evolved were: carbon dioxide (0.38 mole) and methane (2275 ml. at 25° and 737 mm.) per 0.26 mole of diacetyl peroxide. The gas contained less than 5% of nitric oxide.

(5) Coe and Doumani, *J. Am. Chem. Soc.*, **70**, 1516 (1948).

(6) For other papers dealing with the formation of monomeric and dimeric aliphatic nitroso compounds by pyrolysis of dialkyl mercury compounds in the presence of nitric oxide, see Chilton and Gowenlock, *J. Chem. Soc.*, 3232 (1953); 3174 (1954); see also recent work by Müller and Metzger, *Ber.*, 88, 165 (1955), on dimers of nitroso alkanes and the recent work of Gowenlock and Trotman, *J. Chem. Soc.*, 4190 (1955). Note also that F_3CNO exists as a monomer [Jander and Haszeldine, *J. Chem. Soc.*, 912 (1954)].

(7) The "monomer" $(CH_2{=}NOH)$ was first isolated by Dunstan and Bossi, *J. Chem. Soc.*, **73**, 353 (1898). It is a liquid which boils at 83–85°.

(8) Unfortunately, through an oversight we have not demonstrated whether or not the "dimer" can be regenerated from its salts. Neither have Dunstan and Bossi[7] demonstrated that formaldoxime "monomer" can be recovered from its salts. The addition of nitrosoalkane dimers to conjugated dienes is under investigation in this laboratory.

(9) Chilton and Gowenlock, *J. Chem. Soc.*, 3177 (1954).

(10) Müller and Metzger, *Ber.*, **88**, 165 (1955).

(11) Kharasch, Jensen, and Urry, *J. Org. Chem.*, **10**, 390 (1945).

(12) Noyes, *Org. Syntheses*, **Coll. Vol. 2**, 108 (1943).

tetrachloride and which melted at 132°.[13] The latter material was the formaldoxime polymer, since no depression in melting point was noted upon admixture with an authentic sample of the polymer of formaldoxime.

Anal. Calc'd for CH_3NO: C, 26.64; H, 6.73; N, 31.11; Mol. wt., 45. Found: C, 26.88; H, 6.69; N, 31.16; Mol. wt. (in benzene), 90.

The molecular weight in benzene thus indicates that the compound is a "dimer" $(CH_3NO)_2$. The molecular weight of the material as determined by the Rast method (in camphor) was 55.

An aqueous solution of the white solid (m.p. 122°) reduced Tollen's reagent and Fehling's solution upon heating. When boiled with acetic acid, formaldehyde was liberated, as evidenced by the formation of a methone derivative which melted at 189°. The melting point of this material was not depressed by admixture with a known sample of the methone derivative of formaldehyde (m.p. 189°). The procedure used in carrying out the methone test is described by Weinberger[14] and by Vorlander.[15]

Preparation of hydrochloride of $(CH_3NO)_2$. One gram of the material $(CH_3NO)_2$ was dissolved in 150 ml. of dry ether, the whole cooled to 0°, and dry hydrogen chloride was passed into the solution. A white crystalline material separated. The crystals were collected on a Büchner funnel and washed repeatedly with dry ether. The crystals melted (with sublimation) at 140°.

Anal. Calc'd for $(CH_3NO.HCl)$: N, 17.17; Cl, 43.50. Found: N, 17.20; Cl, 43.60.

When prepared under rigorously anhydrous conditions, the hydrochloride is stable. However, it hydrolyzes rapidly in the presence of water with evolution of a gas.

Hydrogenation of $(CH_3NO)_2$. The compound $(CH_3NO)_2$ (0.2772 g.) was dissolved in glacial acetic acid (25 ml.), and hydrogenated over PtO_2 at room temperature. The amount of hydrogen absorbed corresponded to 1.97 moles per mole of CH_3NO. The catalyst was collected on a filter, and the filtrate made up to 50 ml. with absolute alcohol. An aliquot (15 ml.) was treated with 6 ml. of an alcoholic solution of H_2PtCl_6 (5%). The weight of the precipitate $(CH_3NH_2)_2 \cdot H_2PtCl_6$ was 98% of the calculated value. The melting point of the chloroplatinate was 223–225°, and it was not depressed by admixture of the chloroplatinate of an authentic sample of methylamine.

Anal. Calc'd for $(CH_3NH_2)_2H_2PtCl_6$: Pt, 41.4. Found: Pt, 41.5.

The methylamine was further identified by the conversion to *N*-methylbenzamide. The melting point of this material was 81°, and the melting point was not depressed by admixture with an authentic sample of *N*-methylbenzamide.

The reaction of diacetyl peroxide with 3-amyl nitrite. Except for minor modifications in procedure, the decomposition of diacetyl peroxide in 3-amyl nitrite maintained at 90°, proceeded in a manner similar to that described in the case of *sec*-butyl nitrite. The yield of the white solid was somewhat lower. It melted at 122°, and no depression in the melting point was noted upon admixture with the white solid obtained in the decomposition of diacetyl peroxide in *sec*-butyl nitrite.

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(13) The melting point of formaldoxime polymer must be taken in a sealed capillary to avoid sublimation. Depending upon the rate of heating, m.p. varies from 132° to 138°.

(14) Weinberger, *Ind. Eng. Chem., Anal. Ed.*, **3**, 357 (1931).

(15) Vorlander, *Z. Anal. Chem.*, **77**, 241 (1929).

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF J. T. BAKER CHEMICAL COMPANY]

Benzoin Condensation of Anisaldehyde

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Received July 13, 1956

The benzoin condensation of anisaldehyde is shown to be reversible in an ethanol-water reaction medium. Since irreversible side reactions of anisaldehyde lower the yield of anisoin, and it is generally believed that the benzoin condensation is irreversible in the absence of water, attempts have been made to increase the yield of anisoin from anisaldehyde by carrying out the condensation in a nonaqueous medium. The data from a series of such runs indicate that anisoin decomposes even in a nonaqueous medium and suggest that the benzoin condensation of anisaldehyde is reversible even in the absence of water.

Though the benzoin condensation takes place rapidly and goes nearly to completion with benzaldehyde,[2] it is slower and the yields are lower with many substituted benzaldehydes.[3] The reversibility of this reaction in the case of benzaldehyde has been intensively investigated by various authors.[4] Various irreversible side reactions occur (such as destruction of the aldehyde by the Cannizzaro reaction) which reduce the yield of benzoin if the heating period is unduly prolonged. In the case of slower-reacting substituted benzaldehydes a prolonged heating period is usually unavoidable.

In the course of preparative work on anisoin we have investigated the extent of the reversibility of the benzoin condensation of anisaldehyde. The procedure of Bösler[5] is usually employed in converting this aldehyde to anisoin. It involves reflux-

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(2) R. Adams and C. S. Marvel, *Org. Syntheses*, **Coll. Vol. 1**, 2nd ed., 94 (1941).

(3) W. S. Ide and J. S. Buck, *Org. Reactions*, **4**, 269 (1948).

(4) See references cited in Reference 3. In particular, see (*a*) E. Anderson and R. A. Jacobson, *J. Am. Chem. Soc.*, **45**, 836 (1923); and (*b*) A. Lachman, *J. Am. Chem. Soc.*, **46**, 708 (1924).

(5) M. Bösler, *Ber.*, **14**, 327 (1881). For a modification giving improved yields see J. Dewar and J. Read, *J. Soc. Chem. Ind.*, 347 (1936). This procedure in our hands gave 40–45% yields in the first crop and 10–15% in the second.

ing a mixture of potassium cyanide[6] and anisaldehyde in aqueous ethanol for several hours. The data from a series of runs carried out by a slight modification (see EXPERIMENTAL) of the Bösler procedure are presented in Table I. These data show an increasing yield and quality of anisoin for 4–5 hr., followed by a decrease in both yield and quality (as indicated by melting points).

TABLE I

YIELDS OF ANISOIN USING POTASSIUM CYANIDE AND ETHANOL-WATER

Reflux Time, hours,	Yield, %	M.P. of Product, °C.
2	24	103–110
3	34	106–110
4	41	108–111
5	44	105–110
6	40	103–110
10	23	100–110

As a check on the amount of anisoin which might be decomposed during the heating period, a run was carried out employing an equal weight of anisoin in place of the anisaldehyde. After a 4-hr. reflux period there was recovered only 67% of the anisoin along with a 10% yield of anisaldehyde, a small amount of anisic acid and other by-products which were not identified. This evidence, combined with the data in Table I, suggests that a major factor in the low yield of anisoin from anisaldehyde is probably the destruction of the aldehyde by competing side reactions, since the decomposition of anisoin, though quite appreciable, is not complete enough in a 4-hr. heating period to account for the low yields of anisoin tabulated. However, any effect which reduces the decomposition of the anisoin after it is formed should increase the yield.

It is well known[7] that the benzoin condensation proceeds readily in the absence of water, and is generally believed that the presence of water is necessary for the reversal of this reaction.[8] Though the evidence for this belief is small,[9] there appears to be no evidence or statement to the contrary in the literature. Thus, a series of runs have been carried out under essentially anhydrous conditions (see EXPERIMENTAL) using sodium cyanide as a catalyst and the dimethyl ether of ethylene glycol as a solvent. The data are tabulated in Table II. It is quite obvious that anisoin is decomposed on continued heating in this anhydrous medium, since the yield increases to a maximum and then declines in a manner somewhat parallel to that shown in Table I.[10] Though we cannot state positively that the anisoin reverts to anisaldehyde under the conditions of these experiments, the similarity of these results to those obtained from both anisaldehyde and benzaldehyde in ethanol water, in which it is established that the benzoin reverts to the aldehyde, strongly suggests that the benzoin condensation, at least for anisaldehyde, is reversible in the absence of water.

TABLE II

YIELDS OF ANISOIN USING SODIUM CYANIDE AND ETHYLENE GLYCOL DIMETHYL ETHER

Reflux Time, Min.	Yield, %	M.P. of Product, °C.
30	16	108–111
60	25	109–111
90	35	108–111
120	27	105–110
180	15	90–105
360	None	

EXPERIMENTAL

The starting materials. The anisaldehyde was a commercial material which was freshly distilled before use. The potassium and sodium cyanides were reagent grade materials reported to assay 99.8% and 97.2%, respectively. For the anhydrous experiments the latter was dried overnight at 110°. The loss in weight indicated that the only significant "impurity" was moisture. The ethylene glycol dimethyl ether was a commercial material which was dried over sodium before use.

Procedure for the data in Table I. To a mixture of 11.2 g. of potassium cyanide, 45 ml. of water and 75 ml. of 95% ethanol was added by pipet 50 ml. (56 g.) of anisaldehyde. A series of such runs were heated under reflux for varying times as indicated in Table I. After the heating period the reaction mixtures were cooled with seeding and shaking until crystallization was well under way. Then the mixtures were maintained at 0° overnight before filtering. The yields are tabulated, along with the melting points, which indicate the quality of anisoin obtained (lit.[11] m.p. 113°).

(6) During the current work it was noted that the reaction mixture was homogeneous at the start of the heating period, but soon separated into two phases. It was also noted that when an equivalent amount of sodium cyanide was used in place of the potassium salt all of the material remained in one phase throughout the reflux period and the yield of anisoin was considerably reduced, suggesting that the separation into two phases helps prevent the decomposition of the anisoin formed in the reaction. Similarly, the use of methanol water in the place of ethanol water gave one phase throughout the heating period, and a reduced yield of anisoin even with potassium cyanide.

(7) See ref. 3, p. 274.

(8) See ref. 3, p. 277.

(9) The principal evidence seems to be the report of Lachman (see ref. 4b) that no decomposition of benzoin occurs in the presence of sodium or potassium cyanide in anhydrous pyridine. However, neither of these cyanides is appreciably soluble in pyridine. The results of A. A. Morton and J. R. Stevens, *J. Am. Chem. Soc.*, 52, 2031 (1930) indicate no detectable reversibility during the first few hours when benzaldehyde is subjected to a benzoin condensation with sodium cyanide in anhydrous petroleum ether. However, this aldehyde goes to the benzoin in yields of over 90% (see also refs. 2 and 3), so little effect could be expected from the reverse reaction during the earlier stages.

(10) Also see Table I of Reference 4b for similar behavior with benzaldehyde.

(11) Heilbron, *Dictionary of Organic Compounds*, rev. ed., Oxford University Press, New York, 1953, Vol. I.

The decomposition of anisoin. A mixture of 56 g. of anisoin (m.p. 112–113°), 11.2 g. of potassium cyanide, 75 ml. of 95% ethanol, and 45 ml. of water was heated under reflux for 4 hr. It was then cooled with shaking until crystallization was well under way and then left at 0° overnight. There was recovered 37.5 g. (67%) of material of m.p. 105–111°. The mother liquor was diluted with water and extracted with ether. The ether extract was stirred with saturated sodium bisulfite solution, and from the aqueous phase was recovered 5.8 g. (10%) of anisaldehyde by the addition of sodium carbonate to the bisulfite solution. Removal of the ether from the organic phase left 6.0 g. of viscous red oily material.[12] Acidification of the original aqueous phase yielded 3.5 g. of a solid of m.p. 181–183° which gave no depression when mixed with anisic acid (lit.[11] m.p. 184°). On another similar run which was refluxed for 24 hr., cooling yielded no crystalline anisoin, but a 10% yield of anisaldehyde was recovered.

The "anhydrous" runs. These runs were carried out under conditions similar to those for the Grignard and similar reactions. The glassware was dried overnight at 125° before use. Dry nitrogen was used to eliminate moisture from the atmosphere. To the system, being flushed with nitrogen, was added 2 g. of sodium cyanide (dried at 110°), 25 ml. (28 g.) of anisaldehyde, and 40 ml. of anhydrous ethylene glycol dimethyl ether. The runs were heated under reflux for the times indicated in Table II, then stoppered, and maintained at 0° overnight. The anisoin was filtered and washed first with the cold solvent, and then with water to remove sodium cyanide. The yields and melting points are tabulated in Table II.

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(12) No attempt was made to determine the nature of this material. J. C. Irvine, *J. Chem. Soc.*, 79, 668 (1901) has reported the recovery of a similar by-product of complex nature from the benzoin condensation of *ortho*-methoxybenzaldehyde. For the by-products of the benzoin condensation of benzaldehyde see ref. 3, p. 277.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

Phosphinemethylenes.[1] II. Triphenylphosphineacylmethylenes

FAUSTO RAMIREZ AND SAMUEL DERSHOWITZ[2]

Received Aug. 2, 1956

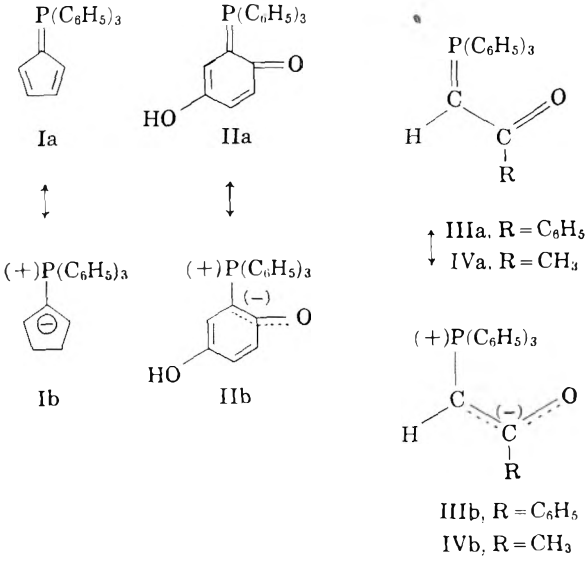
The preparation and some properties of triphenylphosphinebenzoylmethylene (III) and triphenylphosphineacetylmethylene (IV) are reported. Previous formulations of these compounds are rejected.

The properties of the phosphinemethylenes[3] ($R_3P{=}CXY \longleftrightarrow R_3P^+{-}C^-XY$), such as their color, their stability, and their ability to react with aldehydes and ketones,[4] seem to be closely related to the distribution of the negative charge in the molecule.

$$R_3P{=}CXY + H_2O \longrightarrow R_2(YXHC)PO + RH \text{ or } R_3PO + CH_2XY$$

$$R_3P{=}CXY + R'R''CO \longrightarrow R_3PO + R'R''C{=}CXY$$

During an investigation[5] into the structure and properties of the phosphinemethylenes we have examined two types, I and II, which owe their remarkable stability to the incorporation of the negative charge in a nonbenzenoid (I) and a benzenoid (II) aromatic system. The observed dipole moment of triphenylphosphoniumcyclopentadienylide (I)[1] (7.0 *D*) is consistent with its representation as a resonance hybrid to which pentacovalent (Ia) and tetracovalent (Ib) phosphorus structures make roughly equal contributions. I was stable toward concentrated alkali and unreactive toward carbonyl functions. II could be hydrolyzed to triphenylphos-



(1) A convenient way of naming the compounds herein discussed is based on the name "phosphinemethylene" for the parent formulation $H_3P{=}CH_2$ (*cf.* ref. 3 and Collected Formula Index of *Chem. Abs.*). Thus, $(C_6H_5)_3P{=}CH_2$ would be triphenylphosphinemethylene, $(C_6H_5)_3P{=}CH{-}C_6H_5$, triphenylphosphinephenylmethylene, $(C_6H_5)_3P{=}CH{-}CO{-}C_6H_5$, triphenylphosphinebenzoylmethylene. The compounds could be named as derivatives of phosphorane, PH_5 [*cf.* *Chem. Eng. News*, 30, 4515 (1952)]. Thus, $(C_6H_5)_3P{=}CH{-}COC_6H_5$ would be triphenylphenacylidenephosphorane. On this basis, structure Ia ⟷ Ib (for which a rather descriptive name is triphenylphosphoniumcyclopentadienylide) could be named triphenylcyclopentadienylidenephosphorane.

(2) From part of the Ph.D. thesis of S. Dershowitz.

(3) G. M. Kosolapoff, *Organophosphorus Compounds*, John Wiley and Sons, Inc., New York, N. Y., 1950, pp. 28, 355.

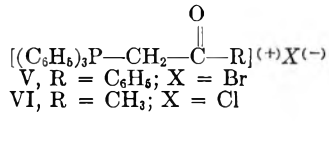
(4) For references see G. Wittig, *Experientia*, 12, 41 (1956); and ref. 5 of this paper.

(5) (*a*) F. Ramirez and S. Levy, *J. Am. Chem. Soc.*, 79, 67 (1957); (*b*) F. Ramirez and S. Dershowitz, *J. Am. Chem. Soc.*, 78, 5614 (1956).

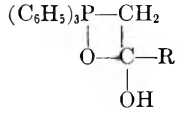
phine oxide and hydroquinone on prolonged heating with dilute alkali.

This paper deals with a closely related system of phosphinemethylenes: the phosphineacylmethylenes,[1] III and IV.

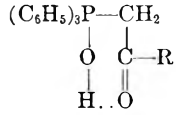
In early investigations, Michaelis and Kohler,[6] studied the action of aqueous alkali on phenacyltriphenylphosphonium bromide (V) and acetonyltriphenylphosphonium chloride (VI). The resulting compounds, m.p. 181° and 200°, respectively, were formulated as cyclic derivatives of pentacovalent phosphorus, VII and VIII, to account for the extra molecule of water apparently disclosed by the elementary analyses. Later, Kröhnke[7] commented on the stability of the benzoyl derivative (VII, in the early formulation) toward alkali. Recently, Wittig and Schöllkopf[8] described the infrared spectra of these so-called "phosphonium betaines" m.p. 181° and 200°. Accepting the empirical formulas deduced by Michaelis,[6] the phosphonium betaines were formulated[8] as IX and X, with pentacovalent phosphorus. The lack of free C—OH and P—OH and the remarkable shift of the carbonyl frequency[8] were taken as evidence for the "chelated" formulas IX and X.



V, R = C_6H_5; X = Br
VI, R = CH_3; X = Cl



VII, R = C_6H_5
VIII, R = CH_3



IX, R = C_6H_5
X, R = CH_3

In our hands, the crystalline substance, m.p. 178–180°, obtained on treatment of phenacyltriphenylphosphonium bromide (V) with alkali was found to have the formula $C_{26}H_{21}OP$; it is therefore regarded as triphenylphosphinebenzoylmethylene (IIIa → IIIb). The substance, m.p. 205–206°, obtained from acetonyltriphenylphosphonium chloride (VI) corresponded to the formula $C_{21}H_{19}OP$ and is regarded as triphenylphosphineacetylmethylene (IVa → IVb). We have confirmed the striking shift of the carbonyl frequency reported by Wittig.[8] The strongest band in the infrared spectrum of the benzoyl derivative III was found at 6.60 μ; the corresponding band for the acetyl derivative, IV, was at 6.54 μ. The low carbonyl frequencies are not unreasonable in the light of the electronic distribution expressed in formulas III and IV.

The ultraviolet absorption spectra of the phosphinemethylenes III and IV are shown in Figs. 1, 2, and 3. The marked bathochromic effect of the benzoyl group is evident. In the hydroxylic solvent some protonation of the phosphinemethylenes is likely; this effect is apparent from a comparison of the curves in ethanol and acetonitrile.

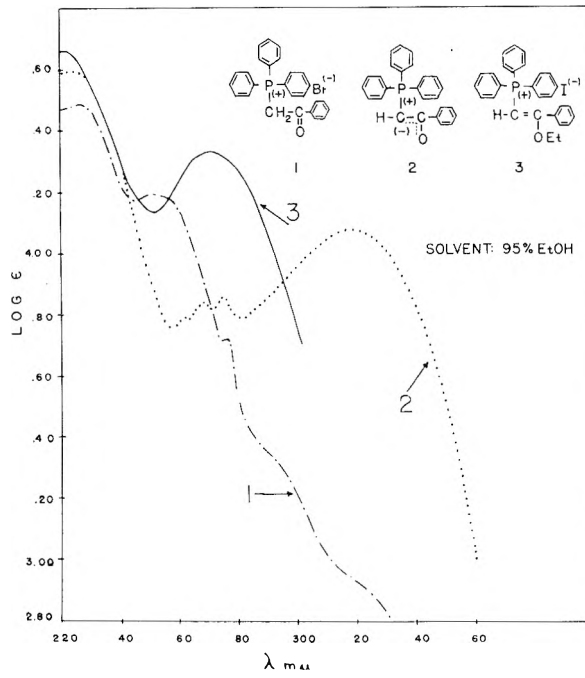


FIG. 1.

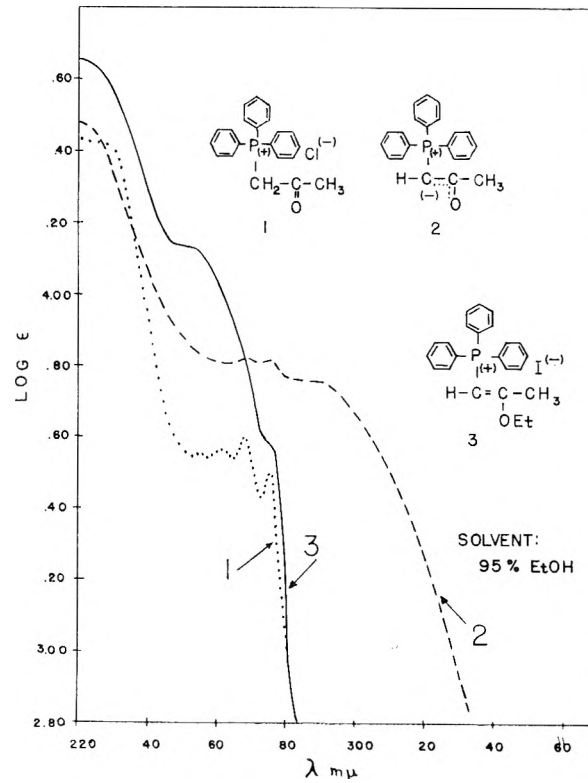


FIG. 2.

(6) A. Michaelis and E. Kohler, *Ber.*, **32**, 1566 (1899).

(7) F. Kröhnke, *Chem. Ber.*, **83**, 291 (1950); *cf.* footnote 4.

(8) G. Wittig and U. Schöllkopf, *Chem. Ber.*, **87**, 1318 (1954). The "phosphonium betaine," m.p. 200°, derived from acetonyltriphenylphosphonium bromide, exhibited a very sharp band at 6.55 μ in the infrared (KBr).

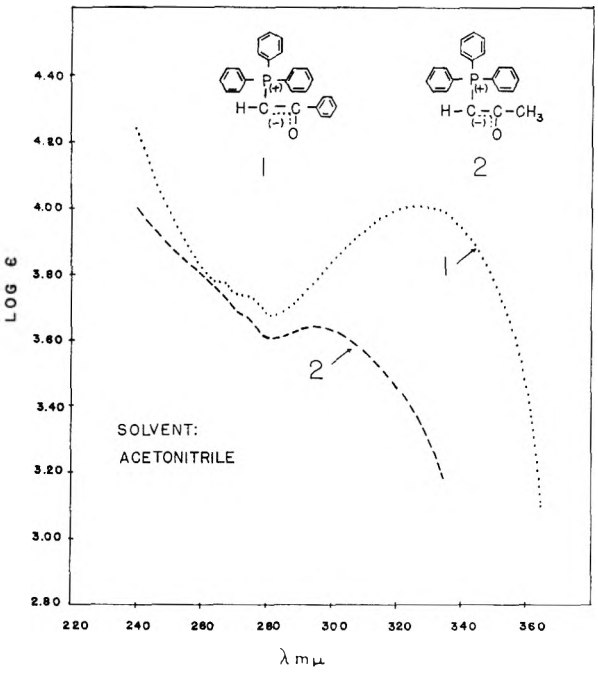
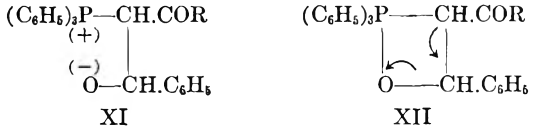


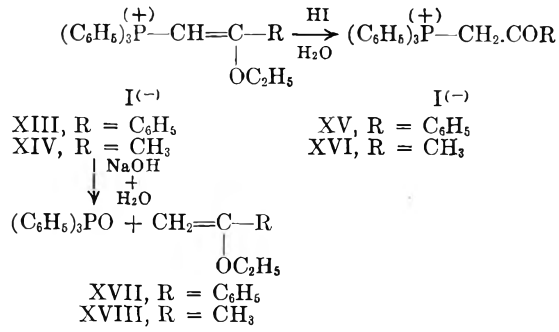
FIG. 3.

Both phosphinemethylenes, III and IV, could be hydrolyzed by prolonged heating in aqueous ethanol with or without added alkali. The intermediate in these hydrolyses may be of type IX and X with pentacovalent phosphorus.[5] Reaction with benzaldehyde was observed in hot tetrahydrofuran. The products—triphenylphosphine oxide and benzalacetophenone (from III) or benzalacetone (from IV)—were isolated in high yields. Wittig[4,8] has interpreted analogous reactions as involving intermediates of type XI and XII.



The behavior of the phosphinemethylenes in alkylation reactions is of interest. With ethyl iodide both III and IV underwent O-alkylation exclusively. The resulting (2-ethoxystyryl)-triphenylphosphonium iodide (XIII) and (2-ethoxypropenyl)-triphenylphosphonium iodide (XIV) (Figs. 1 and 2) were cleaved to the corresponding phenacyltriphenylphosphonium iodide (XV) and acetonyltriphenylphosphonium iodide (XVI) with hydriodic acid. The phosphonium enol ethers XIII and XIV were cleaved to triphenylphosphine oxide and the corresponding enol ethers XVII and XVIII by hot alkali. These alkaline hydrolyses resemble those previously reported[5b] for analogous O-ethers derived from phosphinemethylenes of type II.

The dipole moments of the phosphineacylmethylenes III and IV were found[9] to be 5.45 and 5.54 *D*, respectively.



EXPERIMENTAL[10]

Phenacyltriphenylphosphonium bromide (V). Phenacyl bromide (8.35 g.) was added in portions to a chloroform (75 ml.) solution of triphenylphosphine (10.89 g.). The solution was filtered into one liter of anhydrous ether. The precipitate was collected and dried. Yield: 15 g., m.p. 267–269°. The analytical sample obtained by crystallization from water had m.p. 269–271°; $\lambda_{max.}^{EtOH}$ 253 mμ (ε 15,700), 276 mμ (ε 5200); bands (KBr) at 3.87 (m), 6.08 (strongest), 6.32 (m), 6.80 (m), 7.02 (s), 7.30 (w), 7.60 (m), 7.75 (m), 9.05 (s) and 10.10 (s) μ.

Anal. Calc'd for $C_{26}H_{22}BrOP$: C, 67.7; H, 4.8. Found: C, 67.6; H, 5.1.

The bromide appears to crystallize in a different form, m.p. 279–280°, from methanol–ethyl acetate. This form, when recrystallized from water, melted again at 269–271°. The I.R. spectra of both forms (KBr) are identical.

Alkaline treatment of phenacyltriphenylphosphonium bromide (V). A mixture of phenacyltriphenylphosphonium bromide (V) (1.0 g.), 5% methanolic potassium hydroxide (40 ml.) and some water was heated to reflux for 2 days. The mixture was cooled, diluted with water, and extracted with ether. The residue obtained on removal of the ether was stirred with petroleum ether. The insoluble portion (0.495 g., m.p. 147–152°) was shown to be triphenylphosphine oxide. The petroleum ether solution was evaporated and the residue was dissolved in 95% ethanol (5 ml.) and treated with an aqueous alcoholic solution of 2,4-dinitrophenylhydrazonium sulfate. The precipitate (0.475 g.) was shown to be acetophenone-2,4-dinitrophenylhydrazone (m.p. and mixed m.p. with authentic sample 243–247°).

A mixture of bromide V (7.2 g.) and 5% aqueous sodium hydroxide (80 ml.) also gave triphenylphosphine oxide (4.0 g.) after 42 hr. at reflux temperature.

Triphenylphosphinebenzoylmethylene (III). A mixture of phenacyltriphenylphosphonium bromide (V) (7.5 g.) and 10% aqueous sodium carbonate (300 ml.) was shaken for 15 hr. The mixture was filtered and the insoluble portion was taken up in hot benzene (200 ml.). Some unreacted bromide (0.5 g.) was removed by filtration; addition of petroleum ether to the benzene filtrate afforded 5.8 g. of phosphinemethylene III m.p. 178–180°. For further purification, a benzene solution of the phosphinemethylene III was boiled in order to remove retained water. Concentration and dilution with petroleum ether afforded 4.45 g. of pure III m.p. 178–180°. The analytical sample was dried at 70° (0.1 mm.); $\lambda_{max.}^{EtOH}$ 268 mμ (ε 6900), 274 mμ (ε 7100) and 318 mμ

(9) The dipole moments were measured by Prof. M. T. Rogers, of Michigan State University and will be the subject for a separate communication.

(10) Microanalyses by Micro-Tech Laboratories, Skokie, Ill., and Schwarzkopf Microanalytical Laboratories, Woodside, N. Y.

(ε 11,900); bands (KBr) at 6.32 (m), 6.60 (strongest), 6.80 (m), 7.02 (s) and 9.05 (s) μ.

Anal. Calc'd for $C_{26}H_{21}OP$: C, 82.1; H, 5.6; M.W. 380. Found: C, 82.1; H, 5.7; mol. wt. 369 (isothermal distillation in benzene).

The phosphinemethylene III could be prepared from the bromide V in lower yield (84%) using 5% aqueous sodium hydroxide for 30 min. at steam bath temperature.

When the phosphinemethylene III (0.08 g.) was shaken with 10% aqueous hydrobromic acid, the original bromide V (0.095 g., m.p. 266–269°) was produced.

Phenacyltriphenylphosphonium iodide (XV). A mixture of the phosphinemethylene III (0.50 g.) and 5% aqueous hydriodic acid (35 ml.) was shaken (*ca.* 30 min.) and filtered. The insoluble iodide was stirred with warm benzene (to remove unreacted III) and filtered. The crude iodide (0.60 g.) had m.p. 247–254°. Recrystallization from methanol–ethyl acetate gave the iodide XV m.p. 259–260°; $\lambda_{max.}^{EtOH}$ 222 mμ (ε 44,500), 254 mμ (ε 16,200) and 276 mμ (ε 5900). Bands (KBr) at 3.80 (m-s), 6.08 (strongest), 6.30 (m), 6.80 (m), 7.02 (s), 7.60 (m), 8.35 (s), 9.02 (s), and 10.10 (s) μ.

Anal. Calc'd for $C_{26}H_{22}IOP$: C, 61.4; H, 4.4. Found: C, 61.0; H, 4.7.

The sample m.p. 259–260° melted at 240–242°, when recrystallized from water. The I.R. spectra were identical (KBr).

Hydrolysis of triphenylphosphinebenzoylmethylene (III). A solution of phosphinemethylene (1.0 g.) in 30% aqueous ethanol (80 ml.) was refluxed for 10 hr. The solution was diluted with 40 ml. of water and extracted with ether. Removal of the ether gave a residue, part of which (0.60 g.) was insoluble in petroleum ether and was shown to be triphenylphosphine oxide. The petroleum ether soluble portion afforded acetophenone, identified as its 2,4-dinitrophenylhydrazone (0.62 g.).

Reaction of triphenylphosphinebenzoylmethylene (III) *with benzaldehyde.* A solution of phosphinemethylene III (3.05 g.) and benzaldehyde (0.838 g.) in tetrahydrofuran (100 ml.) was refluxed for 30 hr. The oily residue obtained on removal of the solvent was taken up in 95% ethanol and treated with an aqueous ethanolic solution of 2,4-dinitrophenylhydrazonium sulfate. The crude 2,4-dinitrophenylhydrazone weighed 3.10 g.; after recrystallization from methanol-chloroform it had m.p. 248–250°; if a trace of hydrochloric acid was present during the recrystallization the m.p. was 169–174°. This behavior, as well as the spectra in the U.V. and I.R. identifies the product as benzalacetophenone-2,4-dinitrophenylhydrazone.

The phosphinemethylene III failed to react with cyclohexanone under similar conditions.

(2-Ethoxystyryl)-triphenylphosphonium iodide (XIII). A mixture of triphenylphosphinebenzoylmethylene (III) (0.70 g.) and freshly distilled ethyl iodide was refluxed for 7 hr. The crystalline substance which separated (0.92 g., m.p. 170–184°) was collected and was then shaken with 10% aqueous potassium carbonate (100 ml.) for some time. The insoluble material was collected and treated with 30 ml. benzene. The insoluble iodide XIII (0.85 g.) had m.p. 175–177°. The analytical sample had m.p. 176–178° (from chloroform-benzene-petroleum ether); $\lambda_{max.}^{EtOH}$ 222 mμ (ε 45,400) and 270 mμ (ε 21,200). Bands (KBr) at 6.25 (m), 6.40 (strongest), 8.80 (w), 7.02 (s), 7.65 (s), 9.05 (s) and 9.20 (s) μ.

Anal. Calc'd for $C_{28}H_{26}IOP$: C, 62.7; H, 4.9. Found: C, 63.1; H, 5.0.

When the phosphinemethylene III was alkylated with ethyl iodide in anhydrous methanol solution, a mixture of phenacyltriphenylphosphonium iodide (XV) and (2-ethoxystyryl)-triphenylphosphonium iodide (XIII) was obtained. This can be explained as follows:

$$(C_6H_5)_3\overset{(+)}{P}.CH.CO.C_6H_5\overset{(-)}{} + CH_3OH \rightleftharpoons (C_6H_5)_3\overset{(+)}{P}.CH_2CO.C_6H_5 + CH_3O^{(-)}$$

$$CH_3\overset{(-)}{O} + C_2H_5I \longrightarrow CH_3OC_2H_5 + I^{(-)}$$

No C-alkylation was observed.

Treatment of (2-ethoxystyryl)-triphenylphosphonium iodide (XIII) *with acid.* A mixture of (2-ethoxystyryl)-triphenylphosphonium iodide (XIII) (0.50 g.) and 5% aqueous hydriodic acid (30 ml.) was refluxed for 15 hr. The mixture was cooled and filtered and the collected solid (0.45 g., m.p. 210–235°) was divided into two portions: (*a*) one portion (0.25 g.) was recrystallized and was shown to be phenacyltriphenylphosphonium iodide (XV) by comparison with an authentic sample. (*b*) The second portion (0.20) was shaken (several hours) with 10% aqueous sodium carbonate (25 ml.) affording a solid from which 0.08 g. of triphenylphosphinebenzoylmethylene (III) was obtained on recrystallization (benzene-petroleum ether).

Treatment of (2-ethoxystyryl)-triphenylphosphonium iodide (XIII) *with alkali.* A mixture of iodide XIII (4.8 g.) and 5% methanolic potassium hydroxide containing *ca.* 5% of water was refluxed for 15 hr. Water was added (30 ml.) and the mixture was extracted with ether. The residue obtained by distillation of the ether was stirred with petroleum ether, yielding 2.1 g. of insoluble triphenylphosphine oxide. The oil obtained after removal of the petroleum ether was distilled (bath temperature 95°/15 mm.) giving α-ethoxystyrene (XVII) as a colorless oil. This material had n_D^{20} 1.5312 and decolorized, instantaneously, a chloroform solution of bromine. Its infrared spectrum (in chloroform) had no carbonyl absorption. When the material was treated with an aqueous methanolic solution of 2,4-dinitrophenylhydrazonium sulfate, containing excess sulfuric acid, no immediate precipitate was observed. After several minutes on the steam bath, acetophenone-2,4-dinitrophenylhydrazone was formed.

Acetonyltriphenylphosphonium chloride (VI). A solution of triphenylphosphine (10.0 g.) and chloroacetone (3.25 g.) in chloroform (*ca.* 30 ml.) was refluxed for 45 min. The solution was filtered into anhydrous ether (300 ml.) and the solid collected. Yield: 11.2 g., m.p. 234–237°. Analytical sample: m.p. 237–238° (from chloroform-benzene-petroleum ether); $\lambda_{max.}^{EtOH}$ 255 mμ (ε 3600), 262 mμ (ε 3700), 268 mμ (ε 4000) and 275 mμ (ε 3100); bands (KBr) at 3.68 (m), 5.92 (strongest), 6.32 (m), 6.80 (m), 7.02 (s), 7.40 (s), 8.70 (s), 9.05 (s), and 10.05 (s) μ.

Anal. Calc'd for $C_{21}H_{20}ClOP$: C, 71.1; H, 5.7. Found: C, 70.9; H, 5.9.

Triphenylphosphineacetylmethylene (IV). A mixture of acetonyltriphenylphosphonium chloride (VI) (1.3 g.) and 10% aqueous sodium carbonate was shaken for 8 hr. The solid was collected and dried; yield, 1.07 g., m.p. 199–202°. The analytical sample of IV had m.p. 205–206° (from methanol-water) and was dried at 70°/0.1 mm.; $\lambda_{max.}^{EtOH}$ 268 mμ (ε 6600), 275 mμ (ε 6500) and 288 mμ (ε 5700); bands (KBr) at 6.54 (strongest), 6.80 (m), 7.02 (s), 7.28 (m), 9.05 (s) and 10.22 (s) μ.

Anal. Calc'd for $C_{21}H_{19}OP$: C, 79.3; H, 6.0; mol. wt. 318. Found: C, 79.0; H, 5.9; mol. wt. 329 (isothermal distillation in benzene).

The phosphinemethylene IV precipitated (in 75% yield) upon addition of 5% aqueous sodium hydroxide to an aqueous solution of chloride VI.

Treatment of the phosphinemethylene IV (0.35 g.) in methanol solution (25 ml.) with a few drops of concentrated hydrochloric acid regenerated the phosphonium chloride VI (0.36 g.; m.p. 233–236°), obtained by concentration of the methanol solution and dilution with ethyl acetate.

Acetonyltriphenylphosphonium iodide (XVI). Shaking triphenylphosphineacetylmethylene (IV) (0.30 g.) and 5% aqueous hydriodic acid (25 ml.) for 30 min. at room temperature gave the iodide (0.35 g., m.p. 202–205°). Analytical sample: m.p. 207–209° (from water); $\lambda_{max.}^{EtOH}$ 262 mμ (ε 4000), 268 mμ (ε 4000) and 276 mμ (ε 3100).

Anal. Calc'd for $C_{21}H_{10}IOP$: C, 56.5; H, 4.5. Found: C, 56.7; H, 4.7.

Hydrolysis of triphenylphosphineacetylmethylene (IV). The phosphine methylene IV (1.1 g.) in 40 ml. of water was heated to reflux for 12 hr. The resulting white solid (0.925 g.) was shown to be triphenylphosphine oxide.

Reaction of triphenylphosphineacetylmethylene (IV) *with benzaldehyde.* A solution of the phosphinemethylene IV (1.1 g.) and benzaldehyde (0.367 g.) in tetrahydrofuran was refluxed for 48 hr. The solvent was removed, the residue was dissolved in 95% ethanol and the solution was treated with an aqueous methanolic solution of 2,4-dinitrophenylhydrazinium sulfate. The precipitate was recrystallized (m.p. 218–221°) and was identified as benzalacetone-2,4-dinitrophenylhydrazone.

The phosphinemethylene IV failed to react with cyclohexanone under similar conditions.

(2-Ethoxypropenyl)-triphenylphosphonium iodide (XIV). A mixture of phosphinemethylene IV (1.0 g.) and freshly distilled ethyl iodide (20 ml.) was refluxed for 7 hr. The solid which precipitated (0.40 g.) had m.p. 163–165° and was recrystallized from methanol–ethyl acetate without change in m.p.: $\lambda_{max.}^{EtOH}$ 220 mμ (ε 44,900), 252 mμ (ε 13,700) and shoulder at 275 mμ (ε 3800). Bands (KBr) at 6.30 (w), 7.02 (m), 7.48 (m) and 9.00 (s).

Anal. Calc'd for $C_{23}H_{24}IOP$: C, 58.2; H, 5.1. Found: C, 58.4; H, 5.2.

Hydrolysis of (2-ethoxypropenyl)-triphenylphosphonium iodide (XIV) *with acid.* The iodide XIV (0.65 g.) and 5% aqueous hydriodic acid (20 ml.) were heated to reflux for 15 hr. The solid formed was collected and had m.p. 206–208° (0.56 g.). It was shown to be acetonyltriphenylphosphonium iodide (XVI) by mixed m.p. and comparison of I.R. spectra.

Hydrolysis of (2-ethoxypropenyl)-triphenylphosphonium iodide (XIV) *with alkali.* A mixture of iodide (7.9 g.) and 5% aqueous methanolic potassium hydroxide was refluxed for 15 hr. Water was added and the precipitated solid was collected; it weighed 4.05 g. (m.p. 146–150°) and was shown to be triphenylphosphine oxide. The filtrate was extracted with ether. Fractionation of the ether solution gave isopropenyl ethyl ether, which (1) decolorized bromine-in-chloroform instantaneously and (2) gave no precipitate with an aqueous-methanolic solution of 2,4-dinitrophenylhydrazinium sulfate. After the solution was warmed and allowed to stand overnight, acetone-2,4-dinitrophenylhydrazone (0.48 g., m.p. 119–124°) was precipitated. Comparison with an authentic sample confirmed the identity.

Ultraviolet absorption spectra. The spectra of the phosphinemethylenes III and IV show variations in hydroxylic and aprotic solvents (*cf.* Figs. 1, 2, and 3). The molecular extinction coefficients (ε) at λ max. in 95% ethanol are recorded above. The corresponding values in dry acetonitrile are, for III: 267 mμ (ε 6000), 275 mμ (ε 5500) and 328 mμ (ε 10,200); for IV: 275 mμ (ε 4700) and 295 mμ (ε 4400).

Acknowledgment. The financial assistance of an Eli Lilly research grant is gratefully acknowledged.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

Some Monomeric Organosilicon Compounds of High Thermal Stability

HENRY GILMAN AND JACK J. GOODMAN

Received Aug. 2, 1956

A number of monomeric organosilicon compounds possessing high thermal stability was synthesized. Some organic groups found to impart this property were the *p*-phenoxyphenyl, *m*-tolyl, *m*-trifluoromethylphenyl, and *p*-trimethylsilylphenyl. The molecules containing the 9-fluorenyl group were not promising in this respect. Compounds studied were of the types $(C_6H_5)_3SiR$, $(C_6H_5)_2SiR_2$, $C_6H_5SiR_3$, $C_{12}H_{25}SiR_3$, $HSiR_3$, and SiR_4.

Incidental to studies concerned with the thermal stability of monomeric organosilicon compounds,[1] an examination has been made of the synthesis of a series of R_4Si, $R_3R'Si$, and $R_2R_2'Si$ compounds. In these syntheses both Grignard reagents and organolithium compounds were used. The organolithium compounds were prepared by direct reaction with lithium metal, by halogen-metal interconversion reactions using *n*-butyllithium, and by the direct replacement of hydrogen in a metalation reaction.

Preliminary or orienting screening for thermal stabilities indicates that the following groups tend to increase thermal stability: *p*-phenoxyphenyl, *m*-tolyl, *m*-trifluoromethylphenyl, and *p*-trimethylsilylphenyl.

EXPERIMENTAL

Diphenyl-bis-(p-phenoxyphenyl)-silane. To 105 ml. of an ethereal solution containing 0.090 mole of *n*-butyllithium[2] was slowly added 75 ml. of an ethereal solution containing 22.4 g. (0.090 mole) of *p*-bromophenyl phenyl ether.[3] The temperature of the reaction was maintained at −15°. Color Test II[4] was negative after 2 hr. Then there was slowly added 50 ml. of an ethereal solution containing 9.60 g. (0.038 mole) of diphenyldichlorosilane. The reaction mixture was allowed to come to room temperature and stirred overnight. Color Test I[5] was negative at that time and a white solid was suspended in the reaction mixture. Hydrolysis with 200 ml. of water resulted in two clear liquid layers. The ether layer was separated and a solid began to precipitate from it. There was filtered 8.4 g. of a white solid melting

(1) Burkhard, Rochow, Booth, and Hart, *Chem. Revs.*, 41, 97 (1947); Post, *Silicones and Other Organosilicon Compounds*, Reinhold Publishing Corp., New York, N. Y., 1949; Rochow, *An Introduction to the Chemistry of the Silicones*, 2nd ed., John Wiley & Sons, New York, N. Y., 1951; Gilman and Dunn, *Chem. Revs.*, **52**, 77 (1953).

(2) Gilman, Beel, Brannen, Bullock, Dunn, and Miller, *J. Am. Chem. Soc.*, **71**, 1499 (1949).

(3) Gilman, Langham, and Moore, *J. Am. Chem. Soc.*, 62, 3277 (1940).

(4) Gilman and Swiss, *J. Am. Chem. Soc.*, **62**, 1847 (1940).

(5) Gilman and Schulze, *J. Am. Chem. Soc.*, **47**, 2002 (1925).

over the range 156–159°.[6] The ether layer was dried over anhydrous sodium sulfate and distilled. There was recovered 4.5 g. of *p*-bromophenyl phenyl ether. In addition, the residue contained 1.1 g. of a white solid melting over the range 154–158°. The combined product was recrystallized from a mixture of dioxane and ethanol. There was obtained 7.20 g. (36.8%) of the desired product melting at 162–163°.

Anal.[7] Calc'd for $C_{36}H_{28}O_2Si$: Si, 5.39. Found: Si, 5.34, 5.40.

This procedure outlines the general method used in the work-up of the following reaction mixtures.

Phenyl-tris-(p-phenoxyphenyl)-silane. In analogous fashion there was added 22.4 g. (0.090 mole) of *p*-bromophenyl phenyl ether to 0.0895 mole of *n*-butyllithium. Following this addition, 5.30 g. (0.025 mole) of phenyltrichlorosilane was slowly added. Hydrolysis of the resulting mixture gave 10.1 g. of a white solid melting at 160–169°. Distillation of the dried ether fraction afforded 3.3 g. of a solid melting at 155–160°. Recrystallization of the combined solids from a mixture of dioxane and ethanol yielded 10.2 g. (67.1%) of the desired compound melting at 149–150°.

Anal. Calc'd for $C_{42}H_{32}O_3Si$: Si, 4.57. Found: Si, 4.51, 4.61.

Tetrakis-(p-phenoxyphenyl)-silane. In like manner, to 115 ml. of an ethereal solution containing 0.09 mole of *n*-butyllithium was added 23.7 g. (0.095 mole) of *p*-bromophenyl phenyl ether. There was then added 3.4 g. (0.020 mole) of silicon tetrachloride. Hydrolysis caused the suspension of a white solid between the two layers. This material weighed 10.7 g. and melted at 200–204°. No solid was isolated from the ether fraction. The 10.7 g. was recrystallized from ethyl acetate and there was finally obtained 8.21 g. (58.3%) of the desired product melting at 204°.

Anal. Calc'd for $C_{48}H_{36}O_4Si$: Si, 3.99. Found: Si, 3.95, 3.90.

The compounds, in order of the foregoing listing of preparations, had the following volatilization temperatures at atmospheric pressure: 505–510°, 530–533°, and 550–560°.[8] With the exception of the tetrakis-substituted molecule, b.p. 550–560° which was deep amber, all were pale amber at their boiling points. The melting point of phenyl-tris-(*p*-phenoxyphenyl)-silane was found unchanged when taken on a cooled sample previously tested for thermal stability.

Tris-(p-phenoxyphenyl)-n-dodecylsilane. Following the same procedure, there was added 47.5 g. (0.190 mole) of *p*-bromophenyl phenyl ether to an ethereal solution containing 0.187 mole of *n*-butyllithium. After 2 hr., 17.6 g. (0.057 mole) of *n*-dodecyltrichlorosilane was added. A white precipitate slowly formed during 18 hr. of reflux. Hydrolysis caused the solid to dissolve, and a highly viscous oil was isolated from the ether fraction. This material distilled at 315–320°/0.004 mm. in a Hickman molecular still. The total weight of the pale yellow liquid was 10.3 g. (25.2%).

Anal. Calc'd for $C_{48}H_{32}O_3Si$: Si, 3.99. Found: Si, 4.03, 4.09.

The compound volatilized at 423–425° without any color change.

Diphenyl-bis-(9-fluorenyl)-silane. To 250 ml. of an ethereal solution containing 21.2 g. (0.127 mole) of fluorene[9] were slowly added 150 ml. of an ethereal solution containing 0.127 mole of phenyllithium.[10] The solution became yellow, then orange during the addition. Then 75 ml. of an ethereal solution containing 12.7 g. (0.050 mole) of diphenyldichlorosilane was slowly added. The reaction mixture became a mustard color during this addition. Color Test I was negative after refluxing overnight.

The reaction mixture was hydrolyzed with 250 ml. of water. The ether layer was separated, dried, and distilled. The residual solid was recrystallized from a mixture of dioxane and ethanol, and 2.4 g. of a white solid melting over the range 225–240° was isolated. Several recrystallizations did not narrow the melting point range. Concentration of the original recrystallizing solvent gave 2.7 g. (10.6%) of the pure product melting at 270°.

Anal. Calc'd for $C_{38}H_{28}Si$: Si, 5.47. Found: Si, 5.55, 5.50.

Phenyl-tris-(9-fluorenyl)-silane. In similar fashion, there was added an ethereal solution containing 0.075 mole of phenyllithium to 12.3 g. (0.075 mole) of fluorene. After 4 hr. of reflux, there was slowly added an ethereal solution containing 4.88 g. (0.023 mole) of phenyltrichlorosilane. Hydrolysis of the reaction mixture resulted in the suspension of a white solid between the water and ether layers. This material was filtered and air-dried. It weighed 10.0 g. and had an m.p. of 290–318°. Recrystallization from a mixture of ethyl acetate and ethanol afforded 6.6 g. (46.6%) of the desired compound melting at 333–334°.

The ether layer gave only 2.1 g. of a solid having the odor and melting range of fluorene.

Anal. Calc'd for $C_{45}H_{32}Si$: Si, 4.66. Found: Si, 4.62, 4.50.

Two attempts were made to prepare tetrakis-(9-fluorenyl)-silane. In both cases there were isolated dark brown glass-like solids which have not been further purified. The failure to synthesize the compound may be due in part to steric factors.

Both compounds prepared were wine-red by 330–335°. The remaining material vaporized with considerable decomposition at 455–465° and 410–420° for the bis- and tris-9-fluorenyl molecules, respectively.

Diphenyl-bis(m-trifluoromethylphenyl)-silane. To a solution of 0.087 mole of *n*-butyllithium in 112 ml. of ether at −15° was slowly added an ethereal solution of 19.5 g. of *m*-trifluoromethylbromobenzene in 50 ml. of ether.[11] The solution turned brown during the addition. Color Test II was negative after 2 hr. There was then added 50 ml. of an ethereal solution containing 8.85 g. (0.035 mole) of diphenyldichlorosilane. The temperature was allowed to rise slowly, and then heat was applied to bring the solution to reflux. After 24 hr., Color Test I was doubtful. Hydrolysis with 150 ml. of water resulted in a brown, ether layer and colorless, aqueous layer. The ether fraction was separated, dried, and distilled. There remained an oil which became a semisolid on cooling in an ice bath. Stirring with methanol gave a white solid melting over the range 93–96°. Recrystallization from the same solvent yielded 9.1 g. (56%) of the pure product melting at 97–98°.

Anal. Calc'd for $C_{26}H_{18}F_6Si$: C, 66.0; H, 3.82. Found: C, 65.60, 65.55; H, 3.86, 3.92.

Phenyl-tris-(m-trifluoromethylphenyl)-silane. Similarly, to an ethereal solution containing 0.094 mole of *n*-butyllithium was added 21.2 g. (0.094 mole) of *m*-trifluoromethylbromobenzene. This was followed by an ethereal solution of 5.71 g. (0.027 mole) of phenyltrichlorosilane. The mixture was hydrolyzed and the organic fraction separated and dried. On distillation of the solvent there was obtained an oily residue, which crystallized on standing overnight. This material, recrystallized from methanol, weighed 6.3 g. (43.4%) and melted at 81°.

Anal. Calc'd for $C_{27}H_{17}F_9Si$: C, 60.0; H, 3.15. Found: C, 60.09, 60.24; H, 3.23, 3.20.

Tetrakis-(m-trifluoromethylphenyl)-silane. In analogous manner there was added to 0.190 mole of *n*-butyllithium, an ethereal solution containing 42.7 g. (0.190 mole) of *m*-trifluoromethylbromobenzene. An ethereal solution containing 7.48 g. (0.044 mole) of silicon tetrachloride was then

(6) All melting points are uncorrected. All reactions were carried out under dry oxygen-free nitrogen.

(7) Gilman, Hofferth, Melvin and Dunn, *J. Am. Chem. Soc.*, 72, 5767 (1950).

(8) The volatilization temperatures were determined in accordance with the procedure of Gilman and Oita, *J. Org. Chem.*, 20, 862 (1955).

(9) Ziegler and Wenz, *Ber.*, 83, 354 (1950).

(10) Jones and Gilman, *Org. Reactions*, 6, 354 (1951).

(11) Gilman and Woods, *J. Am. Chem. Soc.*, 66, 198 (1944); Gilman, Brook and Miller, *J. Am. Chem. Soc.*, 75, 3757 (1953).

added. A gelatinous solid was formed during the hydrolysis of the reaction mixture. The organic layer was separated, dried, and distilled. The residual "wet" solid was washed with methanol and recrystallized from petroleum ether (b.p. 60–70°). There was finally isolated 11.1 g. (41.7%) of tetrakis-(*m*-trifluoromethylphenyl)-silane melting at 102–103°.

Anal. Calc'd for $C_{28}H_{16}F_{12}Si$: C, 55.4; H, 2.63. Found: C, 55.47, 55.43; H, 2.67, 2.66.

The volatilization temperatures of the fluorine-containing compounds, in order of increasing molecular weight, are 375–380°, 370–374°, and 362°. All become pale amber at or near the boiling points. The melting point of diphenyl-bis-(*m*-trifluoromethylphenyl)-silane was found unchanged when taken on a cooled sample previously tested for thermal stability.

Triphenyl-m-tolylsilane. To 0.052 mole of *m*-tolyllithium[12] in 75 ml. of ether was slowly added 100 ml. of an ethereal solution containing 13.5 g. (0.046 mole) of triphenylchlorosilane. The mixture became a rust color on completion of the addition. The temperature of the solution was raised to reflux and maintained there for 6 hr. Color Test I was then negative. Hydrolysis with 150 ml. of water turned the ether solvent a pale amber color. The organic layer was separated, dried and distilled. There remained 14.8 g. of a white solid melting over the range 143–148°. After recrystallization from petroleum ether (b.p. 60–70°), 12.3 g. (77%) of the desired product melting at 150–151° was obtained.

Anal. Calc'd for $C_{25}H_{22}Si$: Si, 8.00. Found: Si, 8.02, 8.08.

Diphenyl-bis-(m-tolyl)-silane. Following the same procedure, 8.85 g. (0.035 mole) of diphenyldichlorosilane was added to 0.075 mole of *m*-tolyllithium. After 6 hr. reflux, the reaction mixture was hydrolyzed. The ether layer was separated, dried, and distilled. The residual white solid weighed 11.6 g. and melted over the range 112–116°. Several recrystallizations from a mixture of ethanol and benzene yielded 9.7 g. (76.5%) of the pure product melting at 119–120°.

Anal. Calc'd for $C_{26}H_{24}Si$: Si, 7.69. Found: Si, 7.71, 7.74.

Phenyl-tris-(m-tolyl)-silane. This compound, m.p. 128–129°, was prepared in 76% yield (8.6 g.) by the reaction between 0.096 mole of *m*-tolylithium and 6.38 g. (0.030 mole) of phenyltrichlorosilane by the described procedure.

Anal. Calc'd for $C_{27}H_{26}Si$: Si, 7.40. Found: Si, 7.41, 7.48.

Tetrakis-(m-tolyl)-silane. Following the above procedure, 5.45 g. (0.035 mole) of silicon tetrachloride and 0.154 mole of *m*-tolyllithium gave 8.9 g. (65%) of tetrakis-(*m*-tolyl)-silane melting at 155–156°.

Anal. Calc'd for $C_{28}H_{28}Si$: Si, 7.15. Found: Si, 7.24, 7.19.

The compounds, in order of increasing number of *m*-tolyl groups, had volatilization temperatures of 430°, 435°, 420–425°, and 435–438°. All members of this series turned deep amber before vaporization.

Tris-(m-trifluoromethylphenyl)-silane. Thirty drops of an ethereal solution of 56.4 g. (0.250 mole) of *m*-trifluoromethylbromobenzene were added to a suspension of 6.1 g. (0.25 g. atom) of magnesium turnings and a small crystal of iodine. The solution became turbid after several minutes and the remaining 100 ml. were added at a rate sufficient to maintain gentle reflux. After 2 hr. of stirring, a simple acid titration gave an 81% yield. The Grignard reagent was cooled to 0° and 50 ml. of an ethereal solution containing 8.10 g. (0.060 mole) of trichlorosilane[13] was slowly added. Then the temperature was allowed to rise slowly and heat applied to bring the reaction mixture to reflux. Color Test I was negative at that time. Hydrolysis with 100 ml. of 3 *N* hydrochloric acid resulted in two colorless layers. The ether fraction was separated, dried, and distilled. A deep brown viscous oil remained. Vacuum distillation first gave 4.3 g. of colorless liquid (b.p. 32–50°/0.45 mm.) followed by 25.4 g. (92.2%) of product boiling at 147–150°/0.05 mm., n_D^{20} 1.4948, d_{20}^{20} 1.3500. The product on treatment with aqueous alcoholic potassium hydroxide[14] evolved a gas (H_2) indicating the presence of the silicon–hydrogen bond.

Anal. Calc'd for $C_{21}H_{13}F_4Si$: C, 54.4; H, 2.81; MR_D,[15] 101.48. Found: C, 54.12, 54.25; H, 2.88, 2.91; MR_D, 101.3.

Tris-(p-trimethylsilylphenyl)-silane. Employing the same technique, *p*-trimethylsilylphenylmagnesium bromide was prepared in 93.5% yield by the reaction between 18.7 g. (0.770 g. atom) of magnesium turnings, a small crystal of iodine, and 171 g. (0.750 mole) of trimethyl-*p*-bromophenylsilane.[16] There was then added an ethereal solution containing 27.0 g. (0.20 mole) trichlorosilane. A large quantity of gelatinous solid remained after hydrolysis. This material was filtered and air-dried. The product (54.6 g.) melted over the range 154–158°. From the ether layer there was isolated 10.2 g. melting over the range 156–159°. Recrystallization of the combined solids from a mixture of ethanol and ethyl acetate gave 61.3 g. (64.8%) of the desired compound, m.p. 159–160°.

Anal.[17] Calc'd for $C_{27}H_{40}Si_4$: Si, 23.5. Found: Si, 24.1, 23.8.

This compound volatilized at 452–456° with very little discoloration. The analogous *m*-trifluoromethylphenyl compound boiled at 322–325° with no signs of decomposition.

Attempts to react both tris-(*m*-trifluoromethylphenyl)- and tris-(*p*-trimethylsilylphenyl)-silane with various organolithium compounds, such as *p*-phenoxyphenyllithium, 2-biphenylyllithium, and *m*-tolyllithium were unsuccessful. The lack of reactivity may be due in part to steric factors.

Tris-(p-trimethylsilylphenyl)-n-dodecylsilane. *n*-Dodecyllithium was prepared in 85% yield by the reaction between 0.38 g. (0.055 g. atom) of lithium wire and 6.25 g. (0.025 mole) of *n*-dodecyl bromide in 75 ml. of ether according to the procedure described for the preparation of *n*-butyllithium.

To the organometallic reagent, at 0°, was slowly added 75 ml. of a benzene solution containing 11.4 g. (0.024 mole) of tris-(*p*-trimethylsilylphenyl)-silane. The reaction mixture was heated to the reflux temperature and maintained there for 24 hr. Color Test I was negative at that time. Hydrolysis with 150 ml. of water caused the evolution of a gas. The resultant ether fraction was separated, dried, and distilled. There remained a light brown oil. This material became a "wet" solid on cooling in an ice bath. By fractional crystallization from a mixture of ethanol and ethyl acetate 6.1 g. (53.5%) of starting silane and 5.2 g. of a highly viscous oil were separated. The latter product finally crystallized to a "wet" solid melting over the range 68–75°.

All attempts to recrystallize the product resulted in an oil which has not solidified.

Anal. Calc'd for $C_{39}H_{64}Si_4$: Si, 17.4. Found: Si, 16.7, 16.9.

The pale yellow solid volatilized at 390–392° without further color change.

Acknowledgments. The authors wish to express their appreciation to the Materials Laboratory, Wright Air Development Center, Wright-Patterson Air Force Base, Ohio, for financial assistance. Infrared spectra were obtained through the courtesy of Dr. V. A. Fassel, R. D. Kross, and R. McCord of the Institute for Atomic Research.

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(12) Unpublished studies of Dr. K. Oita. The compound was prepared by the reaction between *m*-chlorotoluene and lithium wire in anhydrous ethyl ether.

(13) Benkeser and Riel, *J. Am. Chem. Soc.*, **73**, 3472 (1951).

(14) Gilman and Dunn, *J. Am. Chem. Soc.*, **73**, 3404 (1951).

(15) Vogel, Cresswell and Leicester, *J. Phys. Chem.*, **58**, 174 (1954).

(16) Gilman and Melvin, *J. Am. Chem. Soc.*, **72**, 995 (1950).

(17) Tseng and Chao, *Science Repts. Natl. Univ. Peking*, 1, No. 4, 21 (1936); *Chem. Abstr.*, **31**, 655 (1937).

[CONTRIBUTION FROM THE HOUDRY PROCESS CORPORATION]

Catalytic Side-Chain Alkylation of Aromatic Compounds

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Received Aug. 6, 1956

The side-chain ethylation of toluene and cumene occurs readily in the presence of organo-alkali metal catalysts about 200°. The ethylation of benzene requires more severe conditions. Alkali metal hydrides are active catalysts for the ethylation of toluene and polymerization of ethylene at 300°. The alkaline earth metal hydrides are inactive at this temperature. Several other hydrides have also been tested. Aniline reacts with ethylene at 200° to form *N*-ethyl aniline. At higher temperatures higher amines are formed. Propylene reacts with toluene to a much lesser extent than ethylene. Butenes did not react under the conditions used in this study.

Numerous studies of ring alkylation of aromatic compounds in the presence of acid catalysts have been made. Such catalysts do not cause side-chain alkylation. Several recent studies have demonstrated that side-chain alkylation takes place in the presence of alkali metals and organo-alkali compounds. Whitman[1] has shown that toluene reacts with ethylene at 225° in the presence of sodium to form *n*-propylbenzene and 3-phenylpentane. The reaction is probably initiated by the formation of benzyl sodium formed by the metalation of toluene. Little[2] and Pines and coworkers[3,4,5] have shown that this type of reaction takes place more readily in the presence of organo-alkali metal compounds. Pines and coworkers[6] have also shown that organo-alkali metal compounds are catalysts for double bond isomerization.

Whitman[7] has alkylated amines with olefins in the presence of alkali metals or alkali metal hydrides. Closson and coworkers have also alkylated amines as well as other types of compounds.[8]

A mechanism for side-chain alkylation has been given by Pines and coworkers.[4] A more detailed study of the mechanism has recently been made by Hart.[9]

The work reported in this paper is concerned with the use of organo-metallic compounds, hydride catalysts, and other catalysts for the ethylation of aromatic compounds. Alkylations with propylene and butenes have also been investigated.

EXPERIMENTAL

A rocking autoclave with a capacity of 200 cc. was used to carry out most of the reactions in this work. In the experiments employing organo-alkali metal catalysts, 2.0 g. of the alkali metal and 0.8 g. anthracene were used. In the experiment with chlorobenzene, 1.0 g. of this compound was used. Four g. of catalyst were used in all the experiments with the alkali metal hydrides, alkaline earth metal hydrides, and the various commercial catalysts tested.

Most of the organic chemicals used in this work were purified by distillation or recrystallization. The hydrides were supplied by Metal Hydrides, Inc.

The gaseous products were analyzed by mass spectrometry. In most instances the liquid products were decanted or filtered off and the residue washed with pentane. The pentane washings were combined with the liquid products and the mixture was distilled and analyzed by infrared spectroscopy.

In most experiments no attempt was made to analyze the solid residues. These materials were often unstable in air when dry. The autoclave was generally emptied under a blanket of nitrogen and the solid residues were promptly disposed of.

RESULTS AND DISCUSSION

Ethylation of alkyl-aromatic compounds with organo-alkali metal catalysts. Initial work in this study was concerned with the alkylation of toluene and cumene with ethylene in the presence of organo-alkali metal compounds. High yields of *n*-propylbenzene and 3-phenylpentane are obtained in the ethylation of toluene with sodium anthracene catalysts at 200°. The yield of alkylated products increases as the ethylene concentration increases. Lithium anthracene is less active for the ethylation of toluene than sodium anthracene. This is an agreement with the activities of other lithium and sodium organo-compounds used as catalysts in other types of reactions.

Sodium reacts at room temperature with chlorobenzene in toluene to form sodium phenyl, which in turn metalates toluene to give sodium benzyl at higher temperatures.[10,11] Sodium chlorobenzene is not so effective as sodium anthracene for the ethylation of toluene, but reasonable yields of ethylated products were obtained with this catalyst.

Cumene is also ethylated in the presence of sodium anthracene to give *t*-amylbenzene. These results with toluene and cumene are comparable to those obtained by Pines, Vesely, and Ipatieff.[4]

Small amounts of ethane and other hydrocarbons (C_3—C_4) and traces of hydrogen and methane are formed in these

(1) Whitman, U. S. Patent 2,448,461 (Sept. 7, 1948).
(2) Little, Jr., U. S. Patent 2,548,803 (April 10, 1951).
(3) Pines and Ipatieff, U. S. Patents 2,670,390 (Feb. 23, 1954); 2,688,044 (Aug. 31, 1954); 2,721,885 (Oct. 25, 1955); 2,721,886 (Oct. 25, 1955); and 2,721,887 (Oct. 25, 1955).
(4) Pines, Vesely, and Ipatieff, *J. Am. Chem. Soc.*, **77**, 554 (1955).
(5) Pines and Mark, Paper No. 33, Division of Organic Chemistry, 127th ACS Meeting, Cincinnati, Ohio, April 1955.
(6) Pines, Vesely, and Ipatieff, *J. Am. Chem. Soc.*, **77**, 347 (1955).
(7) Whitman, U. S. Patent 2,501,556 (March 21, 1950).
(8) Closson, Ligett, and Kolka, U. S. Patents 2,728,802 (Dec. 27, 1955); 2,750,384 (June 12, 1956); 2,750,417 (June 12, 1956); and 2,751,426 (June 19, 1956).
(9) Hart, *J. Am. Chem. Soc.*, **78**, 2619 (1956).
(10) Gilman, Pacevitz, and Blaine, *J. Am. Chem. Soc.*, **62**, 1514 (1940).
(11) Bryce-Smith and Turner, *J. Chem. Soc.*, 1975 (1950).
(12) Morton, Brown, Holden, Letsinger, and Magat, *J. Am. Chem. Soc.*, **67**, 2224 (1945).

ethylations. With lithium anthracene appreciable quantities of gaseous C_4 compounds are obtained; olefins are also present in the liquid product in this case. Pines and coworkers[4] report the formation of ethane and hydrogen in their work.

The ethylation of benzene to ethylbenzene in the presence of an alkyl-sodium compound has been reported.[5] The ethylation of benzene does not take place in the presence of sodium anthracene at 200°. At 300°, appreciable quantities of ethylbenzene, *s*-butylbenzene, and 3-methyl-3-phenylpentane are formed. Considerable amounts of liquid olefins and gaseous C_4 compounds also are formed. Neither toluene nor benzene are thermally alkylated under these conditions.

Alkali metal hydride catalysts. The ethylation of toluene over lithium and sodium hydrides (unsupported) has been investigated. At 200° lithium hydride is completely inactive, and only a trace of *n*-propylbenzene is obtained with sodium hydride. Both hydrides are active for ethylation and polymerization at 300°; typical data are given in Table I. In the presence of toluene, both alkylation and polymerization take place over lithium hydride. With sodium hydride alkylation is the predominant reaction, and only a very small amount of polymerization occurs. In the absence of toluene both hydrides are active for polymerization.

ethylation of toluene and polymerization of ethylene. All three hydrides are inactive for the ethylation of toluene at 300°. A small amount of ethylene polymerization occurred in the ethylation experiment with barium hydride and traces may have also occurred in the ethylation runs with the other two hydrides. In the absence of toluene, however, calcium hydride was the only active catalyst for the polymerization of ethylene.

Samples of Hydrimix (calcium hydride supported on inert salts) were also examined as catalysts for the ethylation of toluene at 300°. The areas of these preparations are generally 2–4 $m.^2/g.$; the supports are nonporous and the surface area depends on the particle size. Appreciable quantities of liquid olefins and some *n*-propylbenzene are formed. Ethylene polymerization is the predominant reaction.

Hydrides of titanium, zirconium, and tantalum. Titanium and tantalum hydrides are inactive for the ethylation of toluene at 300°. With both catalysts, however, liquid olefins are formed. In the absence of toluene these catalysts are inactive even for ethylene polymerization. Zirconium hydride is active both for the ethylation of toluene and ethylene polymerization at 300°. Large quantities of liquid olefins are formed in the ethylation of toluene together with

TABLE I

ETHYLATION AND POLYMERIZATION WITH ALKALI METAL HYDRIDES AT 300°[a]

Expt. No.	Hydrocarbon	Catalyst[b]	Liquid Products	Gaseous Products (Mole) C_2H_4	C_2H_6	Other[c]
1	Toluene[d]	LiH	0.098 mole toluene + 6 cc. liquid (b.p. 111–287°) consisting mostly of *n*-propylbenzene and olefins with small amounts of 3-phenylpentane and unidentified products	0.068	0.083	0.027
2	None	LiH	0.5 g. olefins	0.050	0.15	0.052
3	Toluene[d]	NaH	0.034 mole toluene 0.045 mole *n*-propylbenzene 0.039 mole 3-phenylpentane Small amount of olefins	0.009	0.12	0.004
4	None	NaH	1.1 g. olefins	0.15	0.14	0.014

[a] 0.4 mole of ethylene charged in each experiment at 800–900 p.s.i.g. at room temperature. [b] 4.0 g. hydride used in each experiment. [c] Primarily C_4 with small amounts of H_2, CH_4, C_3, C_5, and C_6. [d] 0.2 mole toluene charged.

The quantities of ethane formed in all these runs are greater by a factor of 10 than those obtained with organoalkali catalysts. Pines, Vesely, and Ipatieff[4] explain the formation of ethane in the presence of organo-sodium catalysts by assuming some of the sodium alkyl-aromatic hydrocarbons decompose to form sodium hydride. The sodium hydride can then react with ethylene to form sodium ethyl; the latter through the metalation of alkyl-aromatic hydrocarbons then forms ethane and sodium alkyl-aromatic compounds. In the experiments described in Table I, appreciable quantities of lithium ethyl and sodium ethyl were probably formed by the interaction of ethylene with the hydrides. Metalation of toluene by the alkali ethyl compounds would lead to the formation of ethane. However, this mechanism cannot be applied to the experiments made without toluene. Metalation of some of the polymeric olefin products could account for the formation of ethane in these runs. This picture is consistent with the results reported by Morton, Brown, Holden, Letsinger, and Magat.[12] They found that butenes and other olefins are readily metalated by sodium amyl; in many instances the metalations occur by substitution.

Relatively large amounts of butenes were present in the gas phase of the runs with lithium hydride.

Alkaline earth metal hydrides. The hydrides (unsupported) of calcium, strontium, and barium were examined both for

appreciable quantities of *n*-propylbenzene. The predominant reaction is ethylene polymerization. Zirconium hydride is even active for polymerization in the absence of toluene.

In many instances in this study, more polymerization of ethylene occurs in the presence of toluene than when it is absent. In several cases, catalysts which appear to be inactive for ethylene polymerization give appreciable yields of liquid olefins in the presence of toluene. When toluene is present, there is a competitive reaction (ethylation of toluene) that can take place. The reason for this activating effect of toluene has not yet been determined. It would be interesting to determine whether other substances have the same effect.

Miscellaneous catalysts. Four commercial petroleum processing catalysts were tested for the ethylation of toluene at 300°. Trace amounts of *n*-propylbenzene and 3-phenylpentane were formed over chromia-alumina. With molybdena-alumina and cobalt molybdate-alumina, trace amounts of methyl-ethyl-benzenes were formed. Both types of ethylation occurred to a small extent over platinum-alumina catalyst. Small amounts of ethylene polymerization were observed in most cases.

Ethylation of amines. A short investigation has been made of the ethylation of aniline and its derivatives in the presence of sodium and sodium anthracene. The experiments reported by Whitman[7] were carried out at higher pressures

TABLE II

ALKYLATION OF TOLUENE WITH PROPYLENE[a]

Expt. No.	Propylene (Mole)	Catalyst[b]	Temp. (°C)	Liquid Product (Mole)		Gaseous Products (Vol.%)		
				Toluene	Isobutylbenzene	C_3H_6	C_3H_8	Other[c]
1	0.2	NaH	300	0.11	Trace	87.4	12.1	0.5
2	0.4	NaH	300	0.12	0.032	68.5	27.3	4.2
3	0.2	Na-anthracene	200	0.16	None	96.6	3.4	...
4	0.4	Na-anthracene	200	0.15	None	95.9	2.0	2.1
5	0.4	Na-anteachrne	300	0.14	0.020	85.1	13.6	1.3

[a] 0.20 mole toluene charged in each experiment. [b] 4 g. NaH or 2 g. Na-anthracene. [c] Includes H_2, CH_4, C_2, C_4-C_6.

than employed in this work and it was desirable to determine whether aromatic amines could be alkylated under conditions under which toluene reacts.

The ethylation of aniline at 200° was studied with both sodium and sodium anthracene. Similar results were obtained in both cases. The liquid product from the experiment with sodium present consisted of 0.024 mole of unreacted aniline and 0.022 mole *N*-ethyl aniline; 0.024 mole unreacted aniline and 0.021 mole *N*-ethyl aniline were obtained with sodium anthracene. In these experiments, 0.2 mole toluene and 0.4 mole of ethylene were initially charged. No ethylene polymerization occurred in these experiments; the ethylene used up in both instances corresponds almost exactly to the amounts of *N*-ethyl aniline formed. The amounts of hydrogen produced in these runs are greater than in corresponding ones in the ethylation of toluene.

The considerable amounts of solid materials obtained from these experiments were not analyzed. They probably contained condensation products of aniline, sodium anilide, and other organo-sodium compounds.

At higher pressures Whitman[7] obtained *N,N*-diethyl aniline as well as *N*-ethyl aniline at 200° in the presence of sodium. *N*-ethyl aniline does not react with ethylene at 200° in the presence of sodium anthracene under the conditions used in this work. *o*-Ethyl aniline likewise does not react under these conditions. The *ortho*-ethyl group could deactivate aniline in the following ways: (1) it may exert a steric effect or (2) the electron-repelling effect of this group could decrease the acidity of the amino hydrogen atoms.

At 300° aniline reacts with ethylene in the presence of sodium or sodium anthracene to give large amounts of *N*-ethyl aniline; *N,N*-diethyl aniline; *N*-*n*-butyl aniline; and higher amines.

Alkylation of toluene with propylene and butenes. In view of the activity of sodium hydride and sodium-anthracene for the alkylation of toluene with ethylene, the alkylations of toluene with propylene and butenes over these catalysts have been investigated.

Typical data for propylene are given in Table II. Propylene reacts with toluene in the presence of either sodium hydride or sodium-anthracene at 300° to give isobutylbenzene. The yields of alkylated products are much lower than those obtained with ethylene under the same conditions. No alkylation occurs with propylene over sodium-anthracene at 200°, whereas large amounts of alkylated products are obtained with ethylene at this temperature.

Neither isobutylene nor butene-2 reacts with toluene at 300° in the presence of sodium hydride or sodium anthracene under the above conditions. Appreciable quantities of butene-1 were formed in the experiments with butene-2. This result means that butene-1 is also inactive for the alkylation of toluene under these conditions. Pines, Vesely, and Ipatieff[4] have shown that butene-1 is isomerized to butene-2 at about 100° in the presence of organo-alkali metal compounds. Under certain conditions isobutylene reacts with toluene to form neopentylbenzene.[5]

SUMMARY

1. Both toluene and cumene are readily ethylated in the side chain in the presence of organo-alkali metal catalysts at about 200°. The ethylation of benzene requires more severe conditions.

2. Lithium and sodium hydrides (unsupported) are active catalysts for the side-chain ethylation of toluene and polymerization of ethylene at 300°. Both hydrides are inactive at 200°.

3. The alkaline earth metal hydrides (unsupported) are inactive for the ethylation of toluene or polymerization of ethylene at 300°.

4. Hydrimix catalysts (calcium hydride supported on inert salts) are active for the polymerization of ethylene at 300°, and some ethylation of toluene occurs at this temperature.

5. Zirconium hydride is active for the ethylation of toluene and polymerization of ethylene at 300°. Titanium and tantalum hydrides are inactive for the ethylation of toluene at 300°.

6. Chromia-alumina, molybdena-alumina, cobalt molybdate-alumina, and platinum-alumina are inactive for the ethylation of toluene at 300°.

7. Aniline is ethylated at 200° to give *N*-ethyl aniline. At 300° the products include *N*-ethyl aniline, *N,N*-diethyl aniline, *N*-*n*-butyl aniline, and other ethylated products.

8. Propylene reacts with toluene in the presence of sodium hydride or sodium anthracene to form isobutylbenzene. The yields of alkylated products are much less than obtained with ethylene under the same conditions. Neither isobutylene nor butene-2 reacts with toluene under these conditions.

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Effect of Structural Changes on Adsorption of Certain Alcohol 3,5-dinitrobenzoates on Silicic Acid[1]

JOHN J. BOST, RICHARD E. KEPNER,[2] AND A. DINSMOOR WEBB

Received Aug. 6, 1956

The relative strengths of adsorption of a number of aromatic alcohol 3,5-dinitrobenzoates on silicic acid have been determined in terms of their rates of travel on a chromatographic column as compared to the rate of travel of ethyl-3,5-dinitrobenzoate (designated as the R_e value). The observed effects of changes in the alcohol side chains containing up to three carbon atoms and of introducing various alkyl groups onto the aromatic nucleus on the strength of adsorption of 3,5-dinitrobenzoate derivatives have been evaluated in terms of electronic and steric factors insofar as possible.

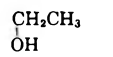
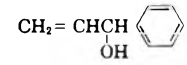
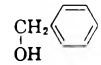
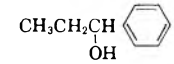
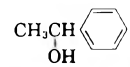
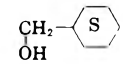
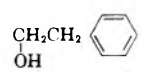
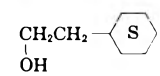
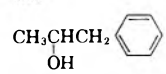
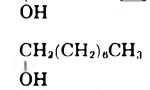
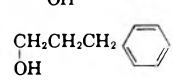
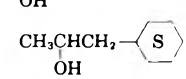
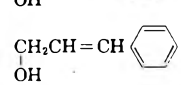
Many aspects of the effect of changes in the structure of organic molecules on the strengths of adsorption on a variety of adsorbents have been investigated.[3] In general, the strengths of adsorption on a material such as silicic acid decrease with increasing chain length and with increasing chain branching in saturated acyclic isomeric systems, with closely similar isomers being inseparable by means of paper or column chromatography. A mathematical function relating the interactions in chromatographic systems on the assumption that adsorption could be accounted for in terms of electron donor-acceptor and hydrogen-bonding theory has been proposed.[4]

During the course of other investigations[5] in these laboratories, 2-phenylethyl 3,5-dinitrobenzoate was observed to separate as a band on silicic acid between the ethyl and methyl 3,5-dinitrobenzoate bands. It was also observed by Drumheller and Andrews[6] that the *p*-nitrobenzoates of the isomeric aromatic alcohols, 1-phenylpropanol and 3-phenylpropanol, formed separable zones on a silicic acid column. The separation of these isomeric aromatic alcohol derivatives as well as the strong adsorption of such aromatic compounds indicated the need for further study of the effect of structural variations in simple aromatic alcohols on the strengths of adsorption. In the work presented herein the effects of certain structural changes in side chains containing one to three carbon atoms, and of introducing methyl, ethyl, or isopropyl groups in various positions on the rings of aromatic alcohol 3,5-dinitrobenzoates on the strengths of adsorption on silicic acid are described.

A reasonably good estimate of the relative strengths of adsorption of substances may often be obtained by the measurement of R_f values on a chromatographic column. In the present work, due to the comparatively strong adsorption of the aromatic 3,5-dinitrobenzoates, the determination of R_f values would not permit sufficient accuracy. Instead, the relative strengths of adsorption were determined by measuring the distances which ethyl 3,5-dinitrobenzoate and any other given 3,5-dinitrobenzoate moved on a chromatographic column during a period of time and designating the ratio of these distances as the R_e value. By a careful control of the chromatographic conditions the R_e values can be determined with an accuracy of about ± 0.02. The observed R_e values are listed in Tables I and II.

TABLE I

EFFECTS OF SIDE CHAIN VARIATION ON CHROMATOGRAPHIC ADSORPTION

Rates of Movement of 3,5-Dinitrobenzoate Derivatives Relative to Ethyl 3,5-dinitrobenzoate	R_e		R_e
	1.00		1.63
	0.96[a]		1.83
	1.36		2.46
	0.76		2.49
	1.34		3.08
	2.35		2.54
	0.65		

[a] No zone separation with the ethyl 3,5-dinitrobenzoate. Rate of movement relative to the cinnamyl derivative was determined and from this the listed value relative to the ethyl derivative calculated.

(1) Abstracted from a thesis submitted by John J. Bost in partial fulfillment of requirements for the M.S. degree. Presented before the Organic Division of the American Chemical Society at Atlantic City in September, 1956.

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(3) Typical examples are contained in the following: (*a*) Strain, *J. Am. Chem. Soc.*, **70**, 588 (1948); (*b*) Smith and LeRosen, *Anal. Chem.*, **23**, 732 (1951); (*c*) White and Dryden, *Anal. Chem.*, **20**, 853 (1948).

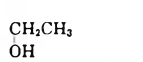
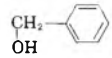
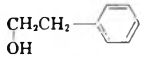
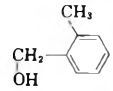
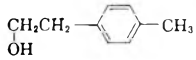
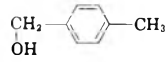
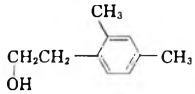
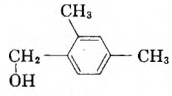
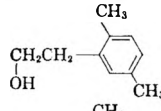
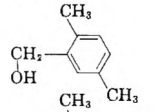
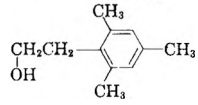
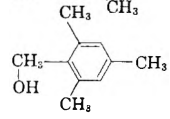
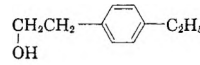
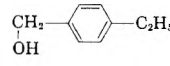
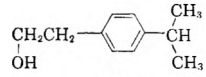
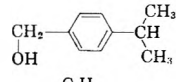
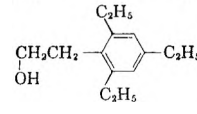
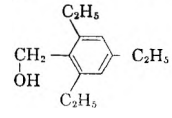
(4) LeRosen, Monaghan, Rivet, and Smith, *Anal. Chem.*, **23**, 730 (1951).

(5) Kepner and Webb, *American Journal of Enology*, **7**, 8 (1956).

(6) Drumheller and Andrews, *J. Am. Chem. Soc.*, **77**, 3290 (1955).

TABLE II

EFFECTS OF RING SUBSTITUTION ON CHROMATOGRAPHIC ADSORPTION

Rates of Movement of Aromatic 3,5-Dinitrobenzoate Derivatives Relative to Ethyl 3,5-dinitrobenzoate	R_e		R_e
	1.00		0.96[a]
	0.76		0.88[a]
	0.85[a]		0.92[a]
	1.00[a]		1.11[a]
	1.29		1.39
	0.1		1.71
	1.31		1.46
	1.39		1.64
	2.11		2.15

[a] No zone separation with the ethyl 3,5-dinitrobenzoate. Rate of movement relative to the cinnamyl derivative was determined and from this the listed value relative to the ethyl derivative calculated.

It has been fairly well demonstrated that in general the saturated alcohol 3,5-dinitrobenzoates are adsorbed by interaction of the ester group and the dinitroaryl nucleus with the adsorbent, with the strength of adsorption steadily decreasing as the alcohol portion becomes larger and bulkier. The increased strength of adsorption of the aromatic alcohol derivatives reported here must then be primarily associated with the ability of the aromatic ring of the alcohol to participate in the donor-acceptor type of interaction with the adsorbent. Contrary to predictions based on such considerations, benzyl 3,5-dinitrobenzoate is adsorbed less strongly than 2-phenylethyl 3,5-dinitrobenzoate, as evidenced by R_e values of 0.96 and 0.76, respectively. A comparison of the various benzyl alcohol derivatives with the corresponding 2-phenylethanol derivatives in Table II shows that the R_e values for the benzyl alcohol derivatives are always somewhat greater. This is most likely due to the increased proximity of the alcohol aromatic group to the ester linkage in the case of the benzyl derivatives resulting in a certain amount of steric inhibition to the adsorption normally associated with the ester linkage and also with the aromatic ring of the alcohol portion of the molecule. The large decrease in strength of adsorption observed for the 3-phenylpropyl 3,5-dinitrobenzoate, R_e 2.35, indicates that the two-carbon side chain is sufficient to overcome any such possible inhibition. Another possible explanation of these differences in strengths of adsorption may be that, other factors being equal, the 2-phenylethyl 3,5-dinitrobenzoate is of such a molecular length and area as to fit the adsorption spaces or cavities on the silicic acid ideally, while the benzyl and 3-phenylpropyl derivatives are not of optimum size. Further study of the nature of silicic acid as an adsorbent, such as has been made on alumina,[7] might prove helpful in deciding between the above possibilities.

The introduction of alkyl groups into the α position of either the benzyl or 2-phenylethyl 3,5-dinitrobenzoates results in a considerable decrease in the strengths of adsorption. A consideration of molecular models suggests that there would be a definite steric inhibition to the adsorption of the ester linkage on a flat surface as a result of the introduction of an α methyl group. Any aid to adsorption associated with the electron-releasing effects of alkyl groups substituted in the α positions is apparently overshadowed by the increase in molecular size and the steric factors.

Cinnamyl 3,5-dinitrobenzoate, R_e 0.65, is, with one exception, the most strongly adsorbed of the compounds investigated. The increased electron availability associated with the double bond in conjugation with the aromatic ring and the resultant planarity of that portion of the molecule far outweigh any tendency toward decreased strength of adsorption due to increase in molecular size. The relatively small increase in strength of adsorption associated with a double bond not in conjugation with an aromatic ring is demonstrated by a comparison of the R_e values for α-vinyl and α-ethylbenzyl 3,5-dinitrobenzoates, 1.63 and 1.83, respectively.

The effects of ring substitution in the 2-phenylethyl derivatives are shown by a trend toward a general decrease in adsorption with increasing number of alkyl groups. The same trend is observed with alkyl substituted benzyl derivatives with the exception of the *o*- and *p*-methylbenzyl 3,5-dinitrobenzoates. The general sequence of decrease in strength of adsorption and increase in R_e value in the *para* substituted derivatives follows what would be expected from a consideration of the electron-releasing ability of the methyl, ethyl, and isopropyl groups. This is also, however, the same sequence which would be expected on the basis of

(7) Russell and Cochran, *Ind. Eng. Chem.*, **42**, 1333 (1950).

the increase in molecular weight and size associated with the particular substituent.

The R_e values, 0.88 for *o*-methylbenzyl 3,5-dinitrobenzoate and 0.92 for *p*-methylbenzyl 3,5-dinitrobenzoate are just outside of experimental error from the R_e value, 0.96, of the unsubstituted benzyl 3,5-dinitrobenzoate and are believed to be real differences. The sequence of strength of adsorption, *o*-methylbenzyl greater than *p*-methylbenzyl greater than benzyl 3,5-dinitrobenzoate, is in line with the reported electronegativities of the *o*-tolyl, *p*-tolyl, and phenyl groups[8] as evidenced by the increasing dissociation constants of the corresponding carboxylic acids. The introduction of a *p*-methyl group into the 2-phenylethyl 3,5-dinitrobenzoate, on the other hand, results in a slight decrease in strength of adsorption. The 2-(2-methylphenyl)ethyl 3,5-dinitrobenzoate was not prepared in this investigation.

The 2,4,6-trialkyl substituted derivatives in general show a much weaker adsorption than the other derivatives prepared. The large decrease in adsorption in going from the 2,4-dimethylbenzyl 3,5-dinitrobenzoate (R_e 1.11) to the 2,4,6-trimethylbenzyl 3,5-dinitrobenzoate (R_e 1.71) quite clearly indicates that the effect can be attributed mainly to steric factors rather than the increased molecular weight and size accompanying the introduction of the methyl group. The R_e value (0.1) observed for the 2-(2,4,6-trimethylphenyl)ethyl 3,5-dinitrobenzoate is completely anomalous as compared to the other trialkyl substituted derivatives. No explanation of this result can be proposed at the present time.

EXPERIMENTAL[9]

Chromatographic procedure. The chromatographic column consisted of an 8 × 350 mm. tube with accessory equipment as described by Ikeda, Webb, and Kepner.[10] The adsorbent, a mixture containing two-thirds silicic acid and one-third analytical grade Celite, was prepared according to the procedure of White and Dryden.[3c] A weighed quantity (7.0 g.) of adsorbent was placed in the column using a standardized procedure designed to give a uniformly packed column approximately 24 cm. in height.

Approximately 15 mg. of ethyl 3,5-dinitrobenzoate and 15 mg. of a second 3,5-dinitrobenzoate derivative, each weighed to the nearest mg., were dissolved in the minimum volume of warm Skellysolve B and placed on the column. The column was then developed using 5% ether in Skellysolve B with a nitrogen pressure of approximately 8 lb. per sq. inch according to the techniques of White and Dryden.[3c] Development was continued until the bands were separated and in the lower half of the column. The bands at this point were usually from 1.0–1.5 cm. in length and the distance the band had traveled at any given time was determined by measuring from the top of the adsorbent column as the zero point to the mid point of the band.

2-Phenylethanol, 1-phenylethanol, benzyl alcohol, cinnamyl alcohol, n-octanol, 3-phenylpropanol, and cyclohexylmethanol. These alcohols were obtained from Eastman Kodak Co. and used directly for the preparation of the 3,5-dinitrobenzoate derivatives. The melting points of the derivatives agreed with the literature values, except for cyclohexylmethyl 3,5-dinitrobenzoate, m.p. 95.0–95.3°, which had not been previously reported.

2-Cyclohexylethanol. Cyclohexyl chloride (0.37 mole), b.p. 138–143°, n_D^{27} 1.4621, prepared from cyclohexanol in 57% yield by the method of Whaley and Copenhaven,[11] was converted into the Grignard reagent and condensed with ethylene oxide using standard Grignard procedures. Fractionation of the dried crude product gave 2-cyclohexylethanol (10% yield), b.p. 96–97° (12 mm.), n_D^{27} 1.4656; 3,5-dinitrobenzoate, m.p. 70.0–70.5°.

1-Cyclohexyl-2-propanol. Cyclohexylmagnesium chloride (0.37 mole) was prepared and condensed with propylene oxide, by the method described above to give 1-cyclohexyl-2-propanol (8.5% yield), b.p. 92–100° (27 mm.); 3,5-dinitrobenzoate, m.p. 69.5–71.2°.

α-Vinylbenzyl alcohol. Interaction of phenylmagnesium bromide (0.62 mole) with acrolein according to the method of Duveen and Kenyon[12] gave α-vinylbenzyl alcohol as a yellow oil (46% yield), b.p. 106–110° (17 mm.), n_D^{25} 1.5435. The alcohol darkened on standing at room temperature so that a freshly prepared sample was used to prepare the 3,5-dinitrobenzoate derivative according to the method of Mills[13] for the esterification of unstable alcohols. Isolation of the derivative gave a yellow oil which could not be crystallized but chromatographed as a single sharp band characteristic of a pure 3,5-dinitrobenzoate derivative.

1-Phenyl-1-propanol. Interaction of phenylmagnesium bromide (0.20 mole) with propionaldehyde as described above gave 1-phenyl-1-propanol (73% yield), b.p. 105–109° (18 mm.), n_D^{25} 1.5200; 3,5-dinitrobenzoate,[13] m.p. 66.5–67.0°.

1-Phenyl-2-propanol. Phenylmagnesium bromide (0.32 mole) was condensed with propylene oxide according to the method of Newman[14] to give 1-phenyl-2-propanol (43% yield), b.p. 100–105° (15 mm.), n_D^{26} 1.5250; 3,5-dinitrobenzoate, m.p. 87.7–88.1°.

o-Methylbenzyl alcohol. Benzylmagnesium chloride (0.41 mole) was condensed with formaldehyde according to the method of Smith and Spillane[15] to give *o*-methylbenzyl alcohol (13% yield), b.p. 115–120° (14 mm.), n_D^{29} 1.5408, m.p. 36° out of Skellysolve A; 3,5-dinitrobenzoate, m.p. 135.0–135.5°.

p-Methylbenzyl alcohol. α-Chloro-*p*-xylene, b.p. 90–94° (20 mm.), n_D^{27} 1.5344, prepared from toluene by the method of Stephen, Short and Gladding,[16] was hydrolyzed following

(8) Ferguson, *Electron Structures of Organic Compounds*, Prentice-Hall, Inc., New York, N. Y., 1952, p. 77.

(9) (*a*) All 3,5-dinitrobenzoate derivatives were prepared according to the procedure given by McElvain [McElvain, *The Characterization of Organic Compounds*, the MacMillan Co., rev. ed., New York, N. Y., 1953, p. 199] unless otherwise specified. The derivatives were purified by chromatography on silicic acid, by recrystallization from Skellysolve A (b.p. 35–50°) or Skellysolve B (b.p. 60–70°), or by a combination of both. (*b*) All melting points are corrected; boiling points are uncorrected. (*c*) Combustion analyses were run on the 18 3,5-dinitrobenzoate derivatives not previously reported in the literature and agreed with the calculated values within ±0.2% for both carbon and hydrogen with the exceptions of the cyclohexylmethyl and 2,4,6-triethylbenzyl 3,5-dinitrobenzoates where the carbon error was about 0.4%.

(10) Ikeda, Webb, and Kepner, *Anal. Chem.*, **26**, 1228 (1954).

(11) Whaley and Copenhaven, *J. Am. Chem. Soc.*, **60**, 2497 (1938).

(12) Duveen and Kenyon, *J. Chem. Soc.*, 1697 (1939).

(13) Mills, *J. Chem. Soc.*, 2332 (1951).

(14) Newman, *J. Am. Chem. Soc.*, **62**, 2295 (1940).

(15) Smith and Spillane, *J. Am. Chem. Soc.*, **62**, 2639 (1940).

(16) Stephen, Short and Gladding, *J. Chem. Soc.*, **117**, 510 (1920).

the procedure of Bennett and Jones[17] to give *p*-methylbenzyl alcohol, b.p. 121–124° (18 mm.), n_D^{26} 1.5268, m.p. 58° after freezing and recrystallization from Skellysolve A; 3,5-dinitrobenzoate, m.p. 117–118°.

2-(p-Methylphenyl)-ethanol. Toluene (1.2 mole) and ethylene oxide (0.29 mole) were condensed using the modified Friedel-Crafts procedure of Matui[18] to give 2-(*p*-methylphenyl)-ethanol (9% yield), b.p. 120–125° (19 mm.), n_D^{26} 1.5225; 3,5-dinitrobenzoate, m.p. 103.5–104.0°.

2,4-Dimethylbenzyl alcohol. 2,4-Dimethylbenzyl chloride (0.10 mole), b.p. 100–105° (14 mm.), n_D^{25} 1.5371, prepared in 27% yield from *m*-xylene by the chloromethylation procedure of Akin, Stamatoff, and Bogert,[19] was hydrolyzed[17] to give 2,4-dimethylbenzyl alcohol (62% yield), b.p. 150–152° (44 mm.), n_D^{26} 1.5349, m.p. 20–21°; 3,5-dinitrobenzoate, m.p. 133.5–135.0°; phenylurethane, m.p. 76–78.5°.

2-(2,4-Dimethylphenyl)ethanol. By reaction with sodium cyanide in aqueous ethanol 2,4-dimethylbenzyl chloride (0.14 mole) was converted into the nitrile which was isolated as a dark brown liquid. The crude nitrile was not further purified but was hydrolyzed directly by the method of Goldberg, Ordas, and Carsch[20] to give 2,4-dimethylphenylacetic acid (79% yield), m.p. 100–101°. The 2,4-dimethylphenylacetic acid (0.068 mole) was reduced with lithium aluminum hydride in absolute ether following the method of Hunter and Hogg[21] except that the reduction was allowed to run 20 hr. After removal of the ether, distillation gave 2-(2,4-dimethylphenyl)ethanol, b.p. 125° (10 mm.), n_D^{26} 1.5289; 3,5-dinitrobenzoate, m.p. 103.5°.

2,5-Dimethylbenzyl alcohol. 2,5-Dimethylbenzyl chloride, b.p. 100–103° (12 mm.), n_D^{26} 1.5366, was prepared in 65% yield by chloromethylation of *p*-xylene (1.0 mole) as described in "Organic Reactions"[22] with the following exception. The crude reaction product was distilled at 2–3 mm. pressure from a distillation flask connected with a short adapter to a receiver cooled in a Dry-Ice–carbon tetrachloride bath in order to separate the desired product from any dichloromethylated products which otherwise tended to cause polymerization in the final distillation. The 2,5-dimethylbenzyl chloride (0.15 mole) was hydrolyzed[17] to give 2,5-dimethylbenzyl alcohol (43% yield), b.p. 140–144° (37 mm.), n_D^{26} 1.5328; 3,5-dinitrobenzoate, m.p. 100.5°.

2-(2,5-Dimethylphenyl)ethanol. 2,5-Dimethylbenzyl chloride (0.45 mole) was converted to the nitrile and hydrolyzed by the method previously described to give 2,5-dimethylphenylacetic acid (94% yield), m.p. 128°. Reduction of 2,5-dimethylphenylacetic acid (0.30 mole) with lithium aluminum hydride[21] gave 2-(2,5-dimethylphenyl)ethanol (38% yield), b.p. 110–113° (5 mm.), n_D^{26} 1.5289; 3,5-dinitrobenzoate, m.p. 119.0–119.5°.

2,4,6-Trimethylbenzyl alcohol. 2,4,6-Trimethylbenzyl chloride (0.65 mole), b.p. 129–131° (22 mm.), n_D^{26} 1.5362, prepared in 22% yield by chloromethylation of mesitylene as described in "Organic Synthesis,"[23] was hydrolyzed[17] to give 2,4,6-trimethylbenzyl alcohol (85% yield), b.p. 138–142° (15 mm.), m.p. 87–88°; 3,5-dinitrobenzoate, m.p. 153.5–154.0°.

2-(2,4,6-Trimethylphenyl)ethanol. 2,4,6-Trimethylbenzyl chloride (0.12 mole) was converted to the nitrile[23] (96% yield), b.p. 160–165° (22 mm.), m.p. 79–80°, which was then hydrolyzed[23] to give 2,4,6-trimethylphenylacetic acid (85% yield), m.p. 168°. Reduction of the acid (0.095 mole) with lithium aluminum hydride[21] gave the crude alcohol which, after recrystallization from Skellysolve B, gave pure 2-(2,4,6-trimethylphenyl)ethanol (12% yield), m.p. 76–78°; 3,5-dinitrobenzoate, m.p. 183–184°.

p-Isopropylbenzyl alcohol. Chloromethylation[23] of cumene (0.83 mole) gave *p*-isopropylbenzyl chloride (10% yield), b.p. 100–105° (14 mm.), n_D^{25} 1.5198, which was then hydrolyzed[17] to give *p*-isopropylbenzyl alcohol (51% yield), b.p. 120–122.5° (13 mm.), n_D^{26} 1.5151; 3,5-dinitrobenzoate, m.p. 91–92°.

2-(p-Isopropylphenyl)ethanol. *p*-Isopropylbenzyl chloride (0.19 mole) was converted to the nitrile and then hydrolyzed by the methods previously described to give the acid as a yellow oil from which a few crystals were obtained by freezing on Dry-Ice. These crystals out of Skellysolve B had a m.p. 49–51°. The crude *p*-isopropylphenylacetic acid was reduced with lithium aluminum hydride[21] to give 2-(*p*-isopropylphenyl)ethanol (43% yield), b.p. 132–133° (11 mm.), n_D^{26} 1.5160; 3,5-dinitrobenzoate, m.p. 108.5–109.0°.

p-Ethylbenzyl alcohol. *p*-Ethylbenzyl chloride (0.065 mole), b.p. 95–100° (11 mm.), n_D^{25} 1.5286, prepared in 18% yield by chloromethylation[23] of ethylbenzene, was hydrolyzed[17] to give *p*-ethylbenzyl alcohol (92% yield), b.p. 110–116° (9 mm.); 3,5-dinitrobenzoate, m.p. 85.0–86.5°.

2-(p-Ethylphenyl)ethanol. *p*-Ethylbenzyl chloride (0.09 mole) was converted to the nitrile by the procedure of Baker, Dippy, and Page.[24] An attempt was made to hydrolyze the crude nitrile without further purification by heating it under reflux with stirring for 18 hr. in a mixture of 40 ml. of concentrated sulfuric acid, 40 ml. of glacial acetic acid and 20 ml. of water following the procedure of Hill and Short.[25] The solution became dark brown soon after the heating period was started. After cooling, the reaction mixture was poured into 100 ml. of water and 300 g. of chipped ice. A brown solid, which separated from the resulting solution, was isolated by filtration and found to be insoluble in 10% sodium hydroxide. The filtrate did not yield any acidic compound on ether extration. The brown residue, which was presumably the amide, was added to a mixture of 25 g. of ethylene glycol and 100 g. of sodium hydroxide in 100 ml. of water, and refluxed for 9 hr. The reaction mixture immediately gave off ammonia. The cooled mixture was filtered and acidified with 20% hydrochloric acid to give a tan precipitate. The tan solid was filtered, washed with water, and redissolved in 100 ml. of 5% sodium bicarbonate. The solution was boiled with 4 g. of Norit, filtered, and acidified with 5% hydrochloric acid to give 4.7 g. (25%) of *p*-ethylphenylacetic acid as colorless crystals, m.p. 88–90°, after crystallization from Skellysolve B.

p-Ethylphenylacetic acid (0.021 mole) was reduced using lithium aluminum hydride in anhydrous ether[21] as previously described with the exception that at the end of 10 hr., additional portions of lithium aluminum hydride and anhydrous ether were added and the mixture stirred for 24 hr. longer. The reaction mixture was worked up as usual and removal of the ether extraction solvent under reduced pressure left 2.5 ml. of a yellow oil. The crude 2-(*p*-ethylphenyl)ethanol was not purified further but was used directly for preparation of the 3,5-dinitrobenzoate, m.p. 112.0–112.5°.

2,4,6-Triethylbenzyl alcohol. 1,3,5-Triethylbenzene was obtained by the method of Smith and Guss[26] from triethylbenzene (Matheson Co.) which was a mixture of isomers. 2,4,6-Triethylbenzyl chloride (0.17 mole), b.p. 115–125° (4 mm.), n_D^{27} 1.5263, prepared in 50% yield by chloromethylation[23] of 1,3,5-triethylbenzene, was hydrolyzed[17] to give 2,4,6-triethylbenzyl alcohol (90% yield) as colorless needles, m.p. 52.5–54.0°; 3,5-dinitrobenzoate, m.p. 117–118°.

(17) Bennett and Jones, *J. Chem. Soc.*, 1815 (1935).

(18) Matui, *J. Soc. Chem. Ind., Japan*, **44**, No. 2 Suppl. binding 88 (1941).

(19) Akin, Stamatoff, and Bogert, *J. Am. Chem. Soc.*, **59**, 1268 (1937).

(20) Goldberg, Ordas and Carsch, *J. Am. Chem. Soc.*, **69**, 260 (1947).

(21) Hunter and Hogg, *J. Am. Chem. Soc.*, **71**, 1922 (1949).

(22) Fuson and McKeever, *Org. Reactions*, **1**, 69 (1942).

(23) Fuson and Rabjohn, *Org. Syntheses*, **25**, 65 (1945).

(24) Baker, Dippy, and Page, *J. Chem. Soc.*, 1774 (1937).

(25) Hill and Short, *J. Chem. Soc.*, 1123 (1935).

(26) Smith and Guss, *J. Am. Chem. Soc.*, **62**, 2625 (1940).

2 - (2,4,6 - Triethylphenyl)ethanol. 2,4,6 - Triethylbenzyl chloride (0.063 mole) was converted to the nitrile and the crude nitrile hydrolyzed as described under the preparation of 2-(*p*-ethylphenyl)ethanol to give 2,4,6-triethylphenylacetic acid (16% yield), m.p. 95–96°. The 2,4,6-triethylphenylacetic acid (0.01 mole) was reduced using lithium aluminum hydride[21] to give 2-(2,4,6-triethylphenyl)ethanol (80% yield), m.p. 39–40°; 3,5-dinitrobenzoate, m.p. 97.5–98.0°.

Acknowledgement. The authors are indebted to Dr. L. J. Andrews for helpful criticism of this manuscript during its preparation.

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Comparison of *N*-Bromoacetamide and *N*-Bromosuccinimide as Brominating Agents[1]

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Received Aug. 6, 1956

A comparison of *N*-bromoacetamide and *N*-bromosuccinimide as brominating agents in reactions which were presumably free radical in type has been carried out especially with reference to their tendencies to give allylic bromination or addition to the double bond. It was found qualitatively that *N*-bromoacetamide showed more tendency toward addition and was the more reactive reagent. *N*-Bromodiacetimide, which closely resembles *N*-bromosuccinimide from the standpoint of electronic configuration but which is more like *N*-bromoacetamide from the standpoint of steric strain, was so reactive it could not be prepared pure. Crude solutions of it reacted with olefins to give bromine addition products as the only ones isolated, but these could have arisen from the reaction with bromine formed by decomposition. An investigation of the fate of the acetamidyl radical during the reaction of *N*-bromoacetamide with styrene to give styrene dibromide showed that when the reactants were carefully mixed so that the reaction proceeded rapidly and smoothly nearly all of the acetamidyl radical could be identified as acetamide. The source of the hydrogen necessary for acetamide formation, at least in some of the cases, must have been either styrene or a brominated product, but no products formed by such hydrogen abstraction could be isolated.

N-Bromoacetamide has been used[2] as a source of bromine atoms for substitution on the allylic position, and N-bromosuccinimide has been developed[3–7] extensively as a brominating agent for allylic positions and aromatic side chains. For each of these *N*-bromo compounds, however, addition of bromine to the double bond has at times been observed under conditions expected to favor free radical reactions. *N*-Bromoacetamide appears to give this type of reaction quite readily.[8,9] In the case of its reaction with styrene the free radical nature of the reaction was especially apparent.[8] Addition with *N*-bromosuccinimide has been observed[10–16] as the main reaction in several cases while in other cases some addition has been observed when substitution was the main reaction.[6,15–19] In several instances there was extensive addition under conditions favorable to free radical reactions.[10–13] In other cases the beneficial effects of antioxidants such as *p-tert*-butylcatechol[15,16] and of halide ion[14,16] in promoting addition reactions have been interpreted in terms of polar mechanisms.

The results of the present investigation are summarized in Table I. In the cases studied *N*-bromoacetamide tended to give addition preferentially and *N*-bromosuccinimide gave the expected allylic bromination where possible. In detail the results of Table I do not always agree with results reported elsewhere. For example, no cyclohexene dibromide was isolated from the reaction with *N*-bromosuccinimide but small amounts have been reported[15–18] under conditions favorable to free radical reactions. No dibromide could be isolated from extended interaction of styrene with *N*-bromosuccinimide in the

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(1) From the Ph.D. Theses of William J. Probst and Robert C. Johnson. Presented before the Organic Division of the American Chemical Society, Cincinnati, Ohio, March, 1955.

(2) Wohl, *Ber.*, **52**, 51 (1919); Wohl and Jaschinowsky, *Ber.*, **54**, 476 (1921).

(3) Schmid, *Helv. Chim. Acta*, **29**, 1144 (1946).

(4) Schmid and Karrer, *Helv. Chim. Acta*, **29**, 573 (1946).

(5) Djerassi, *Chem. Rev.*, **43**, 271 (1948).

(6) Ziegler, Spath, Schaaf, Schumann, and Winkelmann, *Ann.*, **551**, 80 (1942).

(7) Waugh, "*N*-Bromosuccinimide, Its Reactions and Uses," Arapahoe Chemicals, Inc., Boulder, Colo., 1951.

(8) Buckles, *J. Am. Chem. Soc.*, **71**, 1157 (1949).

(9) Buckles and Maurer, *J. Org. Chem.*, **18**, 1585 (1953).

(10) Corey, *J. Am. Chem. Soc.*, **75**, 2251 (1953).

(11) English and Gregory, *J. Am. Chem. Soc.*, **71**, 1115 (1949).

(12) Buchman and Howton, *J. Am. Chem. Soc.*, **70**, 2517, 3510 (1948).

(13) Southwick, Pursglove, and Numerof, *J. Am. Chem. Soc.*, **72**, 1600 (1950).

(14) Braude and Waight, *Nature*, **164**, 241 (1949); *J. Chem. Soc.*, 1116 (1952).

(15) Bailey and Bello, *J. Org. Chem.*, **20**, 525 (1955).

(16) Bello, *Univ. Microfilms., Publ.* No. **10050**; *Dissertation Abstr.*, **14**, 1921 (1954).

(17) Park, Gerovich, Lycan, and Lacher, *J. Am. Chem. Soc.*, **74**, 2189 (1952).

(18) Howton, *J. Am. Chem. Soc.*, **69**, 2060 (1947).

(19) Couvreur and Bruylants, *Bull. soc. chim. Belg.* **61**, 253 (1952).

absence of an efficient hydrogen source or of halide ion, but a small yield has been reported[15,16] under such conditions. In another report[20] styrene was listed as being unreactive to *N*-bromosuccinimide.

TABLE I

REACTIONS OF OLEFINS WITH *N*-BROMOAMIDES

Olefin	*N*-Bromoamide[a]	Mole Ratio[b]	Solvent	Type of Bromination	Total Yield (%) Isolated
2-Methyl-2-hexene	NBS[c]	0.5	CCl_4	Allyl[d]	41
	NBA[c]	1.25	CCl_4	Addition	50
	NBD[c]	0.67	CCl_4	Addition	29
Cyclohexene	NBS[e]	0.2	CCl_4	Allyl	58
	NBA[e]	2.0	CCl_4	Addition	47
	NBA[e]	0.25	CCl_4	Allyl	36
	NBD[e]	2.0	$HCCl_3$	Addition	33
Styrene	NBS[f]	1.0	CCl_4	Addition	0
	NBS[g]	1.0	$CHCl_3$	Addition	26
	NBA[e]	2.0	CCl_4	Addition	34
	NBA[e]	2.0	$CHCl_3$	Addition	52
	NBD[e]	2.0	$HCCl_3$	Addition	24
1,3-Diphenylpropene	NBS[h]	0.83	CCl_4	?[i]	0
	NBA[h]	2.0	CCl_4	Addition	23
	NBD[h]	2.0	$HCCl_3$	Addition	10
Isobutylene	NBS[j]	..	$CHCl_3$	?[k]	0
	NBA[j]	..	$CHCl_3$	Addition	42
Ethyl cinnamate	NBS[l]	1.0	$CHCl_3$	Addition	0
	NBA[e]	2.0	$CHCl_3$	Addition	39
Methyl cinnamate	NBA[e]	2.0	$CHCl_3$	Addition	30
Trans stilbene	NBA[e]	2.0	$CHCl_3$	Addition	42
Tolan	NBA[e]	2.0	CCl_4	Addition	32
Benzalacetophenone	NBA[e]	2.0	$CHCl_3$	Addition	57
Phenylacetylene	NBA[e]	2.0	$CHCl_3$	Addition	37

[a] NBS represents *N*-bromosuccinimide; NBA, *N*-bromoacetamide; NBD, crude *N*-bromodiacetimide. [b] Mole ratio of *N*-bromoamide to olefin. [c] In each of these cases the solution was warmed to start the reaction and the olefin or *N*-bromoamide was added slowly enough to maintain the reaction mixture at or below the boiling point. [d] This product consisted of 27% 2-methyl-4-bromo-2-hexene and 14% of a crude dibromo-2-methyl-2-hexene. [e] The solution was boiled under reflux until there was no test for *N*-bromoamide with moist starch-iodide paper. [f] This entry represents the results of a number of experiments in which the solution was boiled under reflux for as long as 4 days and illuminated with an ultraviolet lamp during that period for 22 hrs. At the end of this maximum period of time, a 95% recovery of NBS and a 75% recovery of styrene were made. With shorter reaction periods even more NBS could be recovered. The addition of a small amount of NBA did not initiate any reaction. [g] Ethyl alcohol (10 ml. per 100 ml. of $CHCl_3$) was added before any change took place with the relatively insoluble NBS. [h] The solution was refluxed for from 15 to 30 min. [i] A residue which gave off hydrogen bromide but would not crystallize was formed. [j] Carried out at room temperature under a Dry Ice reflux condenser as isobutylene was bubbled into the solution. [k] The only product other than succinimide charred and decomposed on distillation. [l] This reaction was carried out under reflux under ultraviolet illumination for 3 days. The NBS was recovered in 92% yield.

(20) Kharasch and Priestley, *J. Am. Chem. Soc.*, **61**, 3425 (1939).

When cyclohexene reacted with excess *N*-bromoacetamide the reaction which took place was addition, but with excess olefin substitution was observed as had been reported.[17] With 2-methyl-2-hexene, on the other hand, the reaction was controlled by adding *N*-bromoacetamide a little at a time so that the olefin was in excess but the addition product was obtained. None of the reaction mixtures gave any isolable amounts of 1:1 adducts of the sort that have been reported for the reactions of *N*-bromosulfonamides,[20,21] *N*-haloamides,[6,17] *N*-bromoimides,[6,15,16] or *N*-bromomorpholine[22] with olefinic compounds.

In connection with the addition of bromine the fate of the nitrogen-containing radical is of interest. When *N*-bromosuccinimide has been involved good yields of succinimide have usually been reported.[10-19] In connection with *N*-bromoacetamide some acetamide and sometimes some bisacetamide hydrobromide have been found,[8] but never enough to account for much of the acetamidyl radical. In the present investigation the reaction of *N*-bromoacetamide and styrene was found to give yields of acetamide as high as 65%. When the acetamide was isolated by precipitation as bisacetamide hydrochloride yields as high as 97% were obtained. Such complete accounting for the acetamidyl radical was possible only when the reaction was carried out with just the right degree of control. In one experiment, where the reagents were mixed too fast, for example, the reaction mixture was extracted as completely as possible with water. It was possible to account for 74.5% of the nitrogen in the water-soluble portion and for 21.7% of the nitrogen in the water insoluble portion. Thus, some of the acetamidyl radical itself can be involved in addition to give water insoluble products.

In order to account for the acetamidyl radical forming acetamide it is necessary for a source of hydrogen to be available. In at least some of the experiments with styrene, where there was no hydrogen available from the solvent, this must have been either the styrene or a brominated product. No products resulting from this type of action could be isolated however. A simple dehydrogenation of styrene would be expected to yield phenylacetylene, but this compound reacted with *N*-bromoacetamide to yield what appeared to be its dibromide which should have been isolable had appreciable amounts been present in the reaction mixture. It seems that the dehydrogenation of either styrene or a brominated product was accompanied by some kind of polymerization, but polystyrene was not formed.[8] The presence of other possible hydrogen donors did not change the situation in general. With chloroform or benzene as solvents there was no evidence of dehydrogenation products arising from

(21) Foldi, *Ber.*, **63**, 2257 (1930).

(22) Southwick and Walsh, *J. Am. Chem. Soc.*, **77**, 405 (1955).

the solvent. Stilbene was brominated and triphenylmethane did not react when they were included in the reaction mixture as possible hydrogen sources.

In the case of the reaction of tolan with *N*-bromoacetamide neither the starting olefin nor the dibromide appear to have been likely sources of hydrogen. From this reaction mixture only a 70% yield of bisacetamide hydrochloride could be isolated. In cases such as this some of the acetamide may have acted as a source of hydrogen, but no products resulting from such a reaction could be isolated.

Ethyl alcohol was evidently an effective hydrogen source since the unreactive combination of *N*-bromosuccinimide and styrene reacted when it was present to give 26% of the dibromide. Even better results have been reported with catechol and *tert*-butylcatechol.[15,16]

Qualitatively there was a striking difference in reactivity between *N*-bromoacetamide and *N*-bromosuccinimide especially in the cases of styrene and ethyl cinnamate which could not undergo allylic bromination. In every case, even when *N*-bromosuccinimide reacted quite rapidly, *N*-bromoacetamide reacted faster.

It had been hoped that a comparison of *N*-bromodiacetimide with the other two *N*-bromoamides would throw some light on the differences in reactivity. The results were disappointing, however, since *N*-bromodiacetimide could be prepared only in an impure solution and its reactions may merely be those of the bromine formed from its decomposition. Its tendency to decompose, however, may be significant in itself. Surely it does act more like *N*-bromoacetamide than like *N*-bromosuccinimide. It may be that the reactivity and instability of *N*-bromoacetamide and especially *N*-bromodiacetimide are caused by steric strain on the nitrogen-bromine bond. Such steric strain would not be a factor in the structure of the cyclic *N*-bromosuccinimide. In any event it is quite evident that in general *N*-bromoacetamide is considerably more reactive than *N*-bromosuccinimide.

The difference in the results of the reactions of these two *N*-bromoamides might be explained on the basis of the reaction scheme outlined in equations 1 to 4. This scheme is consistent with the free radical mechanism proposed for substitution reactions by *N*-bromosuccinimide.[23,24] If the nitrogen-bromine bond were weakened, step 1 and those like step 4 would be particularly affected. If step 2 were faster than 3, but a relatively unfavorable equilibrium, a relatively rapid step 4 would allow step 2 to be relatively slow, but still faster than step 3, and, thus, the predominant path, which would lead to bromine addition. At the same time, a relatively slow step 4 would give the irreversible step 3 a chance to compete successfully with the relatively unfavorable equilibrium of step 2 and substitution would predominate. Decreasing the relative amount of the *N*-bromo compound would have the same effect of favoring step 3 over step 2 while an increase would have the opposite effect.

$$>\mathrm{NBr} + h\nu \longrightarrow >\mathrm{N}\cdot + \mathrm{Br}\cdot \qquad (1)$$

$$>\mathrm{C{=}C{-}CH_2}^- + \mathrm{Br}\cdot \rightleftharpoons >\mathrm{CBr{-}\dot{C}{-}CH_2}^- \qquad (2)$$

$$>\mathrm{C{=}C{-}CH_2}^- + >\mathrm{N}\cdot \longrightarrow >\mathrm{C{=}C{-}\dot{C}H}^- + >\mathrm{NH} \qquad (3)$$

$$\mathrm{R}\cdot + >\mathrm{N{-}Br} \longrightarrow \mathrm{RBr} + >\mathrm{N}\cdot \qquad (4)$$

Thus, if such a scheme were followed *N*-bromosuccinimide would be expected to tend to give substitution and *N*-bromoacetamide to tend to give addition, which results have been observed. In the cases where *N*-bromosuccinimide gave addition step 2 could be an equilibrium favorable enough to compete with step 3 in spite of a slow step 4.

In order to explain the formation of acetamide or succinimide from the addition reaction it is necessary to consider a source of hydrogen ZH_2 entering into the reaction sequence some such way as shown in steps 5 and 6. Such steps in the sequence make available bromine atoms for step 2. The ease with which a step such as 6 would take place would again depend on the reactivity of the *N*-bromo compound. Since two such steps (4) and (6) would be necessary for the addition reaction only reactive *N*-bromo compounds would usually be expected to react effectively in this way:

$$>\mathrm{N}\cdot + \mathrm{ZH_2} \longrightarrow >\mathrm{NH} + \mathrm{ZH}\cdot \qquad (5)$$

$$\mathrm{ZH}\cdot + >\mathrm{N{-}Br} \longrightarrow >\mathrm{NH} + \mathrm{Z}\colon + \mathrm{Br}\cdot \qquad (6)$$

EXPERIMENTAL

N-Bromoacetamide. This compound of m.p. 97–103° was prepared as described[8] for an earlier investigation, but most of the *N*-bromoacetamide used was kindly supplied by Araphoe Chemicals, Inc.

N-Bromosuccinimide. This compound was prepared as described[6] by the alkaline bromination of succinimide, but most of the *N*-bromosuccinimide used was kindly supplied by Arapahoe Chemicals, Inc.

N-Bromodiacetimide. In an all glass system freshly prepared phenyl magnesium bromide [from 15.7 g. (0.10 mole) of bromobenzene] in 200 ml. of anhydrous ether was added to a solution of 10.1 g. (0.10 mole) of diacetimide[25] in 150 ml. of anhydrous ether. A white precipitate formed and the reaction mixture became warm. To this suspension 16 g. (0.10 mole) of bromine was slowly added with stirring. A yellowish semisolid formed during the addition. The yellow solution was decanted and most of the ether was removed by distillation. The concentrated solution was filtered and dissolved in 75 ml. of carbon tetrachloride. This solution was then used in the bromination experiments.

An alternative procedure was the same as the procedure described above until the diacetimidomagnesium bromide was precipitated. This was then filtered from the solution

(23) Bloomfield, *J. Chem. Soc.*, 114 (1944).

(24) Dauben, McCoy, and Youngman, meeting of the American Chemical Society, Chicago, Sept. 1950, p. 11N.

(25) Polya and Tardrew, *J. Chem. Soc.*, 1081 (1948).

TABLE II

PROPERTIES OF BROMINATION PRODUCTS

Product	Brominating Agent	B.P., °C.	Pressure, Mm.	M.P.[a] °C.	d_4^{20}	n_D^{20}
2,3-Dibromo-2-methylhexane[b]	Br_2	73–75	8	...	1.5068	1.4990
	NBA	73–74	8	...	1.5063	1.4963
	NBD	69–73	5	...	1.5015	1.4980
4-Bromo-2-methyl-2-hexene[c]	NBS	43–44	5	...	1.1679	1.4785
Dibromo-2-methyl-2-hexene[c]	NBS	90–92.5	5	...	1.5269	1.5333
1,2-Dibromocyclohexane[d]	NBA	99–102	13	...	1.780	1.5530
	NBD	93–96	10	...	1.777	1.5521
3-Bromocyclohexene[e]	NBS	73–76	16	...	1.393	1.5300
	NBA	73–74	14–15	...	1.405	1.5279
1,2-Dibromo-1-phenylethane[g]	NBS	..	..	71–72	..	..
	NBA	108–110	4	71–72	..	..
	NBD	..	..	72–73	..	..
1,2-Dibromo-1,3-diphenylpropane[f]	Br_2	..	..	108–109	..	..
	NBA	..	..	106–108	..	..
	NBD	..	..	106–108	..	..
1,2-Dibromo-2-methylpropane[g]	NBA	37–38	9	..	1.545	1.4800
		145–146	745	..	1.528	1.4800
Ethyl 1,2-dibromohydrocinnamate[g]	NBA	..	..	73–74	..	..
Methyl 1,2-dibromohydrocinnamate[h]	NBA	..	..	115–116	..	..
trans-α,α'-Dibromostilbene[g]	NBA	..	..	208–209	..	..
meso-α,α'-Dibromobibenzyl[g]	NBA	..	..	243–244	..	..
2,3-Dibromo-3-phenylpropiophenone[13]	NBA	..	..	158–159	..	..
α,β-Dibromostyrene[i]	NBA	101–104	4	..	..	..

[a] All m.p.'s corrected. Mixtures of solid bromination products with authentic samples gave no lowered m.p.'s. [b] Lit. b.p. 99–100° (27 mm.), n_D^{22} 1.5001 [Hurd and Bennett, *J. Am. Chem. Soc.*, **51**, 3675 (1929)]. [c] *Anal.* Calc'd for $C_7H_{12}Br_2$: Br, 60.2%. Found: Br, 58.8%. The product slowly decolorized bromine in carbon tetrachloride and potassium permanganate in acetone. Sodium iodide in acetone gave an immediate white precipitate with some light brown color. [d] Lit. b.p. 97–98° (10 mm.), d_4^{16} 1.7898, n_D^{16} 1.5540 [Coffey, *Rec. trav. chim.*, **42**, 398 (1923)]. [e] Lit. b.p. 69–72° (13 mm.), n_D^{20} 1.5285.[17] [f] Lit. m.p. 112° (block) when prepared from the oily olefin of unknown configuration.[29] [g] Lit. b.p. 54–56° (24 mm.), 149–151° (760 mm.), n_D^{20} 1.5119, d_4^{20} 1.7827 [Krestinsky, *Ber.*, **55**, 2754 (1922)]. Distillation at atmospheric pressure gave rise to fumes of hydrogen bromide and a distillate which decolorized bromine in carbon tetrachloride and potassium permanganate in acetone. [h] Lit. m.p. 117° [Anschütz and Kinnicutt, *Ber.*, **11**, 1214 (1878)]. [i] Lit. b.p. 132–135° (15 mm.) [Nef, *Ann.*, **308**, 273 (1898)].

and kept at 75°. On the day before a bromination was to be carried out 10.2 g. (0.05 mole) of the finely divided diacetimidomagnesium bromide was placed in an all glass vessel in contact with excess bromine vapor and left overnight. The excess bromine was then pumped off and the residue was extracted with two 25 ml. portions of warm chloroform. The orange solution was used in the bromination experiments.

The attempted synthesis of *N*-bromodiacetimide by means of the usual basic brominations which were used in the synthesis of *N*-bromoacetamide and *N*-bromosuccinimide gave no isolable product. The method[26] of bromination of the silver salt of diacetimide in trifluoroacetic acid likewise gave no isolable product.

2-Methyl-2-hexene. This compound was prepared by the condensation of n-butylmagnesium bromide with acetone followed by dehydration of the carbinol formed.[27]

1,3-Diphenyl-1-propanol. A solution of 100 g. (0.48 mole) of benzalacetophenone in 400 ml. of 95% ethyl alcohol was hydrogenated over copper chromite at 1500 lb. per sq. inch and 140°. Distillation of the pale green solution yielded 83 g. (81%) of 1,3-diphenyl-1-propanol, b.p. 150–152° (2

(26) Henne and Zimmer, *J. Am. Chem. Soc.*, **73**, 1103 (1951).

(27) Edgar, Calingaert, and Marker, *J. Am. Chem. Soc.*, **51**, 1483 (1929).

mm.), d_4^{20} 1.0594, n_D^{20} 1.5734 which check well with reported[28] values.

1,3-Diphenylpropene. A mixture of 106 g. (0.50 mole) of 1,3-diphenyl-1-propanol and 45 ml. of 85% phosphoric acid was slowly distilled to yield 80 g. (85%) of 1,3-diphenylpropene, b.p. 144–145° (5 mm.) which was probably the product, b.p. 164–168° (11 mm.), of questionable geometric configuration often obtained in the synthesis of this olefin.[28,29]

Other olefins. Styrene was used without purification with the *tert*-butylcatechol stabilizer present. Cyclohexene was distilled from sodium wire and kept over sodium wire. All of the other olefins were either commercial products or were synthesized by methods appearing in the *Organic Syntheses* series.

Solvents. Chloroform was washed several times with concentrated sulfuric acid and then with water. It was dried over anhydrous potassium carbonate and then distilled. Carbon tetrachloride was distilled from phosphorus pentoxide. Commercial, thiophene-free benzene was used without change.

Bromination Experiments. In general, 0.1 mole of brominating agent was used in 50 to 150 ml. of solvent with varying amounts of olefin. In all of the reactions the *N*-bromoamide was the yield-limiting material. Conditions during the reaction were adjusted to suit the reactivity of the *N*-bromoamide. In general, the *N*-bromoacetamide reactions had to be controlled much more carefully, by adding one of the reagents a little at a time, than did those with *N*-bromosuccinimide. The general results of the brominations are summarized in Table I. The properties of the products are given in Table II. In general, good yields of succinimide were obtained from those reactions from which no *N*-bromosuccinimide could be recovered. Varying amounts of acetamide could be obtained from the reactions involving *N*-bromoacetamide. As much as a 55% was isolated when cooled in an ice-salt bath and as much as 65% was isolated when ether was present.

About 44 experiments of this type were carried out between styrene and *N*-bromoacetamide in order to try to isolate products more completely. In each case 0.1 mole of *N*-bromoacetamide in the solvent was heated to reflux and 0.05 mole of styrene was added as rapidly as the violence of the reaction would permit. The acetamide was precipitated by anhydrous hydrogen chloride to give bisacetamide hydrochloride, m.p. around 131°, in yields of 95–97% in the most quantitative experiments. Attempts to purify the oily residue by crystallization or distillation were usually terminated by the formation of a brittle resinous glass. Oxidation of 10 g. of the residue with hot basic permanganate in one experiment yielded 0.5 g. of benzoic acid as well as the resinous glass.

When such a reaction was carried out in carbon tetrachloride with 0.05 mole of stilbene present a 15% yield of stilbene dibromide and a 34% yield of styrene dibromide were obtained. A 55% yield of stilbene was recovered. With 0.025 mole of triphenylmethane and 0.025 mole of *N*-bromoacetamide with 0.125 mole of styrene in carbon tetrachloride, a 42% yield of styrene dibromide was isolated and 91% of the triphenylmethane was recovered.

One experiment was carried out in carbon tetrachloride on a carefully weighed sample of *N*-bromoacetamide. The reaction mixture was extracted with water. The water layer was divided into portions and shown to contain 74.5% of the nitrogen by Kjehldal analysis and 18.6% of the bromine by silver nitrate precipitation. The carbon tetrachloride solution was evaporated. The residue was shown to contain 21.7% of the nitrogen by Kjehldal analysis and 81.7% of the bromine by hot alcoholic silver nitrate precipitation.

A very careful experiment was carried out with 4.1 g. (0.023 mole) of tolan and 6.3 g. (0.046 mole) of *N*-bromoacetamide in 100 ml. of refluxing carbon tetrachloride. At the end of 20 hr. no more *N*-bromoacetamide was present. From the reaction mixture were obtained 2.5 g. (32%) of crude tolane dibromide and 2.5 g. (70%) of bisacetamide hydrochloride by the general methods described above.

In several cases reactions of the olefins with bromine in carbon tetrachloride were carried out for the purpose of preparing authentic samples of dibromides. The properties of these samples are included in Table II.

Bisacetamide hydrochloride. A solution of 4.0 g. (0.067 mole) of acetamide in 50 ml. of anhydrous chloroform was saturated with anhydrous hydrogen chloride to give 5.4 g. (104%) of bisacetamide hydrochloride, m.p. 128–129°. Crystallization from acetonitrile yielded 5.0 (96%) of the hydrochloride, m.p. 130–131°.

Anal. Calc'd for $C_4H_{11}N_2O_2Cl$: C, 31.07; H, 7.17; N, 18.12; Cl, 22.93. Neutralization equivalent weight, 155.9. Found: C, 31.12; H, 7.15; N, 17.67; Cl, 23.01. Neutralization equivalent weight, 154.6.

Bisacetamide hydrochloride has been reported,[25,30] to have a m.p. varying from 125–135°. It has also been reported[25,31] to be considerably more stable than the 1:1 salt which decomposed with loss of hydrogen chloride to give bisacetamide hydrochloride. No 1:1 salt was ever isolated in the present investigation, but analysis of some samples of bisacetamide hydrochloride of m.p. around 125° showed that they were probably contaminated with this salt. Recrystallization of such samples always gave bisacetamide hydrochloride of m.p. around 131°.

(28) Pfeiffer, Kalckbrenner, Kunze, and Levin, *J. prakt. Chem.*, [2] 119, 109 (1928).

(29) Ramart and Arnagat, *Ann. chim.* [10] 8, 310 (1927).

(30) Pinner and Klein, *Ber.*, 10, 1896 (1877).

(31) Strecker, *Ann.*, 103, 322 (1857).

[CONTRIBUTION FROM THE RESEARCH AND ENGINEERING DEPARTMENT, CHEMICAL RESEARCH LABORATORY, ETHYL CORPORATION]

Synthesis of Higher Alkyltin Compounds from Sodium-Tin Alloys

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Received Aug. 15, 1956

n-Butyl chloride reacts with sodium-tin alloys at 150–180°C., resulting in 25–30% tin conversions to mixtures composed of 10–20% tetrabutyltin and 80–90% tributyltin chloride. *n*-Propyl chloride and *n*-amyl chloride react with NaSn (2% Zn) giving good conversions to the R_4Sn–R_3SnCl mixtures. Under milder conditions, reactions of ethyl chloride or *n*-butyl chloride with sodium-tin alloys result in substantial yields of R_2Sn, readily converted to the corresponding dialkyltin oxide by reaction with oxygen. Mixtures of tetrabutyltin and tributyltin chloride react readily with the theoretical quantity of stannic chloride, yielding dibutyltin dichloride quantitatively.

Reaction of methyl, ethyl, and some propyl halides with sodium-tin alloys is the oldest known method for synthesis of the corresponding alkyltin compounds. Löwig in 1852 reported the reaction of ethyl iodide with a sodium-tin alloy containing 14% sodium (composition NaSn) to form diethyltin.[1] Other reactions with alloys of similar composition and methyl or ethyl halides have appeared in the literature.[2,3,4] Reaction of an alloy of composition Na_2Sn with ethyl bromide has been reported to yield diethyltin,[5] tetraethyltin, or diethyltin dibromide.[6] Further, Harada has shown that NaSn alloy is activated by the presence of varying amounts of zinc in reactions with methyl iodide,[7] ethyl bromide,[8] and with propyl bromide.[9] Mixtures of R_4Sn and R_3SnX were obtained, the compositions varying with reaction conditions.

Reactions of butyl and higher alkyl chlorides with sodium-tin alloys have not been reported. The known references imply, moreover, that even though good yields are obtained with methyl and ethyl halides, the reaction is not satisfactory for higher molecular weight alkyl halides.[10] Reaction of *n*-butyl bromide with zinc-activated sodium-tin alloys has been reported, however, to give good yields of tributyltin bromide.[11]

We have found that *n*-butyl chloride reacts readily with the active ternary alloys NaSn (2% Zn) and $Na_{0.92}K_{0.08}Sn$ at 150–180°C. under autogenous pressure to give good yields of mixtures composed of 10–20 weight % tetrabutyltin and 80–90% tributyltin chloride. At lower reaction temperatures, and especially when the less active binary alloy NaSn is used, the organotin product contains substantial amounts of dibutyltin along with tetrabutyltin and tributyltin chloride. Satisfactory yields of R_4Sn–R_3SnCl mixtures are also obtained from *n*-propyl chloride and *n*-amyl chloride with the active ternary alloys under reaction conditions similar to those used for *n*-butyl chloride.

On the basis of the results of our work the following reactions are proposed to explain the products obtained:

$$2\ NaSn + 2\ RCl \longrightarrow R_2Sn + 2\ NaCl + Sn \quad (1)$$

$$R_2Sn + RCl \longrightarrow R_3SnCl \quad (2)$$

$$2\ R_2Sn \longrightarrow R_4Sn + Sn \quad (3)$$

It appears that dialkyltin compounds are intermediates in the formation of R_4Sn and R_3SnCl. If the R_3SnCl–R_4Sn product contains 80 mole % R_3SnCl, summation of Equations (1)–(3) above would result in the total equation,

$$12\ NaSn + 16\ RCl \longrightarrow 4\ R_3SnCl + R_4Sn + 12\ NaCl + 7\ Sn \quad (4)$$

for which the theoretical tin conversion to organotin product is 42.7%. We have obtained products apparently consisting of R_3SnCl and R_4Sn exclusively in tin conversions of 25–30%.

In reactions with *n*-butyl chloride and NaSn (2% Zn) carried out under mild conditions, *e.g.*, at temperatures below 130°C., or with the less active alloy NaSn, appearance of orange-brown colors in product solutions is taken to indicate intermediate dibutyltin formation, as in Equation (1). Preponderance of tributyltin chloride in the products when reaction conditions were more strenuous, along with absence of colors, and the fact that tin conversions were consistently higher than the theoretical 25% expected by the equation,

$$4\ NaSn + 4\ n\text{-}C_4H_9Cl \longrightarrow (n\text{-}C_4H_9)_4Sn + 3\ Sn + 4\ NaCl$$

suggest direct addition of *n*-butyl chloride to dibutyltin, as shown in Equation (2).

The dark colored solutions are decolorized by the action of chlorine, probably due to conversion of

(1) Löwig, *Ann.*, 84, 308 (1852).
(2) Cahours, *Ann.*, 122, 198 (1862).
(3) Ladenburg, *Ann.*, 8 (Suppl.) 75 (1872).
(4) Kraus and Callis, U. S. Patent 1,639,947 (1927).
(5) Harada, *J. Sci. Research Inst.* (*Tokyo*), 43, 31 (1948).
(6) Neiman and Shushunov, *Doklady Akad. Nauk S.S.S.R.*, 60, 1347 (1950).
(7) Harada, *Bull. Chem. Soc. Japan*, 4, 266 (1929).
(8) Harada, *Sci. Papers Inst. Phys. Chem. Research* (*Tokyo*), 35, 290 (1939).
(9) Harada, *Repts. Sci. Research Inst.* (*Japan*), 24, 177 (1948).
(10) van der Kerk and Luijten, *J. Applied Chem.*, 4, 301 (1954).
(11) Gilman, PB No. 6004, National Defense Research Committee Report, May 2, 1942.

dibutyltin to colorless dibutyltin dichloride [Equation (5)]. However, no attempt was made to isolate dibutyltin dichloride from this reaction in this work. Also, the dark color is destroyed by aeration, forming white polymeric dibutyltin oxide [Equation (6)], which is converted to dibutyltin dichloride by treatment with hydrochloric acid [Equation (7)].

$$(n\text{-}C_4H_9)_2Sn + Cl_2 \longrightarrow (n\text{-}C_4H_9)_2SnCl_2 \quad (5)$$

$$x\,(n\text{-}C_4H_9)_2Sn + \frac{x}{2}\,O_2 \longrightarrow [(n\text{-}C_4H_9)_2SnO]_x \quad (6)$$

$$[(n\text{-}C_4H_9)_2SnO]_x + 2x\,HCl \longrightarrow x\,(n\text{-}C_4H_9)_2SnCl_2 + x\,H_2O \quad (7)$$

In support of Equation (1), formation of dialkyltin compounds from NaSn and lower alkyl halides has been reported.[1] Formation of trialkyltin chlorides as in Equation 2 is also known.[12,13] Equation 3 has a precedent in the report of Frankland that diethyltin on distillation formed tin and tetraethyltin.[14] Pfeiffer *et al.* have demonstrated that diethyltin reacts with air to precipitate diethyltin oxide, and with halogens to form the corresponding diethyltin dihalide,[13] analogous to Equations (5) and (6). These authors also formed dialkyltin dihalides by the action of halogen acids on the corresponding dialkyltin oxide as in Equation (7).[15]

Tetrabutyltin–tributyltin chloride mixtures formed in sodium-tin alloy reactions are converted in essentially quantitative yields to dibutyltin dichloride by reaction with the calculated quantity of stannic chloride. Thus, for a mixture containing 80 mole % tributyltin chloride, reaction is expressed by the equation:

$$4\,(n\text{-}C_4H_9)_3SnCl + (n\text{-}C_4H_9)_4Sn + 3\,SnCl_4 \longrightarrow 8\,(n\text{-}C_4H_9)_2SnCl_2$$

van der Kerk and Luijten recommended temperatures of 230–240°C. for conversion of mixtures of high tetrabutyltin content to dibutyltin dichloride.[10] We have found in converting mixtures of high tributyltin chloride content that temperatures in excess of about 210°C. promote decomposition and undesirable by-product formation, and that a reaction temperature of 180°C. appears to be optimum for conversion to dibutyltin dichloride.

EXPERIMENTAL

Materials. *n*-Alkyl chlorides were all Eastman white label products, with the exception of ethyl chloride, which was redistilled Ethyl Corporation commercial grade. Metals from the following sources were used: tin, 1-lb. bars, Fisher Scientific Company; sodium, Ethyl Corporation, commercial grade; potassium, J. T. Baker Co., C.P.; and zinc, J. T. Baker Co., mossy. Stannic chloride was Fisher anhydrous reagent grade.

Alloy preparation. Alloys were prepared by stirring the calculated quantities of tin, sodium, and ternary metal (when used) at red heat for 15–20 min. in steel bombs under nitrogen. They were broken up by striking the cooled bomb with a hammer and were further comminuted in a large mortar under nitrogen until maximum particle size was about 0.25 inch. While well protected from the atmosphere, alloy samples were weighed into 4-oz. screw-cap bottles for storage prior to use. In this manner, NaSn, NaSn (2% Zn), and $Na_{0.92}K_{0.08}Sn$ were prepared. They were all shiny, gray, brittle solids, rapidly dulling in appearance when contacted with traces of atmospheric oxygen or moisture.

Anal: Calc'd for NaSn: Na, 16.2. Found: total Na, 16.3; active Na, 15.9. Calc'd for NaSn(2% Zn): Na, 15.9. Found: total Na, 15.2; active Na, 15.7. Calc'd for $Na_{0.92}K_{0.08}Sn$: Na, 14.8. Found: total Na, 14.7.

Tetrabutyltin-tributyltin chloride from NaSn (2% Zn). A small monel pressure reactor (170 ml. capacity) was charged under nitrogen with 60 g. of *n*-butyl chloride, 47.8 g. NaSn (2% Zn), and a 5/8-inch steel ball. The sealed bomb was tumbled for 5 hr. in an oil bath at 160–170°C. The bomb was cooled in a dry ice–acetone bath, after which it was opened. The uniform black slurry formed during reaction was washed onto a Büchner funnel with 200 ml. benzene. Filtration resulted in a black powdery solid (free of active sodium when tested with methanol) and a clear light yellow filtrate. Distillation in a Claisen flask yielded a benzene–butyl chloride fraction, and 25.7 g. of a main product fraction of tetrabutyltin–tributyltin chloride collected at 148–151°C. (10 mm.).

Anal: Calc'd for $(n\text{-}C_4H_9)_4Sn$: Sn, 34.2. Calc'd for $(n\text{-}C_4H_9)_3SnCl$: Sn, 36.5; Cl, 10.9. Found for product mixture: Sn, 34.5; Cl, 8.35.

Tin analyses were carried out by the method of Gilman and King.[16] From the analyses, the product mixture contained 23.3% tetrabutyltin and 76.7% tributyltin chloride (based on chlorine content). The calculated tin content of such a mixture is 35.8%. Tin conversion, calculated from the tin analysis, was 22.6%. In subsequent reactions, tin conversions averaged 25–30%. Small portions of a product mixture treated with $AgNO_3$ solution gave an immediate white AgCl precipitate (confirming the presence of tributyltin chloride), and gave no precipitate when treated with NH_4OH solutions (indicating the absence of dibutyltin dichloride which would be expected to form white dibutyltin oxide).

A 16.5-g. portion of the product mixture obtained above was redistilled in a 20-inch concentric tube column at 3–3.5 mm. Five fractions were taken though the boiling point varied only slightly. Data for the distillation are given in

TABLE I

DISTILLATION OF TETRABUTYLTIN-TRIBUTYLTIN CHLORIDE MIXTURE

Fraction No.	B.p., °C.[a]	Wt., g.	n_D^{20}[b]	Wt. % Cl
1	78.5–128.7	0.61	1.4739	
2	129	2.12	1.4853	7.97
3	128.7–129	10.64	1.4866	8.63
4	129 –131.2	2.03	1.4890	
5	131.2–131.4	0.80	1.4900	10.44
Residue	..	0.40	..	

[a] Pressure, 3–3.5 mm. [b] From the literature, n_D^{20} for tetrabutyltin is 1.4730[17]; n_D^{22} for tributyltin chloride is 1.4908.[18]

(12) Krause and Pohland, *Ber.*, **57**, 532 (1924).
(13) Pfeiffer, *Ber.*, **44**, 1269 (1911).
(14) Frankland, *Ann.*, **85**, 340 (1853).
(15) Pfeiffer, Lehnardt, Lustensteiner, Prade, Schnurmann, and Truskier, *Z. anorg. Chem.*, **68**, 102 (1910).
(16) Gilman and King, *J. Am. Chem. Soc.*, **51**, 1213 (1929).
(17) Jones, Evans, Gilwell, and Griffith, *J. Chem. Soc.*, 39 (1935).
(18) Manulkin, *J. Gen. Chem. U.S.S.R.*, **20**, 2004 (1950).

Table I. Though a poor separation was obtained, refractive indices of the fractions vary from that found in the literature for tetrabutyltin to the literature value for tributyltin chloride. Chlorine analyses, also, increase almost to the calculated chlorine content of tributyltin chloride.

Tetrabutyltin–tributyltin chloride from $Na_{0.92}K_{0.08}Sn$. A reaction was carried out similar to the above reaction, using 60 g. of *n*-butyl chloride and 46.4 g. of $Na_{0.92}K_{0.08}Sn$ alloy. The mixture was heated for 4 hr. at 160–165°C. There was obtained on work-up 24.6 g. of crude tetrabutyltin–tributyltin chloride mixture, containing 5.8% chlorine and 38% tin, corresponding to a 53.2% tributyltin chloride content and a tin conversion of 24.2%.

Tetrabutyltin–tributyltin chloride from NaSn. By procedures similar to those described above for the ternary alloys, 69 g. of *n*-butyl chloride was allowed to react with 52.2 g. of NaSn alloy. The mixture was heated for 10 hr. at 140–155°C. The tetrabutyltin–tributyltin chloride product (37.2 g.) contained 9.4% chlorine and 36.3% tin. This corresponds to a tributyltin chloride content of 86.1% and a 30.9% tin conversion.

Other R_4Sn–R_3SnCl *mixtures from NaSn(2% Zn).* Mixtures of R_4Sn and R_3SnCl were obtained in reactions of NaSn(2% Zn) with *n*-propyl chloride and *n*-amyl chloride (Table II) by the procedures described above for *n*-butyl chloride. Reactants were used in the ratio of two moles of RCl per gram-atom of tin in the alloy. The crude products were not completely purified and identified. However, tin conversion calculated from tin analyses on the products serves as a measure of reaction efficiency. Chloride was shown to be present in the products by precipitation of silver chloride.

TABLE II

R_4Sn-R_3SnCl Mixtures from Reactions of RCl with NaSn(2% Zn)

RCl	Temp., °C.	Time, Hr.	R_4Sn–R_3SnCl Product % Sn	% Sn conversion
n-C_3H_7Cl	160	0.3		
	140–145	4	40.3	18.2
n-$C_5H_{11}Cl$	162	4	31.6	27.2

Diethyltin, diethyltin oxide. An apparatus was constructed in which a 1-inch diameter Micrometallic filter disk ($^3/_{32}$-inch thickness, porosity "F") was welded into a steel pipe as a support for NaSn(2% Zn) alloy. After the pipe was charged with alloy (3.18 g.), 2.5 l. of ethyl chloride was passed through the heated reactor (89°C.) over a period of 173 min., under sufficient nitrogen pressure to maintain the ethyl chloride in the condensed phase. After a 30-min. induction period, the clear liquid collected from the reactor began to show a yellow color which gradually deepened to red. Maximum color intensity was obtained after 60 min. Ethyl chloride was distilled from the product solution and was replaced by 100 ml. of *n*-hexane. Aeration of the deep red *n*-hexane solution formed a colorless solution and precipitated 0.98 g. (45% yield) of white diethyltin oxide.

Anal: Calc'd for $[(C_2H_5)_2SnO]_x$: Sn, 61.5%. Found: Sn, 57.9%.

Distillation of *n*-hexane from the filtrate yielded 0.32 g. of colorless oil. The solids removed from the pipe after reaction were found to contain 86% of the expected chloride ion, based on sodium present in the original alloy.

Dibutyltin, dibutyltin oxide. A mixture of 47.7 g. NaSn alloy and 62.2 g. of *n*-butyl chloride was heated in an autoclave for 4 hr. at 162°C. On filtering the mixture and washing the solids with benzene (200 cc.), there was obtained a dark orange-brown product solution. Dry air was bubbled into the solution for 1.5 hr., resulting in a white precipitate of dibutyltin oxide (7.3 g., 8.6% tin conversion). A portion of the white precipitate was heated with concentrated hydrochloric acid, forming a white oil, dibutyltin dichloride, which on recrystallization from petroleum ether melted at 35–37.5°C., undepressed when mixed with an equal weight of authentic dibutyltin dichloride.

Benzene and *n*-butyl chloride were distilled from the clear filtrate from the precipitated dibutyltin oxide, leaving a residue of tetrabutyltin–tributyltin chloride mixture weighing 17.8 g. and containing 38% tin and 5.3% chlorine. This constituted a 16.9% tin conversion with 48.3% tributyltin chloride in the liquid organotin product mixture. Total tin conversion to organotin products was 25.5%.

A dark orange-brown benzene product solution from a second reaction similar to the above was treated with chlorine gas in the dark. The color was destroyed rapidly with evolution of heat, probably through formation of dibutyltin dichloride.

Dibutyltin dichloride. The quantity of stannic chloride necessary to convert 25 g. of a tetrabutytin–tributyltin chloride mixture to dibutyltin dichloride was calculated from the chlorine content of the mixture. The mixture contained 10.1% chlorine, or 92.6% tributyltin chloride. This corresponded to 0.0054 mole of tetrabutyltin and 0.0711 mole of tributyltin chloride. Consequently, 10.7 g. (0.0411 mole) of stannic chloride was pipetted into a 300 cc. flask fitted with a thermometer and reflux condenser and containing the butyltin mixture. The resulting mixture was heated from 160–207°C. over a period of 1.5 hr., after which the tan molten dibutyltin dichloride, obtained in essentially quantitative yield, was decanted into a distilling flask. A clear product was obtained on distillation; 94% of the charge was collected at 140–143°C. at 10 mm. pressure. Crystallization temperature of the distillate was 38.5°C. A small portion of the product, crystallized from petroleum ether, melted at 39.5–40°C. Identity of the product as dibutyltin dichloride was further verified by mixture melting point.

Baton Rouge 1, La.

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

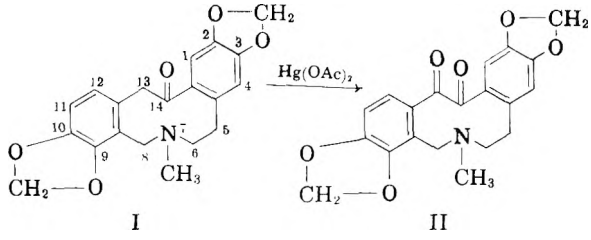
Structure of "Oxyprotopine" and Related Alkaloid Products

NELSON J. LEONARD AND RONALD R. SAUERS[1]

Received May 28, 1956

The structure of "oxyprotopine," the mercuric acetate oxidation product of the alkaloid protopine, has been established as 13-ketoprotopine. Structures have also been assigned to related alkaloid products.

Our interests in mercuric acetate oxidation of tertiary amines[2] and in transannular nitrogen-carbonyl interaction in medium-sized ring aminoketones[3] merged in a reinvestigation of the product "oxyprotopine," obtained by the mercuric acetate oxidation of the alkaloid protopine (I).[4] The $C_{20}H_{17}NO_6$ product, corresponding to a net loss of two hydrogens and gain of one oxygen with respect to protopine, was assigned the 5,14-diketo structure by Gadamer and Kollmar.



I II

(a, 2,3-Di-CH_3O- in place of 2,3-OCH_2O-,
b, 9,10-Di-CH_3O- in place of 9,10-OCH_2O-)

The evidence for their assignment cannot be considered convincing. Positions 6 and 8 were excluded as possibilities for the carbonyl group which was introduced on the basis of the reducibility of the $C_{20}H_{17}NO_6$ product with sodium amalgam to a "tetrahydroöxyprotopine," which was not fully characterized. Position 13 was excluded because of the failure of "oxyprotopine" to condense with *o*-phenylenediamine, although it might well be argued that the 13,14-diketone system would be expected to resist quinoxaline formation not only because of steric resistance to coplanarity but also because of decreased reactivity of the C-14 carbonyl due to transannular interaction (CH_3—$N^{\delta+}$----C=$O^{\delta-}$).[5] Moreover, the light yellow color of the $C_{20}H_{17}NO_6$ compound is strongly suggestive of a 13,14-diketone system, and the C-13 position presents the most highly activated methylene group for oxidative attack by mercuric acetate.

On the assumption that Gadamer's "oxyprotopine" was actually 13-ketoprotopine (II) rather than the 5-keto isomer, we assembled data which established structure II as correct. The ultraviolet absorption spectrum, determined in 95% ethanol (λ_{max} 317 mμ, log ε 3.93; 288 mμ, log ε 3.97), showed close similarity to that of the open analog, 3,3′,4,4′-bis-methylenedioxybenzil (λ_{max}^{EtOH} 324 mμ, log ε 4.12; 281 mμ, log ε 3.98),[6] and was good evidence for the skew-benzil system. Scale molecular models support the preferred residence of a 13,14-diketone system as in II in skew conformations.

Chemical proof of the adjacency of the carbonyl groups in "oxyprotopine" was provided by the following sequence. "Oxyprotopine" was reduced with a large excess of lithium aluminum hydride to a tetrahydro compound, $C_{20}H_{21}NO_6$, with properties similar to those reported by Gadamer and Kollmar[4] for their "tetrahydroöxyprotopine" and an infrared spectrum consistent with the diol structure III.[7]

The diol could be oxidized with periodic acid, and the resulting oxidation product was convertible to a dioxime. Satisfactory representation of the reaction sequence is found solely in the formulas III, IV, and V.

These results show clearly that the $C_{20}H_{17}NO_6$ product of the mercuric acetate oxidation of protopine is 13-ketoprotopine[8] and suggest that the

(1) Standard Oil Foundation, Inc. (Indiana) Fellow, 1955–56.

(2) For leading references, see N. J. Leonard, W. J. Middleton, Paul D. Thomas, and D. Choudhury, *J. Org. Chem.*, **21**, 344 (1956); N. J. Leonard and A. S. Hay, *J. Am. Chem. Soc.*, **78**, 1984 (1956).

(3) For leading reference, see N. J. Leonard and M. Öki, *J. Am. Chem. Soc.*, **77**, 6245 (1955).

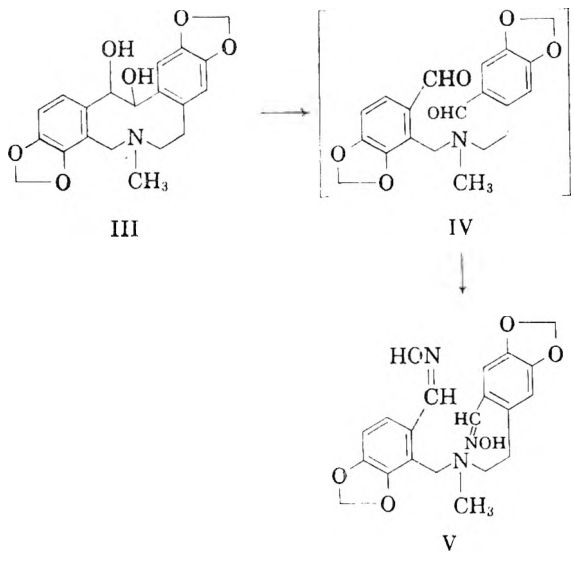
(4) J. Gadamer and H. Kollmar, *Arch. Pharm.*, **261**, 153 (1923).

(5) The low carbonyl reactivity in protopine and cryptopine was ascribed to such N—C$_{CO}$ interaction by W. O. Kermack and R. Robinson, [*J. Chem. Soc.*, **121**, 427 (1922)], and J. Gadamer [*Arch. Pharm.*, **258**, 148 (1920)]; J. Gadamer and F. von Bruchhausen [*Arch. Pharm.*, **260**, 97 (1922)] suggested that in the salt form the ten-membered ring of these alkaloids is transformed to two six-membered rings, with the nitrogen quaternary; *cf.* F. A. L. Anet, A. S. Bailey, and Sir Robert Robinson, *Chemistry and Industry*, 944 (1953); E. H. Mottus, H. Schwarz, and L. Marion, *Can. J. Chem.*, **31**, 1144 (1953); F. A. L. Anet and L. Marion, *Can. J. Chem.*, **32**, 452 (1954).

(6) N. J. Leonard, R. T. Rapala, H. L. Herzog, and E. R. Blout, *J. Am. Chem. Soc.*, **71**, 2997 (1949).

(7) The preservation of the oxygen functions in the presence of excess lithium aluminum hydride simultaneously ruled against location of the mercuric acetate–introduced carbonyl at either C-6 or C-8, in confirmation of the original Gadamer and Kollmar suggestion.

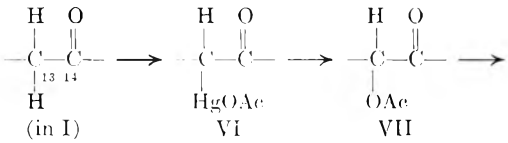
(8) Deuterium exchange reactions with protopine and "oxyprotopine" gave corroborative evidence for this structure assignment (see experimental).



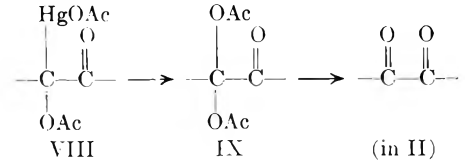
III IV V

products[4] of similar oxidation of the alkaloids cryptopine (Ia) and allocryptopine (Ib) are 13-ketocryptopine (IIa) and 13-ketoallocryptopine (IIb), respectively.

The course of the oxidation at C-13 may well involve a mercury-containing intermediate. The oxidation of cyclohexene with Hg^{++} has been shown to proceed through an intermediate mercurial.[9] Acetoxymercuration of the C-13,14 system (enol ?) could proceed in a manner (VI, VII) similar to that suggested by Barton and Rosenfelder[10] for the action of mercuric acetate on isodehydrocholesteryl *p*-nitrobenzoate. Parallel intermediates have been suggested for the conversion of the similarly activated methylene (Ar—CH_2—C(=N)—) in papaverine[11] to CHOH (papaverinol) and CO (papaveraldine), and the closely related 2-benzylpyridine has been shown to yield 2-pyridylphenylcarbinol on oxidation with mercuric acetate.[12] A repetition of the process (VI, VII) involving acetoxymercuration and replacement of HgOAc by OAc, represented schematically by VIII and IX, would lead logically to the C-13,14 diketone (II).



(in I) VI VII



VIII IX (in II)

Direct α-acetoxylation of less highly activated ketones has been realized under somewhat more vigorous conditions with mercuric acetate.[13,14]

EXPERIMENTAL[15]

Oxidation of protopine with mercuric acetate.[4] To a solution of 2.0 g. (5.7 mmoles) of protopine ($\lambda_{max}^{95\%\ EtOH}$ 293 mμ, log ϵ 3.93) in 20 ml. of water and 0.35 ml. of acetic acid, warmed to 75°, was added during 35 minutes a solution of 9.1 g. (29 mmoles) of mercuric acetate in 25 ml. of 1% acetic acid. After heating and stirring for an additional 30 min., the solution was cooled and filtered, whereupon 2.4 g. of mercurous acetate was collected. An additional 1.9 g. was obtained on heating for 4.5 hr. The excess mercuric acetate was then decomposed by heating with an excess of 98% formic acid. The filtered solution was basified with potassium carbonate and strong potassium hydroxide solution, followed by extraction with chloroform. The dried extracts were evaporated, yielding 1.5 g. of a yellow powder. The product was chromatographed on alumina. A yellow crystalline solid (380 mg., 18%), m.p. 227–230°, was obtained in the ether-acetone eluates. Further elution gave only oily material. The solid was recrystallized from acetone, m.p. 229–230° (reported,[4] 225°).

Anal. Calc'd for $C_{20}H_{17}NO_6$: C, 65.39; H, 4.66; N, 3.81. Found: C, 65.38; H, 4.61; N, 3.56.

The infrared spectrum (chloroform) showed carbonyl absorption at 1668 cm.$^{-1}$ with a shoulder at *ca.* 1680 cm.$^{-1}$.

The nitrate salt was made in water and was recrystallized from methanol-water, m.p. 270–271° (dec.) (reported,[4] 274–275°).

Anal. Calc'd for $C_{20}H_{18}N_2O_9$: C, 55.81; H, 4.22. Found: C, 55.47; H, 4.49.

The infrared spectrum (Nujol) showed two bands in the O—H stretching region: 3620 cm.$^{-1}$ and 3480 cm.$^{-1}$ The carbonyl stretching band appeared at 1701 cm.$^{-1}$ The spectrum appears consistent with the transannular bonded form of the salt as a solid.

Deuterium exchanges. A solution of 100 mg. of protopine with 1.0 g. of sodium methoxide in 3 ml. of deuterium oxide was heated under reflux for 42 hr. The aqueous solution was extracted five times with chloroform, and the chloroform extracts were dried. Evaporation of the chloroform yielded 85 mg. of a tan powder which melted at 206–208° after drying overnight in an Abderhalden. The infrared spectrum (chloroform) showed three weak bands in the C—D stretching region. A few minor changes appeared in other sections of the protopine spectrum.

Anal. Calc'd for $C_{20}H_{17}D_2NO_5$: D, 10.5 atom %. Found: 8.5 atom %.

Under the same conditions 100 mg. of 13-ketoprotopine yielded a tarry solution from which 50 mg. of a tan powder was extracted, m.p. 220–223° (dec.). The infrared spectrum showed no appreciable absorption in the C—D stretching region and was otherwise very similar to that of pure ketoprotopine.

Anal. Found: 3.5 atom % D.

(9) D. A. Shearer and G. F. Wright, *Can. J. Chem.*, **33**, 1002 (1955); see also H. J. Lucas, F. R. Hepner, and S. Winstein, *J. Am. Chem. Soc.*, **61**, 3102 (1939).

(10) D. H. R. Barton and W. J. Rosenfelder, *J. Chem. Soc.*, 2381 (1951).

(11) J. Gadamer, *Arch. Pharm.*, **253**, 274 (1915).

(12) R. Anker, A. Cook, and I. Heilbron, *J. Chem. Soc.*, 917 (1945).

(13) W. Treibs and H. Bast, *Ann.*, **561**, 165 (1949).

(14) P. R. Jefferies, A. K. Macbeth, and B. Milligan, *J. Chem. Soc.*, 705 (1954).

(15) Eastman protopine was used without further purification. Melting points are corrected. Deuterium analyses were performed by Mr. Joseph Nemeth by the falling drop method.

Under these similar conditions, including the arbitrary reaction time, only II among the possible dicarbonyl structures could be expected to take up less deuterium than I, and the relative figures for deuterium content can be taken therefore as qualitatively significant.

Reduction of 13-ketoprotopine with lithium aluminum hydride.[16] To a slurry of 150 mg. (4 mmoles) of lithium aluminum hydride in 30 ml. of dry ether was added rapidly 230 mg. (0.63 mmole) of 13-ketoprotopine in 30 ml. of dry benzene. After stirring for 11 hours at 25° the mixture was decomposed with 10 ml. of 6*N* hydrochloric acid. The aqueous phase was basified with saturated potassium carbonate solution and extracted with methylene chloride. The dried extracts were evaporated to a gray powder, from which 122 mg. (52%) of colorless prisms (III) were obtained on crystallization from acetone, m.p. 257–259° (dec.). Gadamer[4] reported a melting point of 255–256° for "tetrahydroöxyprotopine."

Anal. Calc'd for $C_{20}H_{21}NO_6$: C, 64.68; H, 5.70; N, 3.77. Found: C, 64.67; H, 5.85; N, 3.66.

The infrared spectrum in Nujol showed strong OH absorption at 3260 cm.$^{-1}$ and no carbonyl absorption.

Oxidation of tetrahydroketoprotopine with periodic acid.[17] A solution of 81 mg. (0.22 mmole) of the diol in 0.4 ml. of 1*N* H_2SO_4 was treated with a solution of 50 mg. of periodic acid in 0.8 ml. of water. The resulting solution was allowed to stand at 25° for 27 hr. Basification with saturated potassium carbonate solution was followed by ether extraction. The dried extracts were evaporated to give 64 mg. of a gray powder. The infrared spectrum in Nujol showed carbonyl absorption at 1678 cm.$^{-1}$, characteristic of an aromatic aldehyde (IV).

The powder was treated with 0.5 ml. of methanol followed by 0.5 ml. of 1*N* sodium hydroxide solution and 30 mg. of hydroxylamine hydrochloride. About 50 mg. of dioxime was obtained after 3 hr. at 25°. The dioxime (V) was washed with hot 90% ethanol and dried in vacuum at room temperature (to avoid decomposition), m.p. 209°.

Anal. Calc'd for $C_{20}H_{21}N_3O_6.H_2O$: C, 57.55; H, 5.55; N, 10.07. Found: C, 57.45; H, 5.15; N, 9.50.

The ultraviolet spectrum in 95% ethanol showed maxima at 272 mμ (log ε 4.26) and 306 mμ (log ε 4.09). The values reported by Russell[17] for the dimethoxy analog (Vb) are: 270 mμ (log ε 4.32) and inflexion at 290–310 mμ (log ε 4.00).

URBANA, ILL.

(16) R. Mirza, *Experientia*, **8**, 258 (1952).

(17) P. B. Russell, *J. Am. Chem. Soc.*, **78**, 3115 (1956).

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

Ester Derivatives of Mucic Acid[1]

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Received July 23, 1956

The reaction of "mucic acid lactone" with ethanol and methanol produced monoesters of mucic acid, which were purified and characterized as the tetraacetyl derivatives. Monoethyl mucate was also prepared, in impure form, by partial hydrolysis of the diethyl ester. Tetraacetylmucic acid and one mole of diazomethane gave mainly the dimethyl ester. Mucic acid or tetraacetylmucic acid and one mole of silver nitrate gave the respective disilver salts.

A derivative of mucic acid in which the hydroxyl groups and one carboxyl group are esterified, such as monoethyl tetraacetylmucate, was desired as the starting point for a projected synthesis of inositol.[1] The monoesters of dicarboxylic acids are usually prepared by treatment of the appropriate cyclic anhydride with one mole of alcohol, but this type of compound is not available in the case of mucic acid. Therefore, the preparation of monoethyl mucate was first attempted by partial hydrolysis of the diethyl ester.

A mixture of one mole of diethyl mucate with one mole of potassium hydroxide became neutral in a very short time. Rapid evaporation of the solution to dryness and treatment of the residue with the calculated amount of 1 *M* hydrochloric acid gave a white solid, m.p. 177–179°, with a neutralization equivalent of 200 and a saponification equivalent of 117. Saponification produced mucic acid quantitatively. It appears, accordingly, that the solid was a mixture of 84% monoethyl mucate and 16% mucic acid. Unfortunately, this product could not easily be purified by recrystallization; water would cause some hydrolysis, and all other liquids tried were not sufficiently good solvents.

Monoethyl mucate could be prepared, in somewhat purer form, from Fischer's[4] "mucic acid lactone." This viscous liquid, obtained from an aqueous solution of mucic acid by rapid evaporation to dryness, is, likely, a mixture of lactones and intermolecular esters. From a solution of this substance in anhydrous ethanol there separated, in the course of several days, crystals of monethyl mucate mixed with a little mucic acid, of neutralization equivalent 211. Further purification was effected by first converting this product to the tetraacetyl derivative, which could be purified by crystallization from ethanol, m.p. 181–183°.

Monomethyl mucate was obtained similarly from a solution of mucic acid in anhydrous methanol. Acetylation of the crude ester and crystalliza-

(1) Abstracted from a thesis submitted by M. D. Bealor in partial fulfillment of the requirements for the Ph.D. degree, University of Oregon, June 1956.

(2) Present address, Niagara Chemical Division, Research Department, Middleport, N. Y.

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(4) Fischer, *Ber.*, **24**, 2141 (1891).

tion from toluene gave monomethyl tetraacetylmucate, m.p. 169–172°. Treatment of this compound with diazomethane gave a good yield of dimethyl tetraacetylmucate, identical with the product prepared by the acetylation of dimethyl mucate.

Treatment of the mucic acid lactone with ethanolic hydrogen chloride, gave, even at 10°, a good yield of diethyl mucate.

The preparation of monoesters of mucic acid was also attempted in ways which were not successful. It had been expected that, in dimethyl or diethyl tetrabenzoylmucate, one alkyl ester group would be preferentially hydrolyzed. Accordingly, both dimethyl and diethyl tetrabenzoylmucate were prepared and treated with one mole of dilute ethanolic potassium hydroxide; it was found, however, that at least half of the base was converted to potassium benzoate, while part of the tetrabenzoyl diester was recovered unchanged.

Disodium mucate and disodium tetraacetylmucate were treated with one mole of silver nitrate in the hope of obtaining the mixed silver sodium salt, which might be converted to the half-ester by reaction with methyl iodide. However, this method of preparation gave the disilver salts. In these circumstances solubility determines the nature of the products, and the disilver salt, apparently the less soluble, separates first.

Finally, partial esterification of tetraacetylmucic acid was attempted, using one mole of diazomethane in ethanol. A good yield of dimethyl tetraacetylmucate was obtained (91% based on diazomethane); it would seem that the half-esterified product reacts faster than tetraacetylmucic acid, although why this should happen is not clear. The product was identical with that prepared by acetylation of dimethyl mucate.

EXPERIMENTAL[5,6]

Partial hydrolysis of diethyl mucate. Diethyl mucate (1.33 g., 0.005 mole) in 18 ml. of water was mixed with 19.4 ml. of 0.258 *M* potassium hydroxide (0.005 mole). After mixing, the *p*H of the solution was 6.4. The solution was evaporated to dryness under reduced pressure and the residue triturated with 5.00 ml. of 1.012 *M* hydrochloric acid (0.005 mole). The solid was collected, washed with 3 ml. of water to remove potassium chloride, and dried; m.p. 177–179°; yield 0.70 g. (59%).

Anal. Calc'd: Neut. Equiv. 238.2; Sapon. Equiv. 119.1. Found: Neut equiv. 200; Sapon. Equiv. 117.

Attempts to characterize this compound as the benzylthiouronium salt and the *p*-bromophenacyl ester were unsuccessful.[7]

Monoethyl mucate. Fischer's[4] "mucic acid lactone" (5.2 g.) in 25 ml. of anhydrous ethanol was kept at room temperature for 6 days; a white solid separated slowly, m.p. 174–176°. Yield 1.15 g.

Anal. Calc'd: Neut. Equiv. 238.2. Found: 211 (the neutralization equivalent indicates a mixture of 90% monoethyl mucate and 10% mucic acid).

Monoethyl tetraacetylmucate. Monoethyl mucate (2.3 g.), acetic anhydride (25 g.) and 5 drops of concentrated sulfuric acid were placed in a 50 ml. flask equipped with a reflux condenser. The mixture was gently refluxed for 30 min., and the resulting clear solution evaporated under reduced pressure to 15 ml. The solid which precipitated was collected, washed with acetic anhydride, dried, and crystallized twice from 95% ethanol; white needles, m.p. 181–183°. Yield 0.5 g. (12%).

Anal. Calc'd for $C_{16}H_{22}O_{12}$: C, 47.29; H, 5.46. Found: C, 46.78, H. 5.43.

Monomethyl mucate. Mucic acid lactone (8.64 g.) in 45 ml. of anhydrous methanol was kept at room temperaure for 6 days; a white solid separated, m.p. 188–190° (dec.). Yield 1.5 g.

Anal. Calc'd: Neut. Equiv. 224.2. Found: 191 (the neutralization equivalent indicates a mixture of 85% monomethyl mucate and 15% mucic acid).

Monomethyl tetraacetylmucate. Monomethyl mucate (1.5 g.), acetic anhydride (10.2 g.) and 2 drops of concentrated sulfuric acid were placed in a 25-ml. flask equipped with a reflux condenser. The mixture was refluxed gently for 30 min. and the clear solution was then evaporated to dryness at reduced pressure. The residue was crystallized twice from toluene; white needles, m.p. 169–172°. Yield 0.8 g. (32%).

Anal. Calc'd for $C_{15}H_{20}O_{12}$: C, 45.92; H, 5.14. Found: C, 46.03; H, 5.23.

Reaction of "mucic acid lactone" with ethanolic hydrogen chloride. Mucic acid lactone (7.0 g.) in 100 ml. of absolute ethanol was chilled in an ice-salt bath and saturated with hydrogen chloride. After standing for one day at 10° C. a precipitate of white needles had formed; m.p. 161–163°. Yield 6.1 g. (63%). The m.p. was not depressed on admixture with an authentic sample of diethyl mucate.[8]

Diethyl tetrabenzoylmucate. Diethyl mucate[8] (2.66 g.) and 25 ml. of anhydrous pyridine were warmed until a clear solution resulted. After cooling to room temperature, 7.00 g. of benzoyl chloride was added slowly; the mixture became warm and light red in color, and some solid precipitated. The reaction mixture was poured into 50 ml. ice water and the solution neutralized with 8.5 g. of sodium bicarbonate; the precipitate was collected, washed, first with 5% sodium bicarbonate solution and then with water, dried, and crystallized twice from 95% ethanol; feathery white needles, m.p 151–152.5°. Yield 4.85 g. (70%).

Anal. Calc'd for $C_{38}H_{34}O_{12}$: C, 66.83; H, 5.00. Found: C, 66.98; H, 5.13.

Dimethyl mucate. This compound was prepared according to the procedure of Fischer and Speier[8] from mucic acid, anhydrous methanol, and hydrogen chloride, m.p. 193–195° (dec.). Reported[9] m.p. 165–167° (dec.).

Anal. Calc'd: Sapon. Equiv. 119.1. Found: 120.0.

Dimethyl tetrabenzoylmucate. Dimethyl mucate (11.9 g.), 275 ml. of anhydrous pyridine and 42.0 g. of benzoyl chloride, by the same procedure used for diethyl tetrabenzoylmucate, gave a solid which was crystallized from 95% ethanol acetone; white powder, m.p. 169.8–170.8°. Yield 8.8 g. (27%).

Anal. Calc'd for $C_{36}H_{30}O_{12}$: C, 66.05; H, 4.62. Found: C, 66.20; H, 4.71.

Hydrolysis of diethyl tetrabenzoylmucate. Diethyl tetrabenzoylmucate (3.41 g., 0.005 mole), 200 ml. of absolute ethanol and 20 ml. of 0.25 *M* alcoholic potassium hydroxide (0.005 mole) were placed in a 500 ml. flask equipped with a reflux condenser and the mixture was refluxed 16 hr. Five ml. of 1.00 *M* hydrochloric acid (0.005 mole) was added;

(5) All melting points are corrected capillary tube melting points.

(6) Carbon and hydrogen analyses were done by Micro-Tech Laboratories, 8000 Lincoln Ave., Skokie, Ill.

(7) Shriner and Fuson, *Identification of Organic Compounds*, 3rd ed., John Wiley and Sons, Inc., New York, 1948, pp. 157, 159.

(8) Fischer and Speier, *Ber.*, 28, 3252 (1895).

(9) Curtius, *J. prakt. Chem.*, [2] 95, 244 (1917).

the solution was evaporated under reduced pressure to 25 ml., diluted with 100 ml. of water, and chilled. The precipitate was collected on a filter, washed with water, and dried; m.p. 120–122°. The m.p. was not depressed on admixture with an authentic sample of benzoic acid. Yield 0.3 g. (50% based on potassium hydroxide).

Anal. Calc'd: Neut. Equiv. 122.1. Found: 122.2.

Further chilling of the mother liquor caused a second precipitate to form. Yield 2.05 g. (60%), m.p. and mixed m.p. with an authentic sample of diethyl tetrabenzoylmucate, 150–152°.

Hydrolysis of dimethyl tetrabenzoylmucate. In a 500-ml. flask equipped with a reflux condenser were placed dimethyl tetrabenzoylmucate (3.27 g., 0.005 mole), 200 ml. of anhydrous methanol, and 20 ml. of 0.25 *M* methanolic potassium hydroxide (0.005 mole). The mixture was heated under reflux for 12 hr. and the *p*H was then 6.8. Five ml. of 1.00 *M* hydrochloric acid (0.005 mole) was added, the solution was evaporated under reduced pressure to 50 ml., and chilled. The precipitate was collected and dried. Yield 1.63 g. (50%). Melting point and mixed melting point with an authentic sample of dimethyl tetrabenzoylmucate was 168–170°.

The mother liquor was diluted with 100 ml. of water and chilled. The precipitate was collected and washed with water. Yield 0.24 g. (40% based on potassium hydroxide); m.p. and mixed m.p. with an authentic sample of benzoic acid, 119–122°.

Anal. Calc'd: Neut. Equiv. 122.1. Found: 123.0.

Reaction of disodium mucate with one mole of silver nitrate. To 100 ml. of 0.103 *M* sodium hydroxide (0.01 mole) was added 1.05 g. of mucic acid (0.005 mole), and the mixture was warmed. To the resulting clear solution was added a solution of 0.842 g. of silver nitrate (0.005 mole) in 25 ml. of water. The fine white solid which precipitated was separated by centrifugation, washed with water and acetone, and dried. Yield 2.1 g. (90% based on silver nitrate).

Anal. Calc'd for $C_6H_8O_8Ag_2$: Ag, 50.90. Found: Ag, 49.63.

Reaction of disodium tetraacetylmucate with one mole of silver nitrate. To 50 ml. of 0.103 *M* sodium hydroxide (0.0052 mole) was added 0.98 g. of tetraacetylmucie acid[10] (0.0026 mole), and the mixture was warmed. To the resulting clear solution was added a solution of 0.438 g. of silver nitrate (0.0026 mole) in 15 ml. of water. The fine white solid which precipitated was separated by centrifugation, washed with water and acetone, and dried. Yield 0.5 g. (65% based on silver nitrate).

(10) Skraup, *Monatsh.* **14**, 488 (1893).

Anal. Calc'd for $C_{14}H_{16}O_{12}Ag_2$: Ag, 36.44. Found: Ag, 36.20.

Dimethyl tetraacetylmucate. Dimethyl mucate (2.38 g.), 20 g. of acetic anhydride and 5 drops of concentrated sulfuric acid were placed in a 50-ml. flask equipped with a reflux condenser and the mixture was heated to just under reflux for 30 min. The solid which precipitated on cooling was collected, washed with ethyl acetate, dried, and crystallized from absolute ethanol; white needles, m.p. 195.8–196.6°. Yield 10 g. (25%).

Anal. Calc'd for $C_{16}H_{22}O_{12}$: C, 47.29; H, 5.46. Found: C, 47.31; H, 5.65.

Reaction of monomethyl tetraacetylmucate with diazomethane. To monomethyl tetraacetylmucate (0.50 g.) in 25 ml. of absolute ethanol was added, with swirling, a solution of diazomethane[11] (0.73 g.) in 15 ml. of benzene. The solid which precipitated on cooling was collected, dried, and crystallized from absolute ethanol; white needles, m.p. 195–196°. Yield 0.36 g. (65%). The melting point was not depressed on admixture with a sample of dimethyl tetraacetylmucate prepared as described above.

Reaction of tetraacetylmucic acid with one mole of diazomethane. In a 200-ml. flask equipped with a stirrer, reflux condenser, and dropping funnel were placed 3.78 g. of tetraacetylmucie acid[10] (0.01 mole) and 75 ml. of absolute ethanol. To the clear solution was added dropwise over a period of 30 min. a solution of 0.42 g. of diazomethane (0.01 mole) in 30 ml. of ether, prepared and standardized according to Arndt.[11] The solid which precipitated after chilling was collected, washed with ethanol, and dried; m.p. 190–193°. Yield 1.85 g. (91% based on diazomethane). The melting point was not depressed on admixture with an authentic sample of dimethyl tetraacetylmucate. Concentration of the mother liquor to one half its volume and chilling yielded 1 g. (26.5%) of starting material.

Acknowledgments. The authors wish to thank the Graduate School, University of Oregon, and The Society of The Sigma Xi for grants-in-aid which made this work possible.

EUGENE, ORE.

(11) Arndt, *Org. Syntheses*, Coll. Vol. II, 165–166, 461 (1943).

[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY AND PHARMACOLOGY, ST. LOUIS UNIVERSITY]

Monoquaternary Muscle Paralyzing Agents. I. Synthesis of Quaternary N-(ω-Piperidinoalkyl)-phthalimides[1,2]

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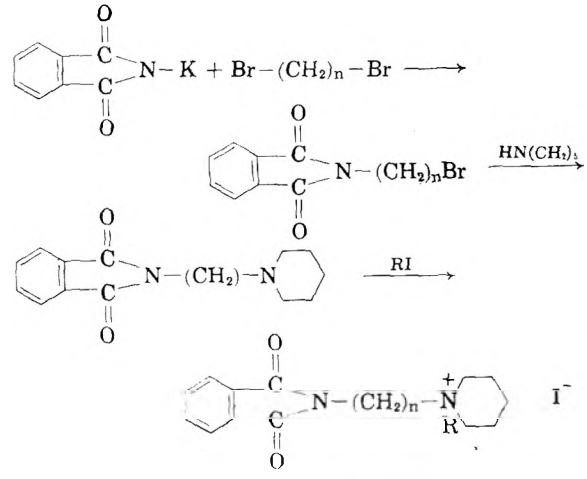
Received Aug. 9, 1956

A series of monoquaternary N-(ω-piperidinoalkyl)-phthalimides has been prepared *via* the intermediate N-(ω-bromoalkyl)-phthalimides. The complete homologous series showed oscillation of melting points and a gradual decrease in water solubility with increasing chain length. Maximum biological activity as striated muscle paralyzing agents resulted when the methylene chain between the quaternary nitrogen and the nitrogen of the phthalimide groups was 7 to 9 carbons in length. The most active compound had approximately $^1/_{10}$ the activity of *d*-tubocurarine in frogs.

In recent years, many new synthetic muscle paralyzants have been prepared based on the structure of *d*-tubocurarine. Although the *bis*-quaternary ammonium structure is a usual prerequisite to high curarelike activity, one of the authors[6] observed that monoquaternary N-(dialkylaminoalkyl)-phthalimides were quite active. Since there are few precedent reports in the literature[7,8] concerning highly active monoquaternary curarelike compounds, it was decided to study the effect on biological activity of various structural modifications of such compounds. The effect of varying (1) the distance between the quaternary nitrogen and the nitrogen of the phthalimide group and (2) the size of the quaternary ammonium group is reported in this paper.

With the exception of the monomethylene free base which was prepared *via* the Mannich reaction according to the method of Moore and Rapala,[9] the following reaction scheme was employed.



Most of the preparations proceeded without difficulty and the expected product was isolated in each case. Although the crude yields were good, considerable difficulty was experienced in obtaining analytically pure samples and the yields reported in Tables I and II can be attained only when carefully purified intermediates are used.

The N-(ω-bromoalkyl)-phthalimides were prepared from potassium phthalimide and a three-to fourfold excess of the appropriate dibromoalkane. The addition of a small amount of dimethylformamide to the reaction mixture decreased the time and temperature usually employed in the Gabriel synthesis but did not materially improve the yield. In addition to small amounts of the *bis*-phthalimidoalkane, the desired product was always accompanied by unidentified oily side products which, in the case of the lower melting members of the series, were extremely difficult to remove. Except for the heptamethylene homolog, the products were low melting white solids. The N-(ω-bromononyl)-phthalimide is previously unreported.

The N-(ω-bromoalkyl)-phthalimides reacted smoothly with excess piperidine in benzene to yield the tertiary free base which was then isolated as the hydrochloride salt. The salt of the monomethylene free base decomposed when heated in solution to give back phthalimide, formaldehyde and piperidine and the pure product was therefore obtained in poor yield. Quaternization of the free bases were readily effected and the crude yields were for the most part quantitative.

Each homologous series exhibited an oscillation of melting points which was closely paralleled by the water solubility, the maximum being reached at $n = 4$. In some instances, especially in the cases of

(1) Presented in part at the 123rd Meeting of the AMERICAN CHEMICAL SOCIETY, Los Angeles, Calif., March 1953.

(2) This work was supported by a Frederick Gardner Cottrell Grant from Research Corporation and was taken from a portion of the Ph.D. dissertations of Sr. Mary Marguerite Christine Neumann, B.V.M. (1954) and Robert J. Seiwald (1954).

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(5) Present address, Raymond Blank Memorial Hospital for Children, Des Moines 14, Iowa.

(6) Kazuo K. Kimura, Ph.D. thesis, University of Illinois, 1949.

(7) Marsh and Herring, *J. Pharmacol. and Exper. Therap.*, **101**, 26 (1951).

(8) Cavallito, Soria, and Hoppe, *J. Am. Chem. Soc.*, **72**, 2661 (1950).

(9) Moore and Rapala, *J. Am. Chem. Soc.*, **68**, 1657 (1946).

TABLE I

N-(ω-PIPERIDINOALKYL)-PHTHALIMIDES AND HYDROCHLORIDES

o-$C_6H_4(CO)_2N$-$(CH_2)_n$-NC_5H_{10}

n	M.P., °C.	Formula	Analyses Carbon Calc'd	Carbon Found	Hydrogen Calc'd	Hydrogen Found	HCl M.P., °C.	Yield,[a] %	Analyses Chlorine Calc'd	Chlorine Found
1	117–118[b]	$C_{14}H_{16}N_2O_2$					185–187[b]	30	12.7	12.4
2	89–90[c]	$C_{15}H_{18}N_2O_2$					241–243	69	12.0	11.9
3	49–50[d]	$C_{16}H_{20}N_2O_2$					232–234	76	11.5	11.5
4	70	$C_{17}H_{22}N_2O_2$	71.29	71.38	7.74	7.93	228	85	11.0	10.9
5	61–62	$C_{18}H_{24}N_2O_2$	71.97	72.20	8.05	7.99	183	79	10.5	10.5
6	69	$C_{19}H_{26}N_2O_2$	72.57	72.80	8.34	8.26	183–184	89	10.1	10.1
7	65	$C_{20}H_{28}N_2O_2$	73.13	73.26	8.59	8.52	170	45	9.72	9.80
8	56	$C_{21}H_{30}N_2O_2$	73.64	74.09	8.83	8.72	161–162	81	9.37	9.43
9	50.5–51.5	$C_{22}H_{32}N_2O_2$	74.12	74.11	9.05	9.24	129–131	80	9.04	9.08
10	59–60	$C_{23}H_{34}N_2O_2$	74.55	74.82	9.25	9.21	116–118	71	8.71[e]	8.37
11	52	$C_{24}H_{36}N_2O_2$	74.96	75.29	9.43	8.99	138	75	8.32	8.32

[a] All yields calculated on basis of hydrochlorides. [b] Reported previously by Moore and Rapala, *J. Am. Chem. Soc.*, 68, 1657 (1946). [c] Kermack and Smith, *J. Chem. Soc.*, 3096 (1931) report 91°. [d] Braun, *Ber.*, 42, 2051 (1909) reported 50°. [e] Calc'd for monohydrate: Cl, 8.35.

TABLE II

N-(ω-PIPERIDINOALKYL)-PHTHALIMIDE ALKYL IODIDES

o-$C_6H_4(CO)_2N$-$(CH_2)_n$-NC_5H_{10}.RI

n	M.P., °C	Yield, %	Formula	Analyses Carbon Calc'd	Carbon Found	Hydrogen Calc'd	Hydrogen Found	Iodine Calc'd	Iodine Found	FROG MPD,[a] Mg./Kg.
(Methiodides, R = CH_3)										
1	199–200	73	$C_{15}H_{19}IN_2O_2$	46.64	46.94	4.96	5.21	32.8	32.7	>400
2	262–263	86	$C_{16}H_{21}IN_2O_2$	48.01	48.04	5.29	5.03	31.7	31.6	>400
3	257–258	64	$C_{17}H_{23}IN_2O_2$	49.28	49.47	5.59	5.84	30.6	30.6	200
4	290–291	93	$C_{18}H_{25}IN_2O_2$	50.49	50.78	5.88	5.70	29.6	29.7	30
5	188	80	$C_{19}H_{27}IN_2O_2$	51.60	51.83	6.15	6.15	28.7	28.7	25
6	167	74	$C_{20}H_{29}IN_2O_2$	52.63	52.52	6.40	6.28	27.9	28.0	20
7	131–132	96	$C_{21}H_{31}IN_2O_2$	53.62	53.76	6.64	6.55	27.0	27.2	25
8	134	99	$C_{22}H_{33}IN_2O_2$	54.55	54.66	6.84	6.82	26.2	26.2	20
9	106–107	71	$C_{23}H_{35}IN_2O_2$	55.41	55.68	7.08	6.90	25.5	25.4	20
10	137.5	56	$C_{24}H_{37}IN_2O_2$	56.24	56.32	7.28	7.44	24.8	25.0	100
11	99	98	$C_{25}H_{39}IN_2O_2$	57.02	57.16	7.47	7.46	24.2	24.1	200
(Ethiodides, R = C_2H_5)										
1	198–199	41	$C_{16}H_{21}IN_2O_2$	48.01	48.02	5.29	5.35	31.7	31.7	>400
2	234–235	80	$C_{17}H_{23}IN_2O_2$					30.6	30.5	200
3	199–200	43	$C_{18}H_{25}IN_2O_2$	50.49	50.40	5.88	6.46	29.6	29.3	60
4	263–264	72	$C_{19}H_{27}IN_2O_2$	51.60	51.68	6.15	5.96	28.7	28.4	40
5	162	73	$C_{20}H_{29}IN_2O_2$					27.9	27.9	20
6	147–148	88	$C_{21}H_{31}IN_2O_2$	53.60	53.17	6.64	6.15	27.0	27.0	20
8	106–107	58	$C_{23}H_{35}IN_2O_2$	55.41	55.68	7.08	7.04	25.5	25.4	40
10	92–93	79	$C_{25}H_{39}IN_2O_2$	57.02	57.03	7.47	7.42	24.2	24.4	120
(Benzyliodides, R = $C_6H_5CH_2$)										
4	262	91	$C_{24}H_{29}IN_2O_2$					25.2	25.4	80
5	196–196.5	72	$C_{25}H_{31}IN_2O_2$					24.5	24.4	60
6	151[b]	70	$C_{26}H_{33}IN_2O_2$					23.8	23.7	>100
d-Tubocurarine chloride (DTC)										2

[a] MPD = minimum paralyzing dose (lymph-sac injection). [b] Forms dihydrate from 95% ethanol, m.p. 90–100°, Calc'd: I, 22.3. Found: I, 22.2.

the five and six carbon compounds, a sintering point accompanied by a color change was observed preliminary to the actual melting point.

PHARMACOLOGIC RESULTS

All quaternary ammonium salts were screened for paralyzing activity in frogs (*Rana pipiens*) by lymph sac injections of 200, 40, and 5 mg./kg. doses. Intermediate dose levels were used to obtain the minimal paralyzing dose. Paralyzed frogs were checked for specificity of muscle paralysis at the neuromyal junction by direct and indirect stimulation of the sciatic nerve. The minimum paralyzing dose (MPD, Table II) of the drugs tested varied from 20 to 400 mg./kg.

A pronounced change in activity resulted when

the number of carbon atoms between the quaternary ammonium group and the phthalimide group was varied. In both series, activity was low until $n = 4$, at which point it abruptly rose until a broad maximum was reached at $n = 7$, 8, and 9. As the chain length was further increased, the activity gradually diminished. It appears, therefore, that there is no critical distance, other than the minimal, between the quaternary ammonium and phthalimide portions of the molecule. Although this does not rule out bond formation between the receptor site and the phthalimide portion of the molecule, the fit must be less specific than that of the *bis*-quaternary ammonium compounds related to *d*-tubocurarine whose nitrogen to nitrogen distance is much more critical.[10]

The "umbrella effect" to which Pfeiffer[11] ascribed the activity of *d*-tubocurarine may also afford a satisfactory explanation for the activity of these monoquaternary salts. The quaternary ammonium portion of the molecule may bond to the receptor sites in a manner similar to *d*-tubocurarine while the large phthalimide nucleus screens the surrounding receptor sites from the approach of the acetylcholine molecules.

Little difference is noted between piperidinomethyl and piperidinoethyl groups on the quaternary nitrogen. Substitution with the bulky benzyl group results in a series with diminished activity. A complete pharmacological report will be presented elsewhere.

(10) Barlow and Ing, *Brit. J. Pharmacol.*, **3**, 298 (1948).
(11) Pfeiffer, *Science*, **107**, 94 (1948).

EXPERIMENTAL[12]

N-(ω-bromononyl)-phthalimide. A mixture of 8.45 g. (0.05 mole) of potassium phthalimide, 57.2 g. (0.2 mole) of 1,9-dibromononane and 3.3 g. (5% by weight) of dimethylformamide was heated at 160° for 1.5 hrs. The solution was filtered to remove precipitated potassium bromide. The filtrate was heated to distill the dimethylformamide and the excess dibromononane removed under reduced pressure. The residue was fractionated under reduced pressure using a free flame and the solid portions of the distillate recrystallized from ethanol. With slight variations in procedure the yield of pure product varied from 40–78%. The analytical sample was first purified on alumina and then recrystallized repeatedly from ethanol, m.p. 37.5°.

Anal. Calc'd for $C_{17}H_{22}BrNO_2$: C, 57.96; H, 6.30. Found: C, 58.08; H, 6.17.

N-(ω-piperidinoalkyl)-phthalimides. A solution of 0.01 mole of the appropriate N-(ω-bromoalkyl)-phthalimide and 3.4 g. (0.04 mole) of piperidine in 30 ml. of benzene was heated on the steam bath for 1 hr. The benzene and excess piperidine were removed under reduced pressure and the residue dissolved in ether. The solution was filtered to remove piperidine hydrobromide and decolorized with charcoal. The dried solution was saturated with hydrogen chloride gas and the white crystalline salt collected on a funnel, washed with ether, and dried.

The free base was liberated from an aqueous solution of the hydrochloride salt with cold sodium carbonate solution. The product was recrystallized from 30–60° petroleum ether.

N-(ω-piperidinoalkyl)-phthalimide alkyl iodides. A solution of 0.005 mole of the N-(ω-piperidinoalkyl)-phthalimide and 0.05 mole of the appropriate alkyl iodide in 100 ml. of dry ether was allowed to stand overnight at room temperature. The precipitated quaternary salt was removed by filtration and the filtrate allowed to stand until no more product was formed. The quaternary salts were recrystallized from either absolute ethanol or isopropanol.

ST. LOUIS, MO.

(12) Analyses are by Du-Good Chemical Laboratory, St. Louis, Mo., and Clark Microanalytical Laboratory, Urbana, Ill. All melting points are corrected.

[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, UNIVERSITY OF MADRAS]

Synthesis of DL-α-Amino-β-(1-skatyl)propionic Acid

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Received Aug. 13, 1956

Skatole has been found to undergo the Mannich reaction with formalin and dimethylamine to give 1-dimethylaminomethylskatole. The methiodide of this base alkylates ethyl acetamidocyanoacetate. The alkylated product after treatment with alkali furnishes DL-α-amino-β-(1-skatyl) propionic acid, a new methyl analog of tryptophan.

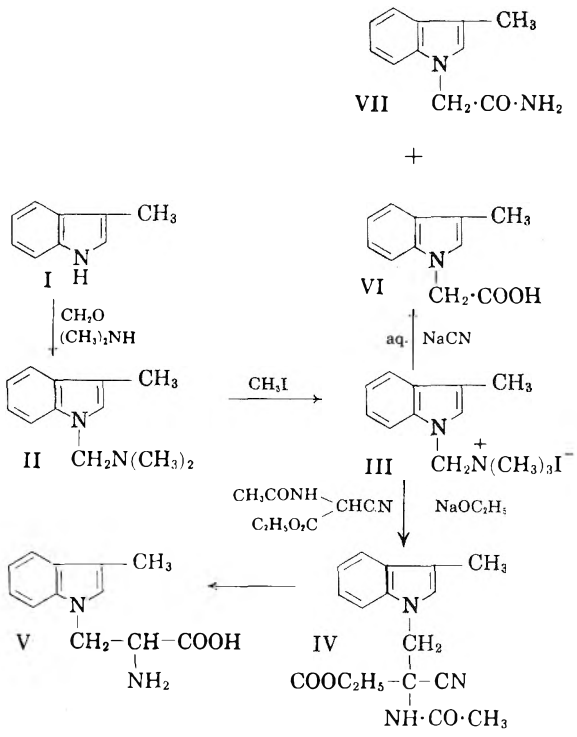
Since the elegant synthesis of tryptophan[1] by ethyl acetamidomalonate with gramine, many analogs of tryptophan have been synthesized with a view to studying their antimetabolite properties. Methyl tryptophans and methyl isotryptophans have been of particular interest in this connection and 1,2,4,5,6, and 7 methyl tryptophans[2a] and 6-methyl-2-isotryptophan[2b] have been prepared. It was of interest to synthesize 3-methyl-1-isotryptophan, *viz.*, α-amino-β-(1-skatyl)propionic acid (V) in

(1) Snyder and Smith, *J. Am. Chem. Soc.*, 66, 350 (1944); Albertson, Archer, and Suter, *J. Am. Chem. Soc.*, 66, 500 (1944).

(2a) Anderson, *Science*, **101**, 565 (1945); Jackman and Archer, *J. Am. Chem. Soc.*, 68, 2105 (1946); Rydon, *J. Chem. Soc.*, 705 (1948); Snyder and Pilgrim, *J. Am. Chem. Soc.*, **70**, 3787 (1948); Snyder and Eliel, *J. Am. Chem. Soc.*, **70**, 3855 (1948); Boon, *J. Chem. Soc.*, S 231 (1949); Snyder, Beilfuss, and Williams, *J. Am. Chem. Soc.*, **75**, 1873 (1953); Jones and Kornfield, U.S. Patent 2621187 [*Chem. Abstr.* **47**, 10557 (1953)].

(2b) Snyder and Cook, *J. Am. Chem. Soc.*, **78**, 969 (1956)

which the amino acid side chain and the methyl group are attached to positions 1 and 3 of the indole nucleus, respectively. The synthesis was achieved as follows:



Skatole reacted with dimethylamine and formalin, according to the procedure of Kuhn and Stein,[3] to give 1-dimethylaminomethylskatole (II) in 71% yield. The base was characterized by its methiodide and picrate. The methiodide III reacted with sodium cyanide solution to furnish 1-skatylacetic acid (VI), 1-skatylacetamide (VII) and skatole. The structures of the acid VI and hence of the base II were confirmed by decarboxylation of the acid to 1,3-dimethylindole which was characterized by means of its picrate. As might be expected of a 1,3-disubstituted indole derivative,[5] VI gave a negative Ehrlich's test.

The methiodide III when reacted with ethyl acetamido-cyanoacetate furnished IV as a viscous liquid which could not be further purified. Treatment of crude IV with sodium hydroxide gave V in 33% yield based on III used. The analytical data for the amino acid revealed the presence of one molecule of water of crystallization which, however, could be removed by drying the sample *in vacuo* at 180°. The amino acid gave a positive ninhydrin test and a negative Ehrlich's test. The R_f value determined in butyl alcohol–acetic acid–water solution (4:1:5) was 0.81.

(3) Kuhn and Stein, *Ber.*, **70**, 567 (1937).

(4) Jackson and Manske, *Can. J. Research*, **13**, 170 (1935); *Chem. Abstr.*, **30**, 455 (1936).

(5) Giral and Laguna, *Ciencia*, **10**, 83 (1950); *Chem. Abstr.*, **44**, 10605 (1950).

Most of the derivatives of indole that have been reported so far to participate in the Mannich reaction do not carry any substituent in the 3 position. In these reactions, the dialkylaminomethyl group enters position 3, probably as a result of the activation of carbon 3 due to the lone pair of electrons on the nitrogen atom of the indole nucleus. Besides skatole, carbazole is the only other known derivative of indole which has been reported to give[6] an *N*-Mannich base. Evidently, when position 3 carries a substituent, the dialkylaminomethyl group gets linked to the nitrogen atom itslef. Electron releasing and electron attracting groups in the 3-position may be expected to favor or hinder the formation of *N*-dialkylaminomethyl Mannich bases. The fact that skatole gives the Mannich base II in good yield and under the same conditions as indole suggests that the electron releasing methyl group probably facilitates the reaction. Further work is in progress to correlate the character of a 3-substituent with the ease of formation of *N*-Mannich bases of indole derivatives.

The Mannich base II, like 1-methylgramine to which it bears a close structural resemblance, is a tertiary base incapable of effecting alkylations through a mechanism[7] of elimination and addition. The alkylations of ethyl acetamidocyanoacetate and sodium cyanide with III must therefore involve a direct substitution mechanism. In fact, some other alkylations which have been carried out with II and III, and which will be described in a later communication, bear out the anticipations based on their structural resemblance to 1-methyl gramine and its methiodide.

EXPERIMENTAL

Skatole was prepared by Fischer cyclization[8] of propionaldehyde phenylhydrazone. The original method was adapted as follows for large scale preparations:

A mixture of 3 g. of fused zinc chloride and 30 g. (0.2 mole) of crude propionaldehyde phenylhydrazone was placed in a 500-ml. round bottomed flask provided with a condenser and dropping funnel and heated in an oil bath. With the bath temperature at 220°, an additional portion (80 g.; 0.53 mole) of propionaldehyde phenylhydrazone was introduced at such a rate as to maintain a gentle reflux. After addition was over, the temperature of the bath was raised to and maintained at 240° for 0.5 hr. The reaction mixture was cooled, diluted with water and steam distilled to give 62.7 g. (64%) of skatole, m.p. 89–92°.

1-Dimethylaminomethylskatole (II). To 60 ml. of an ice-cold 16% solution of dimethylamine (0.21 mole) in water were added successively 40 ml. of glacial acetic acid and 20 ml. of 36% formalin (0.24 mole) at such a rate that the temperature did not rise above 0°. The solution was then mixed with 26.2 g. (0.2 mole) of skatole and the mixture stirred at room temperature. The skatole dissolved in the course of 2 hr. The reaction mixture was allowed to stand overnight in an ice chest and then made alkaline using 5 *N* sodium hydroxide solution. Extraction with ether furnished,

(6) Feldman and Wagner, *J. Org. Chem.*, **7**, 31 (1942); Hellmann and Löschmann, *Ber.*, **87**, 1684, 1690 (1954).

(7) Brewster and Eliel, *Org. Reactions*, **7**, 99 (1953).

(8) Fischer, *Ann.*, **236**, 137 (1886).

after removal of solvent, the product which was distilled *in vacuo* b.p. 146–150°/9 mm.; yield, 26.5 g. (71%).

The *picrate*, after two crystallizations from methanol, melted at 150–151°.

Anal. Calc'd for $C_{18}H_{19}N_5O_7$: C, 51.8; H, 4.6. Found: C, 52.0; H, 4.7.

The methiodide was obtained by mixing equimolar amounts of II and methyliodide in absolute methanol or ethanol solution. The analytical sample was prepared by repeated washing with absolute ethanol and ether, m.p. 210–220° (decomp.).

Anal. Calc'd for $C_{18}H_{19}IN_2$: C, 47.3; H, 5.8. Found: C, 47.4; H, 6.0.

1-Skatylacetamide (VII) and 1-skatylacetic acid (VI). A solution of 8.3 g. (0.025 mole) of III and 5 g. (0.1 mole) of sodium cyanide in 50 ml. of water was refluxed for 2.25 hr. Trimethylamine evolved steadily during this period. The reaction mixture was cooled in an ice-salt mixture and filtered. The semisolid obtained (3.7 g.) was extracted with hot benzene and the benzene extract when cooled deposited crystals of VII (1 g.); m.p. 164–166°. A crystallization from benzene furnished material m.p. 169–170°.

Anal. Calc'd for $C_{11}H_{12}N_2O$: C, 70.2; H, 6.4. Found: C, 70.4; H, 6.3.

The benzene extract was stripped of solvent and the residue sublimed at 100°/1 mm. The sublimed material (98 mg.) was identified as skatole by mixed melting point with an authentic sample and by preparation of the picrate.

The alkaline filtrate left after filtration of the crude amide when acidified deposited crystals (51 mg.) of VI; m.p. 171°. After two further crystallizations from benzene the m.p. was 174° (lit.[4] m.p. 178°).

Anal. Calc'd for $C_{11}H_{11}NO_2$: C, 69.8; H, 5.9. Found: C, 69.8; H, 5.9.

The same acid was obtained in 50% yield by hydrolysis of the amide with ethanolic potassium hydroxide solution.

Decarboxylation of VI to 1,3-dimethylindole. In a microdistillation flask 200 mg. of VI was heated in an atmosphere of nitrogen at 225–230° for 0.5 hr. The brown residual liquid was distilled at 17 mm. with the bath temperature at 170°. The distillate furnished a picrate, which after a crystallization from ethanol had m.p. 140–141°. This melting point was not depressed by admixture with an authentic sample of the picrate of 1,3-dimethylindole prepared as described by Snyder and Eliel.[9]

DL-*α-Amino-β-(1-skatyl) propionic acid (V).* To a solution prepared from 0.86 g. (0.037 g. atom) of sodium and 94 ml. of absolute ethanol were added 12.2 g. (0.037 mole) of III and 6.4 g. (0.038 mole) of ethyl acetamidocyanoacetate and the mixture was refluxed for 43 hr. The reaction mixture was then concentrated *in vacuo* and the residue diluted with water and extracted with ether. The ether extract furnished, after removal of solvent, 9.4 g. of the crude alkylated product IV. This was refluxed with 40 ml. of 15% sodium hydroxide solution for 25 hr. in a copper vessel. The mixture was cooled, filtered, and the filtrate extracted with ether to remove 1.3 g. of some unsaponifiable material. The aqueous solution was treated with animal charcoal and acidified with 9 ml. of glacial acetic acid. The crude amino acid which separated was collected and extracted with five 60-ml. portions of boiling water. The combined aqueous extracts when cooled deposited 2.9 g. of material m.p. 195–196°. The analytical sample (m.p. 217–218°) was obtained after seven recrystallizations from 50% methanol.

Anal. Calc'd for $C_{12}H_{14}N_2O_2 \cdot H_2O$: C, 61.0; H, 6.8. Found: C, 61.0; H, 7.2.

A sample of the amino acid hydrate when dried *in vacuo* for 6 hr. at 178° lost one mole of water of crystallization and had m.p. 214°. The anhydrous sample was analyzed.

Anal. Calc'd for $C_{12}H_{14}N_2O_2$: C, 66.0; H, 6.5. Found: C, 66.0; H, 6.8.

The picrolonate was readily obtained by mixing hot solutions of equal amounts of the amino acid and picrolonic acid in water and was crystallized from water; m.p. 145°.

Anal. Calc'd for: $C_{22}H_{22}N_6O_7 \cdot H_2O$: C, 52.8; H, 4.8. Found: C, 53.1; H, 4.6.

Acknowledgments. We are grateful to Mr. Selvavinayakam for the analyses reported herein. One of the authors (S. R.) is indebted to the government of India for the award of a scholarship.

MADRAS 25, INDIA

(9) Snyder and Eliel, *J. Am. Chem. Soc.*, 70, 1703 (1948).

[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, RADIUM INSTITUTE, UNIVERSITY OF PARIS]

Some 2,3-Polymethylene-indoles and -quinolines. An Attempt to Synthesize Large-Ring Nitrogen Heterocycles

PIERRE JACQUIGNON AND NG. PH. BUU-HOÏ

Received July 23, 1956

Several new 2,3-polymethylene-indoles and -quinolines have been prepared from various macrocyclic ketones by Fischer and Pfitzinger reactions. An attempt to use some of these compounds for the preparation of fully conjugated large-ring nitrogen-containing heterocycles was unsuccessful.

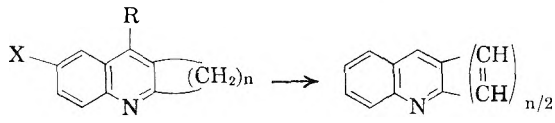
A possibility, at least theoretical, exists for the dehydrogenation of 2,3-polymethylenequinolines (I; R = H) with an even number (n) of methylene groups, to fully conjugated large-ring acridine analogs (II). Similarly, it is theoretically feasible to convert 2,3-polymethyleneindoles (III) bearing an odd number ($n + 1$) of methylene groups to fully conjugated macrocyclic analogs (IV) of 1-aza-2,3-benzazulene (VII). Treibs, Steinert and Kirchhof[1] did, in fact, succeed in preparing the latter substance by treating [(1′,2′-2,3)cyclohept-1′,2′-eno]indole (IIIb) with three moles of chloranil, a reagent frequently used for the aromatization of hydrogenated carbazoles[2] and acridines.[3]

(1) Treibs, Steinert, and Kirchhof, *Ann.*, 581, 54 (1953).

(2) Barclay and Campbell, *J. Chem. Soc.*, 530 (1945); Buu-Hoï, Khôi, and Xuong, *J. Org. Chem.*, 14, 492 (1949); 15, 511, 957 (1950); 16, 315 (1951).

(3) Buu-Hoï, Hoán, and Xuong, *J. Chem. Soc.*, 279 (1952)

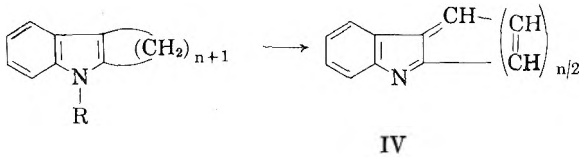
In the framework of a research program on carcinogenesis induced by polycyclic conjugated molecules,[4] an attempt was made to synthesize large-ring nitrogen heterocycles represented by



II

Ia; X = H, R = CO_2H, n = 6
b; X = R = H, n = 6
c; X = Cl, R = CO_2H, n = 6
d; X = Br, R = CO_2H, n = 6
e; X = Cl, R = H, n = 6
f; X = Br, R = H, n = 6
g; X = Br, R = H, n = 13
h; X = R = H, n = 13

the general formulas II and IV. The Pfitzinger condensation of cycloöctanone with isatin gave in excellent yields [(1′,2′-2,3)cycloöct-1′,2′-eno]cinchoninic acid (Ia), which readily underwent thermal decarboxylation to *[(1′,2′-2,3)cycloöct-1′,2′-eno]*-quinoline (Ib). This latter compound, previously obtained as a noncrystallized mass by Ruzicka, Goldberg, and Hürbin[5] through a Friedländer condensation of *o*-aminobenzaldehyde and cycloöctanone, was now prepared in the crystalline state. Condensation of cycloöctanone with 5-chloro- and 5-bromo-isatin similarly yielded 6-chloro- (Ic) and 6-bromo-*[(1′,2′-2,3)cycloöct-1′,2′-eno]*cinchoninic acid (Id), and the halogenated quinolines (Ie) and (If) obtained therefrom by thermal decarboxylation were likewise well crystallized substances. An attempt to dehydrogenate with chloranil either these cinchoninic acids or the corresponding quinolines failed, some of the starting material being recovered, and some undergoing resinification.



IV

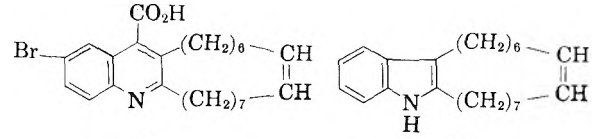
IIIa; R = H
b; R = H, n = 5
c; R = CH_3, n = 5
d; R = CH_3, n = 12

The Pfitzinger reaction was also applied with success to the synthesis of the solid 6-bromo-[(1′,2′-2,3)cyclopentadec-1′,2′-eno]quinoline (Ig) from 5-bromoisatin and cyclopentadecanone (exaltone) *via* the corresponding cinchoninic acid; the nonhalogenated base (Ih) which Ruzicka, Goldberg, and Hürbin[5] obtained through a Friedländer reaction, and Buu-Hoï[6] through a Pfitzinger reaction, was in both instances described as a tallowy mass.

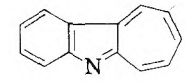
On the other hand, 6-bromo-[(1′,2′-2,3)cycloheptadeca-1′,2′,9′,10′-dieno]cinchoninic acid (V), prepared from 5-bromoisatin and civettone, failed, as did the nonhalogenated substance,[7] to give a crystalline decarboxylation product.

[(1′,2′-2,3)Cycloheptadeca-1′,2′,9′,10′-dieno]-indole (VI), prepared by Fischer cyclization of the phenylhydrazone of civettone,[7] could not be dehydrogenated by means of chloranil to a well defined product.

Other new macrocyclic indoles prepared in the course of this work included [(1′,2′-2,3)cycloöct-1′,2′-eno]indole (IIIb) and its 1-methyl derivative (IIIc), prepared from cycloöctanone phenylhydrazone and N-methyl-N-phenylhydrazone, and 1-



V VI



VII

methyl-[(1′,2′-2,3)cycloöct-1′,2′-eno]indole (IIId), obtained from exaltone N-methyl-N-phenylhydrazone. The theoretical possibility of dehydrogenating compound IIIb to 2′,3′-indolocycloöctatetraene did not materialize in this research. The failure encountered in our dehydrogenation experiments could be accounted for by modern valency studies,[8] the explanation being that beyond a certain critical size (apparently IIIb), the polymethylene chain exists in a sufficiently staggered arrangement that stable conjugated systems are not possible (as, for example, with cycloöctatetraene). Thus, not only does a considerable bond strain resist the dehydrogenation of our macrocycles, but the conjugated systems if formed would have the same reactivity as cycloöctatetraene—in other words, there could be no stabilization by virtue of an aromatic-type conjugation which requires a planar, or near planar, arrangement.

The macrocyclic indoles described in this work gave with tetrachlorophthalic anhydride[9] well crystallized, strongly colored molecular addition compounds, and are best characterized in that way.

In biological tests for carcinogenic properties, 1-aza-2,3-benzazulene proved inactive when painted on the skin of mice.

EXPERIMENTAL

Pfitzinger reaction of cycloöctanone with isatin. A mixture of 13 g. of redistilled cycloöctanone, 15 g. of isatin, and 16

(4) cf. Buu-Hoï, *Arzneimittel-Forsch.*, 6, 251 (1956).
(5) Ruzicka, Goldberg, and Hürbin, *Helv. Chim. Acta*, 16, 1335 (1933).
(6) Buu-Hoï, *J. Chem. Soc.*, 2882 (1949).
(7) Buu-Hoï, *J. Chem. Soc.*, 795 (1946).
(8) See Prelog, *J. Chem. Soc.*, 420 (1950).
(9) Pfeiffer, *Ber.*, 55, 413 (1922); Buu-Hoï and Jacquignon, *Compt. rend.*, 234, 1056 (1952).

g. of potassium hydroxide dissolved in 100 ml. of ethanol was refluxed for 15 hr. on the water bath, and most of the solvent was distilled off. The aqueous layer formed on addition of water was extracted with ether to remove the neutral impurities, acidified with acetic acid, and the precipitate which formed was recrystallized from a mixture of ethanol and benzene. Yield: 80–85% of [(1′,2′-2,3)cyclooct-1′,2′-eno]cinchoninic acid (Ia), in the form of fine, colorless, sublimable prisms, m.p. 342–343° (decomposition above 290° on prolonged heating).

Anal. Calc'd for $C_{16}H_{17}NO_2$: C, 75.3; H, 6.7. Found: C, 75.1; H, 6.6.

[(1′,2′-2,3)Cyclooct-1′,2′-eno]quinoline (Ib). The foregoing acid was dried, heated above its melting point, and the residue vacuum-fractionated. Yield: 90% of a thick yellow base, which solidified on scratching with a glass rod, and crystallized from petroleum ether in fine colorless prisms, m.p. 59°.

Anal. Calc'd for $C_{15}H_{17}N$: C, 85.3; H, 8.1. Found: C, 85.2; H, 8.3.

The corresponding picrate crystallized from ethanol in bright yellow needles, m.p. 206–207° (decomp. above 180°).

6-Chloro-[(1′,2′-2,3)cyclooct-1′,2′-eno]cinchoninic acid (Ic). 5-Chloroisatin was most conveniently prepared by halogenation of isatin with N-chlorosuccinimide in carbon tetrachloride medium[10]; a mixture of 2 g. of 5-chloroisatin, 1.5 g. of cyclooctanone, and 1.7 g. of potassium hydroxide in 10 ml. of ethanol was treated as above. Yield: 85–90% of an acid, crystallizing from a mixture of ethanol and benzene in fine, colorless, sublimable needles, m.p. 348–349° (decomp. above 296° on prolonged heating).

Anal. Calc'd for $C_{16}H_{16}ClNO_2$: C, 66.3; H, 5.5. Found: C, 66.0; H, 5.4.

Thermal decomposition gave an 80% yield of *6-chloro-[(1′,2′-2,3)cyclooct-1′,2′-eno]quinoline* (Ie), crystallizing from methanol in colorless prisms, m.p. 120–121°.

Anal. Calc'd for $C_{15}H_{16}ClN$: C, 73.3; H, 6.5. Found: C, 73.3; H, 6.6.

Its picrate crystallized from ethanol in fine, deep yellow prisms, m.p. 239° (decomp. above 200°).

Anal. Calc'd for $C_{21}H_{19}ClN_4O_7$: N, 11.8. Found: N, 11.5.

6-Bromo-[(1′,2′-2,3)cyclooct-1′,2′-eno]cinchoninic acid (Id). Prepared in 90% yield from 5 g. of cyclooctanone, 9.5 g. of 5-bromoisatin, and 8 g. of potassium hydroxide in ethanol (24 hours' refluxing), this compound crystallized from a mixture of ethanol and benzene in fine, straw-colored prisms, m.p. 350–351° (sublimation and decomposition on prolonged heating above 305°).

Anal. Calc'd for $C_{16}H_{16}BrNO_2$: C, 57.5; H, 4.8. Found: C, 57.6; H, 5.0.

6-Bromo-[(1′,2′-2,3)cyclooct-1′,2′-eno]quinoline (If) crystallized from ethanol in fine, shiny, colorless needles, m.p. 129–130°.

Anal. Calc'd for $C_{15}H_{16}BrN$: C, 62.1; H, 5.5. Found: C, 61.8; H, 5.5.

Its picrate crystallized from ethanol in deep yellow prisms, m.p. 238–239° (decomp. above 210°).

Anal. Calc'd for $C_{21}H_{19}BrN_4O_7$: N, 10.8. Found: N, 11.0.

Attempted dehydrogenation of quinolines Ia, Ic, and Id. These quinolines (1 mole) were heated in xylene medium with 3 moles of chloranil for 6 hr., most of the solvent was distilled off in a vacuum, and the dark violet residue then treated with an ethanolic solution of picric acid; in each instance, only the picrate of the starting material could be isolated.

[(1′,2′-2,3)Cyclooct-1′,2′-eno]indole (IIIb). A mixture of 4 g. of cyclooctanone and 3 g. of phenylhydrazine was heated for 20 min. at 120–130° with removal of water. To the crude phenylhydrazone thus obtained a solution of hydrogen chloride in acetic acid was added and the mixture was refluxed for a few seconds, then poured into water. The cyclization-product was taken up in benzene and purified by vacuum-distillation. Yield: 90% of a product, b.p. 215–216°,18 mm., crystallizing from petroleum ether (b.p. 35–65°) in fine colorless needles, m.p. 71°, turning yellow on exposure to the light and air. This compound was recovered in part unchanged, and in part resinified on treatment with 3 moles of chloranil in boiling xylene.

Anal. Calc'd for $C_{14}H_{17}N$: C, 84.4; H, 8.6. Found: C, 84.5; H, 8.8.

The corresponding picrate crystallized from ethanol in silky, brown-violet needles, m.p. 97°. The addition compound with tetrachlorophthalic anhydride, prepared by dissolving equimolar amounts of the indole and the anhydride in hot acetic acid, crystallized from that solvent in shiny, dark red needles, m.p. 132°.

Anal. Calc'd for $C_{22}H_{17}Cl_4NO_3$: Cl, 29.3. Found: Cl, 28.8.

1-Methyl-[(1′,2′-2,3)cyclooct-1′,2′-eno]indole (IIIc). Similarly prepared in 70% yield from 3 g. of N-methyl-N-phenylhydrazine and 4 g. of cyclooctanone, this indole was a pale yellow oil, b.p. 212–213°/17 mm., n_D^{23} 1.6005.

Anal. Calc'd for $C_{15}H_{19}N$: C, 84.5; H, 9.0. Found: C, 84.4; H, 9.0.

The picrate crystallized from petroleum ether in silky, dark violet needles, m.p. 77°. The addition-compound with tetrachlorophthalic anhydride crystallized from acetic acid in shiny bright red needles, m.p. 112°.

Anal. Calc'd for $C_{23}H_{19}Cl_4NO_3$: Cl, 28.4. Found: Cl, 28.1.

1-Methyl-[(1′,2′-2,3)cyclopentadec-1′,2′-eno]indole (IIId). Prepared in 70–75% yield from 2.5 g. of cyclopentadecanone and 1.7 g. of N-methyl-N-phenylhydrazine, this indole was a pale yellow oil, b.p. 300–302°/40 mm., $n_D^{23.5}$ 1.5151, with an unpleasant, burnt horn odor.

Anal. Calc'd for $C_{22}H_{33}N$: C, 84.8; H, 10.7. Found: C, 8.50; H, 10.5.

The picrate crystallized from ethanol in silky violet needles; the addition-compound with tetrachlorophthalic anhydride crystallized from acetic acid in orange prisms, m.p. 147°.

[(1′,2′-2,3)Cycloheptadeca-1′,2′,9′,10′-dieno]indole (VI). This compound, prepared from 1 g. of civettone and 0.5 g. of phenylhydrazine, was resinified on heating with 8 moles of chloranil in xylene; its addition-compound with tetrachlorophthalic anhydride crystallized from acetic acid in bright red prisms, m.p. 113°.

Anal. Calc'd for $C_{31}H_{33}Cl_4NO_3$: Cl, 23.3. Found: Cl, 23.5.

6-Bromo-[(1′,2′-2,3)cyclopentadec-1′,2′-eno]cinchoninic acid. Prepared in 90% yield from 2.2 g. of cyclopentadecanone, 2.2 g. of 5-bromoisatin, and 1.6 g. of potassium hydroxide in 10 ml. of ethanol, this acid crystallized from acetic acid in fine colorless prisms, m.p. 312° (decomp. above 290°).

Anal. Calc'd for $C_{23}H_{30}BrNO_2$: C, 63.9; H, 6.9. Found: C, 64.0; H, 6.8.

6-Bromo-[(1′,2′-2,3)cyclopentadec-1′,2′-eno]quinoline (Ig) purified *via* its picrate (bright yellow needles, m.p. 194–195°, from ethanol), crystallized from petroleum ether in fine colorless prisms, m.p. 55°.

Anal. Calc'd for $C_{22}H_{30}BrN$: C, 67.0; H, 7.7. Found: C, 67.7; H, 8.0.

6-Bromo-[(1′,2′-2,3)cycloheptadeca-1′,2′,9′,10′-dieno]cinchoninic acid (V). Prepared from 1 g. of civettone, 0.9 g. of isatin, and 0.7 g. of potassium hydroxide in 10 ml. of ethanol, this acid crystallized from ethanol in yellowish needles, m.p. 270° (decomp. above 260°).

Anal. Calc'd for $C_{25}H_{32}BrNO_2$: C, 65.5; H, 7.0. Found: C, 65.2; H, 6.9.

(10) Buu-Hoï, *Rec. trav. chim.*, **73**, 197 (1954).

PARIS (V°) FRANCE

Notes

A department for short papers of immediate interest.

Cyclopropanes XXII.[1] Determination of Geometrical Isomers by Spectrophotometric Methods

LEE IRVIN SMITH AND ROBERT J. BROTHERTON[2]

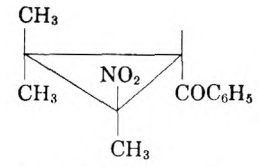
Received Oct. 18, 1956

It has been demonstrated that *cis* and *trans* isomers of certain aroyl ethylene oxides[3] and ethylenimines[4] can be identified by spectrophotometric methods. In the ultraviolet absorption spectra, the maximum arising from the aroyl group of the *trans* isomer occurs, in every case, at a lower frequency (higher wave length) than does the corresponding maximum of the *cis* isomer. Also the extinction coefficient, $\epsilon_{max.}$, of the *trans* compound is always greater than that of the *cis* isomer. In the infrared absorption spectra, in most cases, the carbonyl stretching frequency of the *trans* compound occurs at lower values than that of the *cis* isomer.

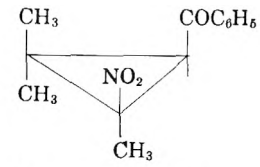
Cromwell has discussed these observations in terms of increased hyperconjugation through the three-membered ring with *trans* substituents and has suggested that *cis* and *trans* aroyl cyclopropanes could be distinguished by similar spectrophotometric differences.[5] He suggested that any differences in the absorption spectra of stereoisomeric cyclopropanes would be apparent only in the ultraviolet spectra, and not in the infrared region. No clear-cut examples of the separation of *cis-trans* isomers of simple aroyl cyclopropanes have been reported, but a number of aroyl nitrocyclopropanes have been described in earlier papers of this series, and geometrical isomers have been separated in two cases where this proposed "*trans* hyperconjugation" might occur.

The two possible isomers of 1-benzoyl-2-nitro-2,3,3-trimethylcyclopropane (I) have been prepared.[6] The infrared absorption spectrum of each isomer (in Nujol) showed a band at 1670 cm.$^{-1}$.

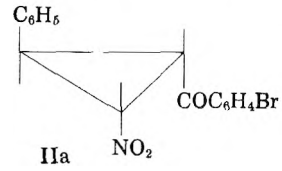
The ultraviolet spectrum of the isomer melting



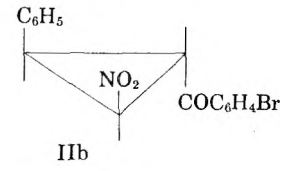
Ia, m.p., 55° (*trans*)



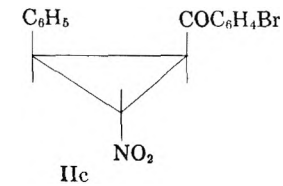
Ib., m.p., 101° (*cis*)



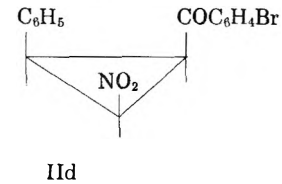
IIa



IIb



IIc



IId

at 55° showed a maximum at 249 mμ ($\epsilon_{max.}$ 14.9 × 10^{-3}); that of the isomer melting at 101° showed a maximum at 248 mμ ($\epsilon_{max.}$ 13.5 × 10^{-3}). In analogy with the spectrophotometric differences shown by ethylene oxides and ethylenimines, the lower melting isomer must be the *trans* form, Ia. The following observations also support this designation: the 55° isomer is isolated in 98 to 1 excess over the 101° isomer when these cyclopropanes are prepared by dehydrobromination of the corresponding bromonitro ketone, and the 55° isomer is stable toward methanolic ammonia whereas the 101° isomer is converted to the 55° compound by the same reagent.

Kohler[7] reported three of the four possible geometrical isomers of 1-(*p*-bromobenzoyl)-2-nitro-3-phenylcyclopropane (II). Smith and Holly[8] have re-investigated these isomers and reported melting points of 120°, 135°, and 169°.[9]

(1) Paper XXI, Smith and Kohlhase, *J. Org. Chem.*, 21, 816 (1956).

(2) Du Pont Postdoctoral Fellow 1954–1955.

(3) Wasserman and Aubrey, *J. Am. Chem. Soc.*, 77, 590 (1955); Cromwell and Setterquist, *J. Am. Chem. Soc.*, 76, 5752 (1954).

(4) Prostenik, Salzman, and Carter, *J. Am. Chem. Soc.*, 77, 1856 (1955); Cromwell, Barker, Wankel, Vanderhorst, Olson, and Anglin, *J. Am. Chem. Soc.*, 73, 1044 (1951).

(5) Cromwell and Hudson, *J. Am. Chem. Soc.*, 75, 872 (1953); Cromwell and Graff, *J. Org. Chem.*, 17, 414 (1952).

(6) Smith, Kohlhase, and Brotherton, *J. Am. Chem. Soc.*, 78, 2532 (1956).

(7) Kohler and Williams, *J. Am. Chem. Soc.*, 41, 1649 (1919).

(8) Smith and Holly, *J. Am. Chem. Soc.*, 78, 1472, 1475 (1956).

(9) Since publication of the work of Smith and Holly, it has been discovered that the "isomer" of II melting at 120° is actually a mixture of the other two isomers. This fact, however, does not invalidate the arguments presented here, or in the paper by Smith and Holly,[10] as to the configurations of the isomers of II melting at 135° and 169°. We are greatly indebted to Prof. Weldon G. Brown and his student, Mr. John Neumer, for calling to our attention, in a private communication, that their evidence obtained in a study of these compounds indicated strongly that the "isomer" melting at 120° was not a pure compound.

(10) Smith and Holly, *J. Am. Chem. Soc.*, 78, 1480 (1956).

The structure IId which has three substituents on one side of the planar cyclopropane ring would be a comparatively unstable one, and in the following discussion it will be assumed that the isomer with this structure has not been isolated. The carbonyl stretching frequencies in the infrared spectra (in Nujol) of the two isomers melting at 135° and 169° are located, respectively, at 1674 and 1670 cm.$^{-1}$. Table I shows that the maximum in the ultraviolet absorption spectrum of the isomer melting at 169° occurs at the higher wave length and has the larger extinction coefficient. This suggests that it should be the "*trans*" compound.

TABLE I[a]

ULTRAVIOLET ABSORPTION MAXIMA OF THE ISOMERS OF II

Melting Point	Solvent	Concentration	λ Max., Mμ	$\epsilon \times 10^{-3}$
135°	95% ethanol	2.1×10^{-5}	261.0	18.80
	Abs. ethanol	4.213×10^{-5}	262.7	20.30
169°	95% ethanol	2.19×10^{-5}	264.0	21.70
	Abs. ethanol	4.258×10^{-5}	263.5	22.10

[a] All spectra were obtained on a Beckman Model D Spectrophotometer.

In the case of this cyclopropane, "*trans*" means that the phenyl (electron donor in this case) and *p*-bromobenzoyl (electron acceptor) groups are on opposite sides of the plane of the cyclopropane ring. However, this is true in both structures, IIa and IIb. The nitro group is also an electron acceptor and will conjugate with a *trans* phenyl group as in IIa in competition with the aroyl group. Structure IIb with the nitro group in a noncompetitive position *cis* to the phenyl group is probably the compound melting at 169°. In this case the isomer melting at 135° can be either IIa or IIc. The other possibility, considered to be less likely, is that structure IIa represents the isomer melting at 169° and the 135° compound is IIc.

The former conclusion, *i.e.*, the 169° compound is best represented as IIb and the 135° isomer is either IIa or IIc, is supported by other chemical and physical evidence reported by Smith and Holly.[10]

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3-Isoxazolidone

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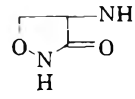
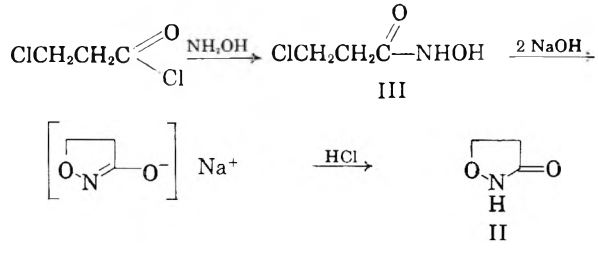
Received September 27, 1956

Cycloserine has been shown to be D-4-amino-3-isoxazolidone (I)[1,2] and a synthesis has been reported.[3] The synthesis of I involved the cyclization of an α-substituted β-halopropionohydroxamic acid. In order to determine the conditions necessary for this reaction, the preparation of a simple analog, 3-isoxazolidone (II),[4] was first undertaken.



I

β-Chloropropionohydroxamic acid (III) was prepared by the reaction of β-chloropropionyl chloride with aqueous hydroxylamine at −10°. The resulting acid (III) gave a red-violet color with ferric chloride.[5] Treatment of III with two equivalents of aqueous sodium hydroxide at 50° gave a solution of *ca.* *p*H 9. An aliquot of this solution after acidification failed to give a color with ferric chloride, showing that the hydroxamic acid was no longer present. Neutralization of the solution with one equivalent of acid yielded 3-isoxazolidone (II). The compound is a crystalline solid which, after reaction with hydroxylamine, gives a red-violet color with ferric chloride. This indicates that 3-isoxazolidone reacts with hydroxylamine in a manner similar to that of a lactone[5] to give a hydroxamic acid (probably 3-aminoxypropionohydroxamic acid).



III

II

EXPERIMENTAL[6]

β-Chloropropionohydroxamic acid. Hydroxylamine hydrochloride (27.5 g.) was dissolved in 167 ml. of 2.5*N* sodium hydroxide and the solution was cooled to −10°. To this solution, β-chloropropionyl chloride (25.0 g.) was added dropwise with stirring. The temperature was maintained at −5° to −10° during the addition and for 30 min. longer. The resulting solution was extracted with four portions of butanol and the combined extracts were dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue solidified on cooling. The solid was extracted with several portions of refluxing ether, and the extracts were combined and concentrated to a small volume. The crystalline precipitate that separated was redissolved in ether and

(1) Kuehl, Wolf, Trenner, Peck, Howe, Hunnewell, Downing, Newstead, Buhs, Putter, Ormond, Lyons, Chaiet, and Folkers, *J. Am. Chem. Soc.*, 77, 2344 (1955).

(2) Hiddy, Hodge, Young, Harned, Brewer, Phillips, Runge, Stavely, Pohland, Boaz, and Sullivan, *J. Am. Chem. Soc.*, 77, 2345 (1955).

(3) Stammer, Wilson, Holly, and Folkers, *J. Am. Chem. Soc.*, 77, 2346 (1955).

(4) After this work had been completed the cyclization of ethyl 3-aminoxypropionate with alkali to 3-isoxazolidone (isolated as the potassium and silver salts) was reported (ref. 2).

(5) Feigl, *Spot Tests II*, Elsevier Publishing Co., Houston, Tex., 1954, pp. 170–171.

(6) Analyses by R. N. Boos and associates; infrared spectrum by R. W. Walker. Melting points were determined on a Kofler micro hot stage.

Darco was added. The mixture was filtered, concentrated, and cooled giving 10.6 g. of β-chloropropionohydroxamic acid, m.p. 104–106°. This compound gives an intense red-purple color with aqueous ferric chloride.[6] A sample was recrystallized for analysis, m.p. 106–107°.

Anal. Calc'd for $C_3H_6ClNO_2$: C, 29.2; H, 4.9; N, 11.3. Found: C, 29.7; H, 5.1; N, 11.1.

3-Isoxazolidone. One gram of β-chloropropionohydroxamic acid was dissolved in 150 ml. of water, 16.5 ml. of 1*N* sodium hydroxide (a slight excess over two equivalents) was added, and the solution was warmed to 50°. The reaction was complete after 5 min. as shown by the fact that an aliquot of the solution after acidification did not give a color with aqueous ferric chloride. The solution was concentrated to 5 ml. under reduced pressure, 8.2 ml. of 1*N* hydrochloric acid was added, and the resulting solution was evaporated to dryness under reduced pressure. The crystalline residue was extracted with ethanol. Evaporation of the ethanol left 0.70 g. of a crystalline residue which was extracted with three 100-ml. portions of boiling ether. The ether extracts were combined and concentrated to 20 ml. On cooling, 3-isoxazolidone separated as a white crystalline solid m.p. 68–70°; wt. 0.38 g. Recrystallization did not raise the melting point. The compound did not give a color with ferric chloride. However, when hydroxylamine was added first,[7] a positive test for a hydroxamic acid was obtained. The infrared spectrum in the solid state showed absorption in the 3–4 μ region, a broad absorption band at 5.8–6.0 μ and a strong 6.1 μ band. In solution (chloroform) it showed absorption at 3–4 μ and a strong band at 5.9 μ. The sample for analysis was sublimed *in vacuo*, m.p. 69–69.5°.

Anal. Calc'd for $C_3H_5NO_2$: C, 41.4; H, 5.8; N, 16.1, eq. wt. 87.1. Found: C, 41.9; H, 5.9; N, 16.6; eq. wt. 88.4.

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(7) The method of Boxer and Everett [*Anal. Chem.*, 21, 670 (1949)] for the determination of total penicillins was used.

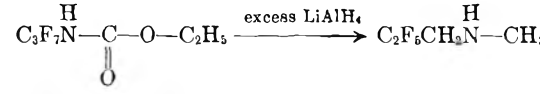
Reduction of *N*-Perfluoroalkyl Urethans with Lithium Aluminum Hydride

RALPH L. DANNLEY AND ROBERT G. TABORSKY[1]

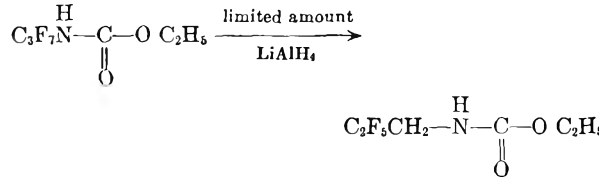
Received Sept. 11, 1956

The reduction of simple N-alkyl urethans to the corresponding methylalkylamines by means of lithium aluminum hydride has been reported by several authors.[2] The present work was undertaken to determine the behavior of N-perfluoroalkyl urethans with the same reagent.

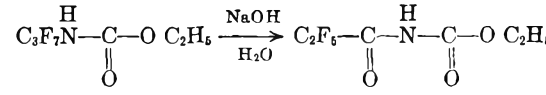
Since the reaction of perfluoroalkyl isocyanates with excess lithium aluminum hydride has been found[3] to produce 1,1-dihydroperfluoroalkylmethylamines, treatment of the corresponding urethans with an excess of the same reducing agent might be expected to give the identical amine products. This has now been confirmed, for the reaction of an excess of lithium aluminum hydride with ethyl N-*n*-perfluoropropylcarbamate and ethyl N-*n*-perfluoroheptylcarbamate produced the corresponding 1,1-dihydroperfluoroalkylmethylamines in yields of 60% and 51%, respectively.



Treatment of an N-perfluoroalkyl urethan with only a limited quantity of the hydride provided a competitive reaction in which only the most susceptible of the available functional groups could undergo reduction. Under these conditions it has been found that ethyl N-perfluoropropylcarbamate gives the corresponding N-1,1-dihydroperfluoroalkyl urethan in 63% yield. Therefore, the hydride reacts with the fluorine atoms alpha to the nitrogen in preference to the carbethoxyl group.



The hydrolysis of ethyl N-*n*-perfluoropropylcarbamate was attempted as a synthesis of ethyl N-perfluoropropionylcarbamate, a by-product in the reduction of the urethan. It was found that mild aqueous alkaline hydrolysis of the urethan gave an essentially quantitative yield of ethyl N-*n*-perfluoropropionylcarbamate.



This again emphasizes the susceptibility to displacement reactions of the fluorine atoms alpha to nitrogen. This type of reactivity has previously been observed[4] in the treatment of these urethans with alcohol.

EXPERIMENTAL

Reagents. Ethyl N-*n*-perfluoropropylcarbamate and ethyl N-*n*-perfluoroheptylcarbamate were prepared by treating the appropriate isocyanates with stoichiometric quantities of alcohol.[4] Ethereal solutions of lithium aluminum hydride were prepared in a Soxhlet apparatus and standardized by measuring the hydrogen evolved upon addition to butanol.

Ethyl N-Perfluoropropylcarbamate reduction with excess lithium aluminum hydride. A solution of 25 g. (0.0973 mole)

(1) From the thesis to be submitted by Robert G. Taborsky to the Graduate School of Western Reserve University in partial fulfillment of the requirements for the Doctor's degree.

(2) (a) Wessely and Swoboda, *Monatsh.*, 82, 621 (1951); (b) Karrer and Nicolaus, *Helv. Chim. Acta.*, 35, 1581 (1952); (c) Haggis and Owen, *J. Chem. Soc.*, 389 (1953); (d) Bruchhausen and Knabe, *Arch. Pharm.*, 287, 601 (1954); (e) Dannley, Lukin, and Shapiro, *J. Org. Chem.*, 20, 92 (1955); (f) Knabe, *Arch. Pharm.*, 288, 469 (1955).

(3) Dannley, Taborsky, and Lukin, *J. Org. Chem.*, 21, 1318 (1956).

(4) Dannley and Lukin, *J. Org. Chem.*, 21, 1036 (1956).

of the urethan in 50 ml. of ether was added dropwise to 0.195 mole of lithium aluminum hydride dissolved in 140 ml. of ether. After the addition was complete, the mixture was refluxed for an hour and the excess hydride decomposed with water. A solution of 57 g. of potassium sodium tartrate in 100 ml. of water was added and, after stirring for an hour, the organic layer was separated and the aqueous layer extracted with three 100-ml. portions of ether. The combined ether solutions were dried over Drierite and distilled through a Todd spiral-wire column to give 9.6 g. (60% yield) of methyl-1,1-dihydroperfluoropropylamine (b.p. 61–62°), 1.5 g. of ethyl N-1,1-dihydroperfluoropropylcarbamate (b.p. 63–66° at 2 mm.), and 1.7 g. of nonvolatile residue.

The methyl-1,1-dihydroperfluoropropylamine was identified by conversion to the *p*-nitrobenzamide, m.p. 56–57.5° (lit.[3] m.p. 56–57°). Admixture with an authentic sample of the *p*-nitrobenzamide gave no depression of the melting point.

The intermediate fraction (b.p. 63–66° at 2 mm.) solidified on standing and after recrystallization from methanol-water had a m.p. of 57–57.5°. Mixture with an authentic sample of ethyl N-1,1-dihydroperfluoropropylcarbamate (see the following experiment) gave no depression of the melting point.

Reaction of lithium aluminum hydride with an excess of ethyl N-n-perfluoropropylcarbamate. This reaction was carried out in the same manner as the reduction just described, except that the ether solution of the hydride was added dropwise to the urethan to insure an excess of the carbamate at all times. From 25 g. (0.097 mole) of the urethan and 0.048 mole of lithium aluminum hydride were obtained 13.5 g. (63% yield) of ethyl N-1,1-dihydroperfluoropropylcarbamate (b.p. 81–83° at 16 mm.) and 6.5 g. of ethyl N-perfluoropropionylcarbamate (b.p. 102–104° at 16 mm.).

The ethyl N-1,1-dihydroperfluoropropylcarbamate melted at 57–58° after recrystallization from ethanol-water and the melting point was not depressed by admixture with an authentic sample. The authentic sample was prepared for comparison purposes by adding 0.016 mole of sodium hydroxide in 2 ml. of water to a well stirred mixture of 1.5 g. (0.008 mole) of 1,1-dihydroperfluoropropylamine hydrochloride,[5] 10 ml. of water, 5 ml. of ether, and 0.88 g. (.008 mole) of freshly distilled ethyl chlorocarbonate. The mixture, kept at 5° during the addition of the sodium hydroxide, was allowed to warm to room temperature, the organic layer was separated, and the aqueous layer was extracted with two 4-ml. portions of ether. The combined ether layers were dried over Drierite and the ether evaporated to give 1.5 g. (87.5% yield) of crude ethyl N-1,1-dihydroperfluoropropylcarbamate. One recrystallization from chloroform gave white crystals, m.p. 57.5–58°.

Anal. Calc'd for $C_6H_9F_5NO_2$: C, 32.60; H, 3.63. Found: C, 32.61; H, 3.83.

The identity of the ethyl N-perfluoropropionylcarbamate fraction (m.p. 59–60° after recrystallization from toluene) was established by admixture with an authentic sample (see the following experiment) to give no depression of the melting point.

Hydrolysis of ethyl N-n-perfluoropropylcarbamate. Addition of 5 g. (0.0194 mole) of ethyl N-*n*-perfluoropropylcarbamate to 6 ml. of 10% sodium hydroxide resulted in an exothermic reaction. When the reaction subsided, a crystalline precipitate formed which was separated by filtration and dried. This material, 4.9 g. (100% yield), melted at 60–61° (lit.[4] m.p. 60–61°) after recrystallization from toluene. The structure was confirmed by conversion to urethan and perfluoropropionamide by the method previously reported.[4]

Ethyl N-n-perfluoroheptylcarbamate reduction with excess lithium aluminum hydride. By a procedure identical with that described in the N-*n*-perfluoropropylurethan experiment, 17 g. (0.037 mole) of ethyl N-*n*-perfluoroheptylcarbamate in 35 ml. of ether were reduced with 0.09 mole of lithium aluminum hydride in 70 ml. of ether to give 6.81 g. (51% yield) of methyl-1,1-dihydroperfluoroheptylamine (b.p. 57–59° at 26 mm.; n_D^{20} 1.3120), 3.92 g. of ethyl N-1,1-dihydroperfluoroheptylcarbamate (b.p. 108–110° at 10 mm.), and 0.73 g. of nonvolatile residue.

The methyl-1,1-dihydroperfluoroheptylamine was identified by the similarity of its physical properties to those reported[3] for the amine (n_D^{20} 1.3119; b.p. 55° at 26 mm.) and by conversion to the benzamide, m.p. 63.5–64° (lit.[3] m.p. 63°).

The ethyl N-1,1-dihydroperfluoroheptylcarbamate was recrystallized from carbon tetrachloride to yield a white solid, m.p. 43–44°.

Anal. Calc'd for $C_{10}H_8F_{13}NO_2$: C, 28.5; H, 1.92. Found: C, 28.47; H, 2.00.

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(5) Haszeldine and Leedham, *J. Chem. Soc.*, 1548 (1953).

Preparation of 3-Substituted-2,5-Oxazolidinediones

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Received Aug. 24, 1956

Of the many 2,5-oxazolidinediones that have been prepared as intermediates for the formation of polyamino acids,[2] only a few contain substituents on the nitrogen. They include N-phenyl,[3] N-*p*-tolyl,[4] N-benzyl[5] and several N-alkyl groups.[6–8] None of these is a strongly electrophilic substituent. Therefore, it was of interest to study the effect of further variations in the nature of the nitrogen-bearing substituent on the ease of formation of the oxazolidinediones.

The N-substituted glycine derivatives were converted to the N-carboxy anhydrides by the phosgenation method of Farthing[9]:

$$RNHCH_2COOH \xrightarrow[COCl_2]{} O{-}CO{-}NR{-}CH_2{-}CO$$

The initial experiments in which R was *p*-methoxyphenyl were unsuccessful, since an N-chlorocarbonyl derivative was formed, which could not be cyclized. This result was unexpected, in view of the

(1) From the M.S. theses, University of Delaware, of F. L. McCarthy, 1956, R. L. Johnson, 1952, and E. V. Nagle, 1951.

(2) E. Katchalski, *Advances in Protein Chemistry*, Academic Press, New York, 1951, Vol. VI, p. 136.

(3) H. Leuchs and W. Manasse, *Ber.*, **40**, 3235 (1907).

(4) F. Fuchs, *Ber.*, **55**, 2943 (1922).

(5) W. E. Hanby, S. G. Waley, and J. Watson, *J. Chem. Soc.*, 3009 (1950).

(6) D. Coleman and A. C. Farthing, *J. Chem. Soc.*, 3218 (1950).

(7) F. Wessely, K. Riedl, and H. Tuppy, *Monatsh.*, **81**, 861 (1950).

(8) S. G. Waley and J. Watson, *Proc. Roy. Soc.* (*London*), A **199**, 499 (1949).

(9) A. C. Farthing, *J. Chem. Soc.*, 3213 (1950).

TABLE I

PREPARATION OF 3-SUBSTITUTED-2,5-OXAZOLIDINEDIONES

3-Substituent	Yield, %[a]	Solvent[b]	M.P., °C.[c]	Calculated C	Calculated H	Calculated N	Calculated Mol. Wt.	Found C	Found H	Found N	Found Mol. Wt.[d]
p-HOOCC$_6$H$_4$—	20	T	ca. 236[e]	54.33	3.20	6.33	221	54.52	3.70	6.27	255
p-NO$_2$C$_6$H$_4$—	45	T or D	193–195	48.65	2.72	12.61	222	47.93	2.41	12.42	223
p-CH$_3$COC$_6$H$_4$—	40	T or D	170			6.40	219			6.35	218
CH$_3$CO—	32	E	138	41.27	3.52	9.78	143	41.64	3.76	9.55	142
p-CNC$_6$H$_4$—	12[f]	E	167			13.86				13.87	

[a] Yield of pure material. [b] Solvent for recrystallization, used with petroleum ether; T = tetrahydrofuran, D = dioxane, E = ethyl acetate. [c] All substances melted with decomposition. [d] From neutral equivalent. [e] Decomposition not sharp, beginning at this temperature. [f] Yield could be improved by continuous extraction with ethyl acetate.

fact that 3-*p*-tolyl-oxazolidinedione was satisfactorily prepared by Fuchs.[4] Subsequent work showed that, when strongly electron-attracting substituents were present on the nitrogen, the oxazolidine ring was formed with moderate ease. Five examples of compounds of this type are given in Table I.

These oxazolidinediones showed no tendency to form polymers in the presence of water as initiator. This is parallel to the reluctance to polymerize of the higher N-alkyl derivatives studied by Wessely, Riedl, and Tuppy.[7]

EXPERIMENTAL

Known N-substituted glycine derivatives. N-Acetylglycine was obtained by Dakin's method.[10] N-*p*-Carboxyphenylglycine, prepared by the method of Mauthner and Suida,[11] had a melting point (258°) in agreement with that of Takeda and Kuroda[12] (255°), not that of the former authors (219–221°). N-*p*-Nitrophenylglycine[13] was most conveniently prepared from bromoacetic acid, previously used only for the ortho isomer.[14]

N-p-cyanophenylglycine. A solution of 6.0 g. (0.05 mole) of recrystallized *p*-aminobenzonitrile and 10 g. (0.11 mole) of chloroacetic acid in 150 cc. of hot water was refluxed until the product began to separate out. On cooling, 4.3 g. of product (49% yield) was obtained, m.p. 234° after washing with ether and recrystallizing twice from water.

Anal. Calc'd for C$_9$H$_8$N$_2$O$_2$: N, 15.91. Found: N, 15.69, 15.83. Alcoholysis gave the known *p*-carbethoxyphenylglycine ethyl ester.[15]

N-p-acetylphenylglycine. A mixture of 2 g. (0.0148 mole) of *p*-aminoacetophenone and 2 g. (0.0144 mole) of bromoacetic acid was heated at 100–115° for 20 min., then cooled and treated with 100 ml. of 3*M* ammonium hydroxide. After standing for 12 hr., the ammonia solution was filtered, the insoluble part reextracted with ammonia, and the product precipitated from the extracts with concentrated hydrochloric acid; m.p. 225° with decomposition, yield 22%.

Anal. Calc'd for C$_{10}$H$_{11}$NO$_3$: N, 7.25; neut. equiv., 193. Found: N, 7.24; neut. equiv. 195.

N-p-anisyl-N-chlorocarbonylglycine. Phosgenation of N-*p*-anisylglycine[16] (0.05 mole) in dioxane gave a 36% yield of this substance, m.p. 131–132° after separation from unreacted N-*p*-anisylglycine with ether and recrystallization from ethyl acetate by adding petroleum ether.

Anal. Calc'd for C$_{10}$H$_{10}$ClNO$_4$: N, 5.75. Found: N, 5.86, 5.79. The substance did not undergo ring closure by heating at 40°.

Oxazolidinediones. The N-substituted amino acid (0.01 to 0.03 mole), suspended in about 250 ml. dioxane, was treated with phosgene for 2 to 4 hr. at room temperature, except for the last two substances in Table I, which required a temperature of 40–45°. After the amino acid had dissolved, the solvent was removed at 35–40° and 2 mm., and the residue crystallized from a suitable solvent by the addition of low-boiling petroleum ether. Under these conditions N-*o*-nitrophenylglycine did not react with phosgene.

All the oxazolidinediones gave an immediate reaction with aniline with the evolution of carbon dioxide. However, when the compounds were exposed to moisture at room temperature or at 100–135°, polymers were not formed. On standing in air-filled, closed specimen bottles for a year, the *p*-nitrophenyl-, *p*-cyanophenyl- and *p*-acetophenyl-oxazolidinediones reverted to the original free acids, and the *p*-carboxyphenyl derivative was partly converted. The N-acetyloxazolidinedione was stable under these conditions.

Determination of oxazolidinediones by acidimetry. The possibility of analysis by the neutral equivalent was tested[17] on four of the oxazolidinediones. Three of these reacted rapidly with aqueous base, giving results having an accuracy of ±0.5% (shown as molecular weights in Table I). Samples varying from 10 to 100 mg. were dissolved in an excess of 0.1*N* sodium hydroxide, which was back-titrated with standard hydrochloric acid to the phenolphthalein endpoint. A blank titration was also run. When applicable, this method requires fewer special solutions than the sodium methylate titration of Berger, Sela, and Katchalski.[18]

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(10) H. D. Dakin, *J. Biol. Chem.*, 82, 439 (1929).
(11) J. Mauthner and W. Suida, *Monatsh.*, 11, 380 (1890).
(12) Z. Takeda and S. Kuroda, *Chem. Zent.*, I, 2304 (1925).
(13) W. Borsche and J. C. Titsingh, *Ber.*, 40, 5016 (1907).
(14) J. Plöchl, *Ber.*, 19, 7 (1886).
(15) A. D. Ainley and R. Robinson, *J. Chem. Soc.*, 453 (1937).
(16) R. G. Coghill and T. B. Johnson, *J. Am. Chem. Soc.*, 47, 189 (1925).
(17) The use of this method was suggested by Jerome Gourse.
(18) A. Berger, M. Sela, and E. Katchalski, *Anal. Chem.*, 25, 1554 (1953).

Cyclodehydrations in Liquid Sulfur Dioxide

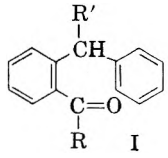
CHARLES K. BRADSHER AND E. FAYE SINCLAIR

Received Aug. 22, 1956

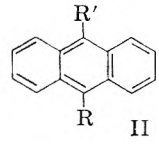
Phosphorus pentoxide has long been used as a cyclizing agent, commonly in suspension in boiling benzene or toluene. It is usual that the phosphorus pentoxide in such a medium forms a sticky coagu-

lum[1] which adheres to the reaction vessel and fairly effectively removes itself from the sphere of the reaction. While this difficulty is somewhat mitigated by the use of a dispersing agent such as Filter-Cel,[1] it is by no means eliminated.

We have found that with vigorous stirring, phosphoric anhydride can be maintained in a fairly fine suspension in liquid sulfur dioxide. Despite the low temperature of this mixture (−10°), it is effective in bringing about the aromatic cyclodehydration of some *o*-benzylbenzophenones (I). As ordinarily carried out, the cyclization I → II appears to be acid-catalyzed[2] and is usually thought of as in-



I



II

volving a conjugate acid formed by addition of a proton to the ketone (I).[3-5] One would expect that a Lewis acid could function in the place of a proton, and would add the present cyclization to the growing list of instances in which phosphorus pentoxide has been found to function in the manner expected of a Lewis acid.[6]

The cyclization selected for detailed study was that of *o*-benzylbenzophenone[7] (I, R = C_6H_5; R′ = H) to yield 9-phenylanthracene (II, R = C_6H_5; R′ = H), and detailed results may be seen in Table I.

It will be seen that an insignificant increase in yield is effected by increasing the time of reaction or the quantity of phosphoric anhydride used, and in each case, ketone was usually recovered. It was not found beneficial to add the pentoxide at 1-hr. intervals. Sulfur dioxide which had been predried over phosphorus pentoxide worked no better than the commercial grade; addition of a small amount of water, however, stopped the cyclization. When the reaction was carried out at room temperature by use of a sealed tube, it gave an unidentified black solid plus some unreacted ketone. Finally, the addition of various reagents including trifluoroacetic acid and anisole was without benefit.

TABLE I

CYCLIZATION OF *o*-BENZYLBENZOPHENONE

P_2O_5, g.[a]	Time, Hr.	Conditions	Phenylanthracene, %[b]
2	2	...	50
2	3	...	52
2	6	...	59
5	2	...	59[c]
5	6	...	57.5[d]
4[e]	4	Portionwise addition	58
0.5	2	...	[f]
5[g]	2	Dry SO_2	53
2[h]	2	H_2O	...[i]
2[j]	19	Room temperature	...[k]
5[l]	2	CH_3COOH	...[m]
5[n]	2	$CH_3OC_6H_5$	44[c]

[a] In all runs, 500 mg. of *o*-benzylbenzophenone was used. [b] Except as noted, all yields are for products melting not lower than 150° (lit.[7] 154–155°). [c] Average of two runs. [d] M.p. 149–152°. Evaporation of the mother liquor yielded 110 mg. of material (m.p. 45–52°) which was probably impure ketone (m.p.[7] 50–52°). [e] One gram of phosphorus pentoxide was used at the start, and then one gram added hourly. [f] No hydrocarbon was isolated. The product melted at 49–52°. [g] Liquid sulfur dioxide was dried over phosphorus pentoxide and then distilled into the reaction vessel. [h] Six drops of water added. [i] The ketone (500 mg.), m.p. 49–52°, was recovered. [j] The reaction was carried out in a sealed tube which was rotated at room temperature for nineteen hours. Only 30 ml. of liquid sulfur dioxide was used. [k] A considerable quantity of an unidentified black carbon tetrachloride-insoluble product was formed. No hydrocarbon was insolated. [l] Trifluoroacetic acid (13 ml.) was added. [m] Only 57 mg. of impure material was obtained, m.p. 130–140°. While this could have contained some hydrocarbon, the over-all yield in the reaction must be less than 12%. [n] Anisole (12 ml.) was added.

It was a consistent observation that a sizable fraction of the starting material could not be accounted for either as recovered starting material or as product. When pure 9-phenylanthracene was exposed to the action of phosphorus pentoxide for 2 hr. under the conditions of the reaction, only 81% of it could be recovered and a portion of this appears to have been lost as a water-soluble fraction.[8]

The new cyclodehydration medium was tried with several additional ketones and the results are shown in Table II.

The behavior of the last two ketones (I) deserves some comment. The 2-benzyl-4′-cyanobenzophenone (I, R = p-C_6H_4CN; R′ = H) which failed to cyclize with phosphorus pentoxide is converted to 9-(p-carboxyphenylanthracene by the ac-

(1) Johnson, *Org. Reactions*, 2, 170 (1944).

(2) The recently announced discovery [Vingiello and Borkovec, *J. Am. Chem. Soc.*, 78, 3205 (1956)] that cyclizations of this type may be carried out by heating the ketones (I) with activated alumina may indicate the possibility of another pathway for the reaction.

(3) Berliner, *J. Am. Chem. Soc.*, 64, 2894 (1942).

(4) Bradsher and Smith, *J. Am. Chem. Soc.*, 65, 854 (1943).

(5) Bradsher and Vingiello, *J. Am. Chem. Soc.*, 71, 1434 (1949).

(6) *E.g.*, Lecher, *Ber.*, 46, 2664 (1913); Steinkopf, *Ann.*, 413, 343 (1917); Steinkopf and Schubert, *Ann.*, 424, 1 (1921); Hartough and Kosak, *J. Am. Chem. Soc.*, 69, 3098 (1947); Perfetti and Levine, *J. Am. Chem. Soc.*, 75, 626 (1953); Luder and Zuffanti, *The Electronic Theory of Acids and Bases*, John Wiley and Sons, Inc., New York, N. Y., 1946, pp. 116, 132.

(7) Bradsher, *J. Am. Chem. Soc.*, 62, 486 (1940).

(8) The recent observation [Lecher, Chao, Whitehouse, and Greenwood, *J. Am. Chem. Soc.*, 76, 1045 (1954)] that benzene heated at 275° with P_2O_5, followed by hydrolysis, produced phenylphosphonic acid in good yield, suggests the possibility that the much more reactive anthracene nucleus might be attacked similarly at a much lower temperature. It is also possible that a polar solvent, such as sulfur dioxide might favor the attack on the aromatic nucleus.

TABLE II

CYCLIZATION OF OTHER *o*-BENZYLPHENONES (I)

R′	R	P_2O_5, g.[a]	Yield II, %
C_6H_5	C_6H_5[b]	2	48.5[c]
C_6H_5	C_6H_5	5	60[d]
H	p-C_6H_4Cl[e]	5	44[f]
H	p-C_6H_4CN[g]	4[h]	...[i]
H	p-$C_6H_4OCH_3$	5[j]	60[k]

[a] Except as noted, 500 mg. of ketone was used. [b] Bradsher and Smith, *J. Am. Chem. Soc.*, 65, 451 (1943). [c] M.p. 245–247° (lit.[b] 245–247°). [d] M.p. 240–243.5°. [e] Ref. 5. [f] M.p. 176.5–179° (lit.[5] 179–180°). In addition, 97 mg. of ketone, m.p. 72–73° (lit.[9] 73°) was recovered. [g] Ref. 9. [h] Reaction using 370 mg. of ketone. [i] Ketone (258 mg.) was recovered, m.p. 103.5–105° (lit.[9] 104.5–105°). [j] M.p. 69–70°, Ref. 10. [k] Yellow shiny needles, m.p. 165.5–166.5°. The analytical sample, crystallized from ethanol, melted at 168–168.5°. *Anal.* Calc'd for $C_{21}H_{16}O$: C, 88.73; H, 5.65. Found: C, 89.03; H, 6.05.

tion of hydrobromic and acetic acids.[9] The attempted cyclization of 2-benzyl-4′-methoxybenzophenone (I, R = *p*-$C_6H_4OCH_3$; R′ = H) with hydrobromic and acetic acids yielded only an impure brown oil.[10]

In a single preliminary experiment, it was shown that the dehydration of *o*-benzylbenzoic acid to anthrone could be brought about in 39% yield using the sulfur dioxide medium. While the sulfur dioxide–phosphorus pentoxide combination, when used in the cyclization of *o*-benzyl phenones, gives a yield almost consistently poorer than that obtained with the boiling hydrobromic-acetic acid mixture, the low temperature at which cyclodehydration occurs in the sulfur dioxide medium makes it of possible interest in cyclizations involving heat-sensitive compounds.

EXPERIMENTAL

General procedure. The entire apparatus, consisting of a 200 ml. 3-necked flask with a mechanical stirrer and dry ice condenser fitted with a calcium chloride tube, was dried by heating with a flame before use. About 50 ml. of liquid sulfur dioxide from a tank was run into the flask and the ketone (usually 500 mg.) was added. Stirring was begun and the phosphorus pentoxide added. The reaction mixture (usually yellow) was mechanically stirred for several hours, at the end of which about 20 ml. of carbon tetrachloride was added. The mixture was allowed to stand until the ice first formed had melted, and most of the sulfur dioxide had evaporated. The carbon tetrachloride and water layers were separated, and the water washed twice more with carbon tetrachloride. The carbon tetrachloride layer was washed three times with water, dried over calcium chloride, and then concentrated. Ethanol was added to the concentrate and the solution concentrated further to remove the carbon tetrachloride and to induce crystallization.

Effect of the cyclizing medium upon 9-phenylanthracene. The reaction vessel was charged with 50 ml. of liquid sulfur dioxide and 467 mg. of 9-phenylanthracene (theoretical yield from 500 mg. of ketone), and 2 g. of phosphorus pentoxide. The mixture was stirred for 2 hr. and worked up in the usual way. In two runs, the yield was 373 mg. (80%), m.p. 151–153.5° in the first and 384 mg. (82%), m.p. 151–154.5° in the second. Evaporation of the mother liquors yielded a dark reddish brown material (50 mg.; 26 mg.).

Cyclization of o-benzylbenzoic acid. One-half gram of *o*-benzylbenzoic acid[11] in 50 ml. of sulfur dioxide was stirred for 2 hr. with 5 g. of phosphorus pentoxide and the mixture worked up as in the standard procedure. Light yellow needles of 9-anthrone were obtained, m.p. 152–154° (lit.[12] 154°); yield, 176 mg. (39%).

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(9) Bradsher and Vingiello, *J. Org. Chem.*, 13, 786 (1948).
(10) F. A. Vingiello, Ph.D. thesis (1947).
(11) Barnett, Cook and Nixon, *J. Chem. Soc.*, 504 (1927).
(12) Lagodzinski, *Ber.*, 38, 2301 (1905).

Symmetrical N,N,N′,N′-Tetraalkylpiperazinium Di-alkylsulfates

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Received Aug. 21, 1956

Smith, Curry, and Eifert[1] have described the preparation of a series of symmetrical N,N′-dialkylpiperazines, in which the alkyl groups were *n*-octyl, *n*-decyl, *n*-dodecyl, *n*-tetradecyl, and *n*-hexadecyl. From them they prepared the corresponding dihydrobromides, N,N′-dialkyl-N,N′-dimethylpiperazinium di-methiodides and N,N′-dialkyl-N,N′-diethyl-piperazinium di-ethiodides. They described one piperazinium di-alkylsulfate, N,N′-di-*n*-tetradecyl-N,N′-dimethyl-piperazinium di-methylsulfate.

Extending our studies in the fields of morpholinium and thiamorpholinium alkyl sulfates[2] the above series of symmetrical N,N′-dialkylpiperazines has been lengthened to include N,N′-di-*n*-octadecylpiperazine and two series of N,N′-dialkyl-N,N′-dimethyl-piperazinium di-methylsulfates and N,N′-dialkyl-N,N′-diethyl-piperazinium di-ethylsulfates have been prepared.

EXPERIMENTAL

N,N′-Dialkylpiperazines were prepared by refluxing 0.05 mole of anhydrous piperazine (Bios Laboratories, Inc.) with 0.12 mole of alkyl bromide in 30–40 ml. of absolute alcohol for 18–24 hr. After cooling, the resultant salt was filtered and redissolved in alcohol. The solution was made alkaline with dilute sodium hydroxide and the resultant precipitate of the free amine was filtered, washed with water, refiltered, and, after air drying, was recrystallized from ethyl acetate. The dialkylpiperazines are white waxy solids, insoluble in water and only slightly soluble in cold alcohol and ethyl acetate. The yields obtained varied from 55% to 85%. The melting points were in substantial agreement with those given by Smith, Curry, and Eifert.[1] N,N′-di-*n*-octadecylpiperazine melts at 97–98°C., uncorr.

(1) D. R. Smith, J. W. Curry and R. L. Eifert, *J. Am. Chem. Soc.*, 72, 2969 (1950).
(2) W. F. Hart, M. E. McGreal and J. B. Niederl, *J. Am. Chem. Soc.*, 66, 1610 (1944); 68, 714 (1946); 70, 618 (1948); 71, 3569 (1949); *J. Org. Chem.*, 14, 579 (1949).

TABLE I

SYMMETRICAL N,N,N',N'-TETRAALKYLPIPERAZINIUM DI-ALKYLSULFATES
$[(R)(R')N(CH_2CH_2)_2N(R)(R')]^{++}2R'SO_4^-$

R	R'	Formula	M.P., °C.[a]	C Calc'd	C Found	H Calc'd	H Found	N Calc'd	N Found
n-Decyl	Methyl	$C_{28}H_{62}N_2O_8S_2$	179–180	54.31	54.10	10.09	9.68	4.52	4.85
n-Decyl	Ethyl	$C_{32}H_{70}N_2O_8S_2$	165–166	56.93	57.11	10.45	10.49	4.15	4.10
n-Dodecyl	Methyl	$C_{32}H_{70}N_2O_8S_2$	275 dec.	56.93	57.16	10.45	10.39	4.15	4.08
n-Dodecyl	Ethyl	$C_{36}H_{78}N_2O_8S_2$	250 dec.	59.13	58.92	10.75	10.90	3.84	3.87
n-Tetradecyl[b]	Methyl	$C_{36}H_{78}N_2O_8S_2$	265 dec.	59.13	58.14	10.75	10.40	3.84	3.76
n-Tetradecyl	Ethyl	$C_{40}H_{86}N_2O_8S_2$	236 dec.	61.02	61.75	11.01	11.23	3.55	3.44
n-Hexadecyl	Methyl	$C_{40}H_{86}N_2O_8S_2$	260 dec.	61.02	61.02	11.01	11.10	3.55	3.52
n-Hexadecyl	Ethyl	$C_{44}H_{94}N_2O_8S_2$	250 dec.	62.66	63.20	11.23	11.19	3.32	3.29
n-Octadecyl	Methyl	$C_{44}H_{94}N_2O_8S_2$	258 dec.	62.66	63.16	11.23	10.91	3.32	3.20
n-Octadecyl	Ethyl	$C_{48}H_{102}N_2O_8S_2$	242 dec.	64.09	64.81	11.43	11.56	3.11	3.05

[a] Melting points are uncorrected. [b] Reference 1.

Anal. Calc'd for $C_{40}H_{82}N_2$: C, 81.20; H, 13.98; N, 4.73. Found: C, 80.89; H, 14.02; N, 4.77.

N,N,N',N'-Tetralkylpiperazinium di-alkylsulfates were prepared by dissolving 0.02 mole of the dialkylpiperazine in a sufficient volume of boiling ethyl acetate, adding 0.042 mole of the redistilled dialkyl sulfate and refluxing for 3 hr. The reaction mixture was chilled filtered, and the product recrystallized from ethyl acetate. In the case of N,N'-di-*n*-octadecylpiperazine, ethyl isovalerate was used as the reaction solvent. The yields obtained varied from 35 to 45%.

The dialkyl sulfates are white waxy solids, insoluble in ether and are only slightly soluble in cold alcohol and ethyl acetate. They are only slightly soluble in hot mineral oil.

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The Conjugative Effect of the Dimethylsulfonio Group in an Aliphatic System

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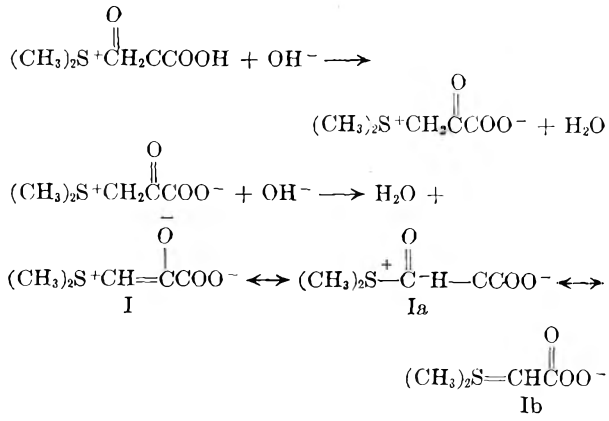
Received Aug. 20, 1956

In connection with the preparation of sulfonium compounds as possible lipotropic agents,[1] we observed that dimethylsulfoniopyruvic acid bromide



behaves as a diprotic acid. Indeed, the two endpoints are readily determined with methyl orange and phenolphthalein, respectively. The corresponding methyl and ethyl esters behave as monoprotic acids, pK_a, 5.5. The potentiometric titration curves for acid and ester are shown in Fig. 1. It seemed unlikely that the unusually high acidity is due solely to the inductive effect of the electron-withdrawing dimethylsulfonio group, but rather to the resonance stabilization of the conjugate base (I) in which the dimethylsulfonio group is conjugated with the keto group by expanding its sulfur valence shell to ten

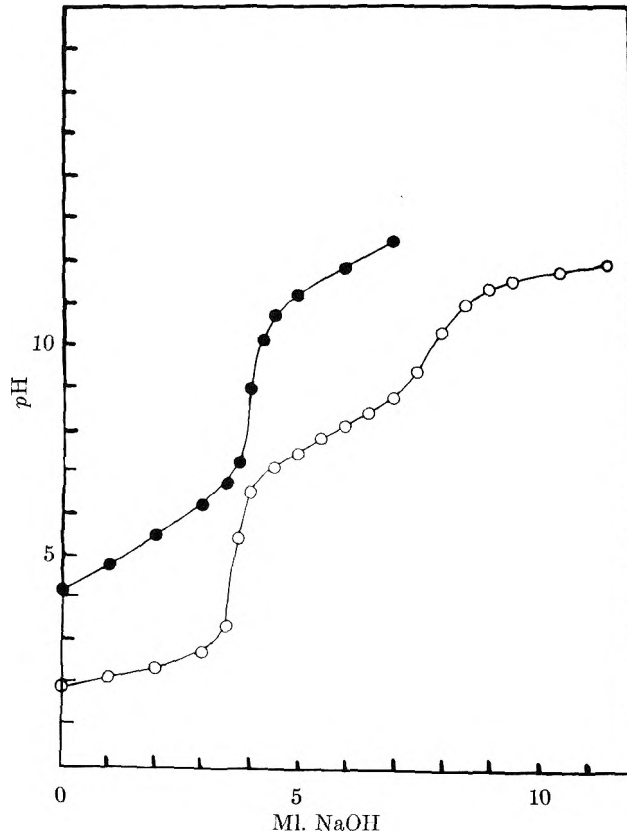


Fig. 1.—TITRATION CURVES FOR DIMETHYLSULFONIO DERIVATIVES OF PYRUVIC ACID. DOTS, ESTER; CIRCLES, ACID.

(1) N. F. Blau, J. W. Johnson, and C. G. Stuckwisch, *J. Am. Chem. Soc.*, **76**, 5106 (1954).

electrons. Structure (Ib), having no separation of charge, might be expected to contribute significantly to the resonance stability and thus favor the acidity of the methylene group.

For purposes of comparison we prepared the corresponding trimethylammonio derivative of pyruvic acid which cannot conjugate by expansion of the nitrogen valence shell. This derivative behaves as a monoprotic acid. Bordwell and Boutan[2] have reported a similar con ugative effect in *p*-dimethylsulfonio phenols.

Bromopyruvic acid and its methyl and ethyl esters react rapidly with dimethyl sulfide to give excellent yields of the corresponding dimethylsulfonio compounds. The reactions with the esters are best carried out without a solvent or a solvent in which the product is insoluble. Polar solvents such as alcohols are conducive to the formation of trimethylsulfonium bromide and alkyl methylmercaptopyruvates.[3]

Ethyl chloropyruvate reacts more slowly with dimethyl sulfide than the corresponding bromo compound and the reaction products are difficult to purify. Since chloropyruvic acid is difficult to prepare, dimethylsulfoniopyruvic acid chloride was obtained from the corresponding bromide.

EXPERIMENTAL

Bromopyruvic Acid. Triply distilled pyruvic acid[4] was brominated essentially in accordance with the procedure of Wegman and Dahn.[5] The crystalline mass was dissolved in the minimum volume of ether and diluted with petroleum ether to incipient turbidity. After several crystallizations pearly, white crystals were obtained, melting at 77–79°.[6] Bromopyruvic acid does not deteriorate when stored under petroleum ether in a refrigerator.

Dimethylsulfoniopyruvic acid bromide. To an ice cold solution of 8.35 g. (0.05 mole) bromopyruvic acid in 15 ml. of nitromethane was added 3.2 g. of dimethyl sulfide. On vigorous shaking a solid mass was formed. After standing overnight at room temperature the solid product was broken upon a sintered-glass filter and washed well with ether until it was reduced to a colorless powder. This was dissolved in a minimum volume of methanol and reprecipitated with ether, yielding 11.0 g. (95%) of crystals, m.p. 131–133°.

Anal. Calc'd for $C_5H_9BrO_3S$: Br, 34.92; neut. equiv., 114.5. Found: Br, 34.77; neut. equiv., 115.3.

Methyl bromopyruvate. Methyl pyruvate[7] was brominated according to the procedure of Archer and Pratt[8] for ethyl pyruvate. The compound was obtained in a 62–65% yield, b.p. 82–84° (10 mm.), n_D^{25} 1.4770, d_{20}^{25} 1.656, MRD: calculated 31.10, found, 30.96.

Anal. Calc'd for $C_4H_5BrO_3$: Br, 44.2. Found: Br, 44.4.

Ethyl dimethylsulfoniopyruvate bromide. Ethyl bromopyruvate,[8] 19.5 g. (0.1 mole) was added to 6.8 g. (0.11 mole) of dimethyl sulfide and cooled in an ice bath. After standing overnight, at room temperature, the solid cake was washed with acetone and then with ether until the crystals were no longer sticky. The crystals were dissolved in a minimum amount of cold methanol and precipitated with ether. The yield of product, melting at 88–90°, was 24.3 g., 95%.

Anal. Calc'd for $C_7H_{13}BrO_3S$: Br, 31.1; neut. equiv., 257. Found: Br, 31.2; neut. equiv., 261.

Repeated crystallizations of the sulfonio esters from polar solvents cause a gradual rise in melting point with a concomitant increase in the neutral equivalent due to the formation of $(CH_3)_3SBr$.

Methyl dimethylsulfoniopyruvate bromide. This compound was prepared in 85% yield by the procedure described for the analogous ethyl ester. M.p. 102–103°.

Anal. Calc'd for $C_6H_{11}BrO_3S$: Br, 32.9; neut. equiv., 243. Found: Br, 32.0; neut. equiv., 246.

Dimethylsulfoniopyruvic acid chloride. The chloride was prepared from the corresponding bromide by treatment with silver chloride in the usual manner. M.p. 140–141°.

Anal. Calc'd for $C_5H_9ClO_3S$: Cl, 19.23; neut. equiv., 184.5. Found: Cl, 19.28; neut. equiv., 186.

Trimethylammoniopyruvic acid bromide. Bromopyruvic acid, dissolved in methanol, was treated with excess trimethylamine. The precipitate formed on addition of ether was collected on a filter and washed with ethyl ether. The product was dissolved in absolute alcohol and acidified with hydrogen bromide. Addition of acetone precipitated trimethylammonium bromide. The filtrate from this mixture was diluted with ether and refrigerated overnight. The trimethylammoniopyruvic acid bromide which formed was collected on a filter and was recrystallized from an ethyl alcohol-ethyl ether mixture. M.p. 180–181° dec.

Anal. Calc'd for $C_6H_{12}BrNO_3$: Br, 35.4; neut. equiv., 226. Found: Br, 35.2; neut. equiv., 223.

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(2) F. G. Bordwell and Pierre J. Boutan, *J. Am. Chem. Soc.*, **78**, 87 (1956). This paper presents an excellent discussion, with pertinent references, on the conjugative effect of various sulfur groupings.

(3) Einar Biilmann and K. A. Jensen [*Bull. soc. chim. France*, **3**, 2310 (1936)] observed the same result with ethyl 2-bromopropionate and dimethyl sulfide. As in our case, the corresponding acid did not behave in this manner.

(4) V. E. Price and L. Levintow, *Biochemical preparations*, Eric G. Ball, Editor, John Wiley and Sons, Inc., New York, 1952, p. 22. For the instability of pyruvic acid in storage see C. M. Montgomery and J. L. Well, *Science*, **120**, 843 (1954).

(5) J. Wegman and H. Dahn, *Helv. Chim. Acta*, **29**, 415 (1946).

(6) D. B. Sprinson and E. Chargall [*J. Biol. Chem.*, **164**, 424 (1946)] report a melting point of 74°. Wegman and Dahn, ref. (5), give the melting point as 54–55°. Our product was analyzed for bromine, was converted to the 3,5-dinitrophenylhydrazone, m.p. 180°, and was condensed with benzamide to yield 2-phenyloxazole-4-carboxylic acid, m.p. 206–208°.

(7) A. Weissberger and C. J. Kebler, *Org. Syntheses*, Coll. Vol. 2, 610 (1955).

(8) S. Archer and M. G. Prat, *J. Am. Chem. Soc.*, **66**, 1956 (1944).

Base Strength of Monovinylpyridines

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Received July 31, 1956

The base strengths have been determined for the monovinylpyridines and from these the σ values for

(1) Student affiliates of the AMERICAN CHEMICAL SOCIETY, University of Pittsburgh. This work was done as part of a student affiliate project.

the *m*- and *p*-vinyl groups have been calculated.

This investigation was undertaken in order to provide substituent constants (σ) for use in the Hammett equation[2] for the vinyl group. The large value of the reaction constant (ρ) for the dissociation of the substituted pyridinium ions[3] makes this system a good one in which to look for small effects. Accordingly the pK_a values of the following series of compounds were determined: pyridine, 2-vinylpyridine, 2-methyl-5-vinylpyridine, and 4-vinylpyridine. The 2-vinylpyridine was included to complete the series; the 2-methyl-5-vinylpyridine was used in place of the 3-vinylpyridine which is not commercially available.

Results and discussion. The pK_a values and σ-values obtained are given in Table I. It is of interest to note that in the *meta* position the vinyl group exerts an electron withdrawing effect (σ positive) which may be attributed to an electron withdrawing inductive effect while in the *para* position the vinyl group exerts an electron releasing effect (σ negative) which may be attributed to an electron releasing resonance effect which is more powerful than the inductive effect from the *para* position. The 2-vinylpyridine has almost the same base strength as is calculated for the 3-vinylpyridine indicating that the increase in the inductive effect in going from the *meta* to the *ortho* position is approximately balanced by the resonance effect in the *ortho* position. The resonance which is possible in the pyridine system may cause the σ value for the *para* vinyl group to be more negative in the pyridine system than in other systems.

TABLE I

THERMODYNAMIC DISSOCIATION CONSTANTS OF THE VINYLPYRIDINES

Compound	pK_a 25°C.	pK_a Literature Values	$\sigma_{CH_2=CH-}$[b]
Pyridine	5.15	5.17,[c] 5.18,[d] 5.29[e]	
2-Vinylpyridine	4.92	4.92[f]	
3-Vinylpyridine[a]	4.87		+0.049
4-Vinylpyridine	5.62		−0.083
2-Methyl-5-vinylpyridine	5.67		

[a] Calculated on the basis of a contribution of +0.80 by the methyl group in 2-methyl-5-vinylpyridine. See H. C. Brown, D. H. McDaniel and O. Häfliger, "Dissociation Constants," in *Determination of Organic Structures by Physical Methods*, Edited by E. A. Braude and F. C. Nachod, Academic Press, New York (1955), p. 594 footnote a. [b] Calculated using a value of ρ of 5.685. See Ref. 3. [c] H. C. Brown and X. R. Mihm, *J. Am. Chem. Soc.*, **77**, 1723 (1955). [d] R. K. Murmann and F. Basolo, *J. Am. Chem. Soc.*, **77**, 3484 (1955). [e] Ref. 3. [f] H. E. Reich and R. Levine, *J. Am. Chem. Soc.*, **77**, 4913 (1955). See footnote 10.

(2) (a) L. P. Hammett, *Physical Organic Chemistry*, McGraw-Hill Book Co., Inc., New York, N. Y., 1940, Chapter VII; (b) H. H. Jaffe, *Chem. Revs.*, 53, 191 (1953).

(3) H. H. Jaffe and G. O. Doak, *J. Am. Chem. Soc.*, **77**, 4441 (1955).

EXPERIMENTAL

The vinylpyridines were obtained from the Reilly Tar and Chemical Corporation. They were purified by distilling under reduced pressure, preparing the picrates from the distillate and, after recrystallizing the picrates, hydrolyzing with dilute hydrochloric acid. The picric acid was extracted with benzene and the aqueous layer was then neutralized with dilute sodium hydroxide. The vinylpyridine was extracted with ether and the ether was evaporated under reduced pressure. The vinylpyridine was then rapidly distilled under vacuum and immediately solutions were made for the determination of pK_a. A 50 ml. sample of approximately 0.08*M* vinylpyridine was then titrated with 0.1*N* hydrochloric acid and the *p*H obtained during the course of the titration with a Beckman Industrial Model "M" *p*H meter. All determinations were carried out at room temperature (30°C. ± 1°C.). Values for pK' were obtained as the *p*H at the mid-point of the titration. Corrections for ionic strength were made using the Debye-Hückel equation and corrections for variation of the *p*K with temperature were made using the values given by Albert.[4] The thermodynamic pK_a values at 25° are given in Table I. These values are about 0.05 unit lower than the pK' values.

The authors would like to acknowledge the participation of Anthony Bartis in the preliminary stages of this work. They are grateful for the help given by various members of the Department of Chemistry of the University of Pittsburgh in guiding the project and providing materials and equipment.

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(4) A. Albert, *The Acridines, Their Preparation, Physical, Chemical and Biological Properties and Uses*, Edward Arnold and Co., London, 1951, p. 118.

Synthesis of 7-Nitroindole

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Received Aug. 8, 1956

Rydon and Siddappa[2] were unable to confirm the findings of earlier workers[3] reporting the Fischer cyclization of ethyl pyruvate *o*-nitrophenylhydrazone. Indole derivatives were not obtained in attempted ring closures with various acid catalysts under a variety of conditions; however, a material isomeric with the hydrazone was obtained under certain conditions. Since the analytical results reported by the earlier workers were unsatisfactory for both 7-nitroindolecarboxylic acid and 7-nitroindole, Rydon and Siddappa suggested that these compounds may not have been indoles and quoted a communication from the earlier workers who were in agreement with this conclusion.

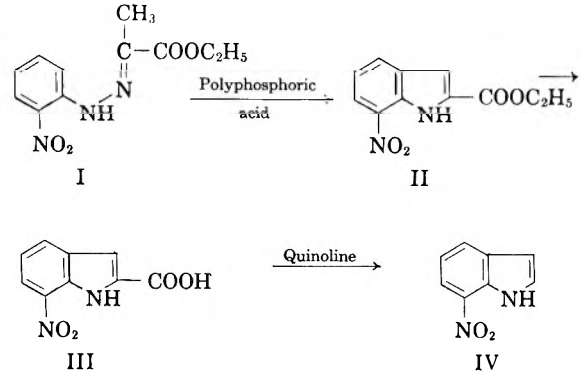
(1) Rosalie B. Hite, Post-doctoral Fellow, 1955–56. Present address: Department of Biochemistry, School of Medicine, University of Utah.

(2) H. N. Rydon, and S. Siddappa, *J. Chem. Soc.*, 2462 (1951).

(3) G. K. Hughes, F. Lions and E. Ritchie, *J. Proc. Roy. Soc. N. S. Wales*, **72**, 209 (1939); *Chem. Abstr.*, **33**, 6837 (1939).

During the course of some recent work with indolecarboxylic acids,[4,5] we also attempted ring closure of ethyl pyruvate *o*-nitrophenylhydrazone. In essence, results analogous to those of Rydon and Siddappa were obtained including the formation of a material isomeric with ethyl pyruvate *o*-nitrophenylhydrazone.

Recently Rydon and Tweddle[6] were successful in the cyclization of some substituted phenylhydrazones by means of polyphosphoric acid. We, therefore, re-investigated the ring closure of ethyl pyruvate *o*-nitrophenylhydrazone (I) with this reagent and were able to isolate ethyl 7-nitro-2-indolecarboxylate (II). Hydrolysis of this product gave 7-nitro-2-indolecarboxylic acid (III) which was decarboxylated to form 7-nitroindole (IV).



7-Nitroindole at a concentration of 100 γ per ml. inhibits the growth of *Lactobacillus arabinosus* 17–5. However, the growth inhibition is not reversed by anthranilic acid, indole, tryptophan or 7-indolecarboxylic acid.

EXPERIMENTAL[7]

Ethyl 7-nitro-2-indolecarboxylate. To 10 g. of polyphosphoric acid was added 2 g. of ethyl pyruvate *o*-nitrophenylhydrazone, and the mixture was stirred on a steam bath until it was homogeneous. The dark brown colored reaction mixture was then heated in an oil bath until a bath temperature of 195° was attained. The reaction mixture was allowed to remain at this temperature for 5 minutes and then removed from the oil bath. When the temperature of the mixture had decreased to 50°, 25 ml. of water was added and the mixture was heated on a steam bath. The solid material was broken by stirring and the suspension poured into a beaker. The remainder of the deep brown insoluble gum was stirred with an additional 25 ml. of water on the steam bath, and the aqueous mixture was combined with the first water suspension.

The water phase which contained a considerable amount of dark solid was extracted with three 50-ml. portions of ether. The ether layer, orange colored, was washed with 5% sodium bicarbonate, with water, and finally dried over sodium sulfate. After drying, the ether was removed on a steam bath, and the residual oil was dissolved in 95% ethanol. To this solution, water was added until it became quite cloudy. This mixture was allowed to cool for several hours in a refrigerator. The yellow-orange needles separating were filtered and recrystallized from aqueous ethanol after treatment with charcoal. On cooling, lemon yellow needles were obtained. Yield of material melting at 92–93° was 250 mg. (13.4%).

Anal. Calc'd for $C_{11}H_{10}N_2O_4$: C, 56.41; H, 4.30; N, 11.96. Found: C, 56.50; H, 4.35; N, 11.95.

7-Nitro-2-indolecarboxylic acid. Ethyl 7-nitro-2-indolecarboxylate (100 mg.) was added to 10 ml. of a 10% aqueous solution of potassium hydroxide. The mixture was heated with stirring on a steam bath for several minutes. At the end of this time the deep red solution was filtered and allowed to cool. An equal volume of water was added to the mixture which was then vigorously shaken. This mixture was filtered and the filtrate was acidified with 6*N* hydrochloric acid. The cream-yellow solid was removed by filtration and recrystallized twice from aqueous ethanol. The very pale yellow needles were dried at 140° for 4 hours. Yield of material melting at 271–272° was 49.5 mg. (56%).

Anal. Calc'd for $C_9H_6N_2O_4$: C, 52.43; H, 2.93; N, 13.59. Found: C, 52.54; H, 3.24; N, 13.62.

7-Nitroindole. To 3 ml. of redistilled quinoline containing a trace of copper chromite was added 100 mg. of 2-carboxy-7-nitroindole. This mixture was heated in an oil bath at 205° for 2 hours with occasional stirring. At the end of this time, the hot black mixture was poured into a solution of 4 ml. of concentrated hydrochloric acid and ice. The mixture was filtered, and both the precipitate and the filtrate were extracted several times with ether. The ether extracts were combined and dried over sodium sulfate. Evaporation of the ether on a steam bath with subsequent cooling gave deep yellow needles. This material was recrystallized from aqueous ethanol. Yield of material melting at 95–96° was 39 mg. (49.5%); λ_{max} (95% ethanol): 232 mμ, 364 mμ; a plateau at 242–251 mμ with a slight maximum at 248–250 mμ; λ_{min}: 285 mμ. This solid when dissolved in Kovac reagent (Ehrlich reagent using isoamyl alcohol as solvent) gave a deep red color.

Anal. Calc'd for $C_8H_6N_2O_2$: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.61; H, 4.03; N, 17.21.

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(4) H. Singer and W. Shive, *J. Am. Chem. Soc.*, **77**, 5700 (1955).

(5) H. Singer and W. Shive, *J. Org. Chem.*, **20**, 1458 (1955).

(6) H. F. Rydon and J. C. Tweddle, *J. Chem. Soc.*, 3499 (1955).

(7) All melting points are corrected; the authors are indebted to Dr. C. G. Skinner and Mr. J. Russell Claybrook for the microanalyses reported. The ultraviolet spectrum was determined on a Beckman Model DK-2 Recording Spectrophotometer.

Palladium Catalyzed Reduction of *p,p'*-Dihydroxybenzophenone

M. LEVINE AND S. C. TEMIN

Received July 12, 1956

Hydrogenation of *p,p'*-dihydroxybenzophenone (I) to *p,p'*-dihydroxydiphenylmethane(II) was carried out in excellent yield with palladium on carbon black. No report had previously been made on the use of a palladium catalyst in the reduction of a dihydroxybenzophenone. Bradlow and Van der

Werf[1] reported the only previous reductive system used on (I), a modified Clemmensen method which was unsatisfactory because of the formation of resinous products.

In general, the Clemmensen[1] and the Wolff-Kishner,[2] or modifications of these, are used for the reduction of aromatic ketones. Benzophenone has been reduced in excellent yield by both of these methods.[1,2] Using the techniques of the modified Clemmensen method, however, Bradlow and Van der Werf[1] obtained only a 25% yield of (II). The Wolff-Kishner reduction has apparently not been applied to (I), but the reduction of *p,p'*-dichlorobenzophenone[3] by this method gave only 21% of *p,p'*-dichlorodiphenylmethane.

Although catalytic methods have not been widely used for the reduction of ketones, a number of studies have been made. Hartung and Crossley[4] reduced a number of propiophenones with palladized carbon, and the work was extended to a few aromatic systems by Baltzly and Buck.[5] Horning and Reisner[6] described the palladium catalyzed reduction of several β-aroylpropionic acids to the α-arylbutyric acids.

As a result of the limited number of hydrogenations previously reported using palladium, it was not possible to predict what effect hydroxyl substituents on benzophenone would have on the reduction. Thus, it was interesting that catalytic reduction of (I) with palladium-carbon catalyst absorbed 100% of the theoretical hydrogen uptake. On using platinum under similar conditions, the hydrogenation resulted in the reduction of the aromatic ring.

EXPERIMENTAL

To a solution of 10.7 g. (0.05 mole) of *p,p'*-dihydroxybenzophenone in 100 ml. isopropyl alcohol was added 3 g. of 5% palladium on carbon powder (Baker and Co., Inc.). The reduction, carried out in a low pressure Parr hydrogenator, was complete in about 5 hours at 25°C. with a 100% theoretical hydrogen uptake. The catalyst was removed by filtration, and after the filtrate was reduced to a small volume, a crystalline solid settled out upon addition of an equal volume of water. Recrystallization of this material from water gave a 95% yield of *p,p'*-dihydroxydiphenylmethane, m.p. 161–162°.[7] A diacetoxy derivative was prepared, m.p. 70–71°.[7]

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(1) H. L. Bradlow and C. A. Van der Werf, *J. Am. Chem. Soc.*, **69**, 1254 (1947).

(2) K. W. Rosenmund, F. Zetzche and C. Flutsch, *Ber.*, **54**, 2888 (1921).

(3) O. Grummitt and A. Jenkins, *J. Am. Chem. Soc.*, **68**, 914 (1946).

(4) W. H. Hartung and F. S. Crossley, *J. Am. Chem. Soc.*, **56**, 158 (1934).

(5) R. Baltzly and J. S. Buck, *J. Am. Chem. Soc.*, **65**, 1984 (1943).

(6) E. C. Horning and D. B. Reisner, *J. Am. Chem. Soc.*, **71**, 1036 (1949).

(7) W. Staedel and C. Beck, *Ann.*, **194**, 318 (1878).

Some New Quaternary-Substituted Alkyl Morpholinium Chlorides and Pyrrolidinium Alkyl Sulfates[1]

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Received Aug. 13, 1956

Studies in the fields of morpholinium halides and alkyl sulfates and thiamorpholinium alkyl sulfates[2] have been extended to include a group of N-alkyl-N-substituted alkyl morpholinium chlorides and two series of symmetrical, N,N-dialkyl pyrrolidinium alkyl sulfates prepared from a group of five N-alkyl pyrrolidines. These quaternary morpholinium and pyrrolidinium compounds were prepared for the purpose of determining their bactericidal properties in comparison with those of quaternary morpholinium and thiamorpholinium compounds previously described. The results of these bacteriological tests are as yet not complete.

No systematic study of the longer chain N-alkyl pyrrolidines and the corresponding N-alkyl pyrrolidinium alkyl sulfates has been made. A recent German patent[3] describes the preparation of N-*n*-dodecyl-N-methyl pyrrolidinium methosulfate. Ames, Bowman, Buttle and Squires[4] have described the preparation of N-*n*-dodecyl pyrrolidine and the hydrochloride of this compound. Jerchel and Kimmig[5] have prepared N-*n*-dodecyl-N-phenyl pyrrolidinium bromide. Erickson and Keps[6] have recently described the preparation of N-*n*-dodecyl and N-*n*-octadecyl pyrrolidine and N,N-di-*n*-dodecyl and N,N-di-*n*-octadecyl pyrrolidinium chlorides by the reaction of the appropriate primary or secondary amine with 1,4-dichlorobutane in the presence of excess sodium carbonate in butyl alcohol solution. The N-alkyl pyrrolidines were analyzed as their picrates.

EXPERIMENTAL

N-Alkyl morpholines were prepared by the method previously described.[2]

N-Alkyl-N-substituted alkyl morpholinium chlorides were prepared by reacting equimolar quantities (approximately 0.02 mole) of the N-alkyl morpholine and the substituted alkyl chloride without solvent or in an equal volume of dry

(1) Presented before the Division of Organic Chemistry, Delaware Valley Regional Meeting of the American Chemical Society, Philadelphia, Feb. 16, 1956.

(2) W. F. Hart, M. E. McGreal and J. B. Niederl, *J. Am. Chem. Soc.*, **63**, 1476 (1941); **66**, 840 (1944); **66**, 1610 (1944); **67**, 1227 (1945); **68**, 714 (1946); **70**, 618 (1948); **71**, 3569 (1949); *J. Org. Chem.*, **14**, 579 (1949).

(3) H. Krzikalla and A. Tartter, to Badische Anilin and Soda-Fabrik, Ger. Pat. 805,521 (May 21, 1951); *C. A.*, **46**, 9612 (1952).

(4) D. E. Ames, R. E. Bowman, G. A. H. Buttle and S. Squires, *J. Chem. Soc.*, 1057 (1952).

(5) D. Jerchel and J. Kimmig, *Ber.*, **83**, 277 (1950).

(6) J. G. Erickson and J. S. Keps, *J. Am. Chem. Soc.*, **77**, 485 (1955).

TABLE I

N-ALKYL-N-SUBSTITUTED ALKYL MORPHOLINIUM CHLORIDES $[O(CH_2CH_2)_2N(R)(R')]^+Cl^-$

	R	R′	Formula	M.P., °C.[a]	Analysis C Calc'd	C Found	H Calc'd	H Found	N Calc'd	N Found	Cl Calc'd	Cl Found
I	*n*-Hexadecyl	Methoxymethyl	$C_{22}H_{46}ClNO_2$	179–180	...	...	...	...	3.57	3.56	9.04	9.09
II	*n*-Hexadecyl	1-Nitropropyl	$C_{23}H_{47}ClN_2O_3$	171–172	63.48	63.62	10.88	10.96	6.43	6.32	8.14	8.15
III	*n*-Hexadecyl	Cyanomethyl	$C_{22}H_{43}ClN_2O$	150–152	...	...	...	...	7.25	7.30	9.16	9.11
IV	*n*-Hexadecyl	α-Naphthylmethyl	$C_{31}H_{50}ClNO$	132–134	76.26	76.50	10.32	10.38	2.86	2.80	7.26	7.12
V	*n*-Hexadecyl	Acetoxymethyl	$C_{23}H_{46}ClNO_3$	178	68.36	68.67	11.47	11.50	3.46	3.53	8.77	8.65
VI	*n*-Hexadecyl	*o*-Chlorobenzyl	$C_{27}H_{47}Cl_2NO$	174–175	68.61	68.29	10.02	10.08	2.96	2.92	15.00	14.91
VII	*n*-Decyl	Acetoxymethyl	$C_{17}H_{34}ClNO_2$	175–176	63.81	64.43	10.71	10.81	4.37	4.49	11.08	11.12
VIII	*n*-Decyl	*o*-Chlorobenzyl	$C_{21}H_{35}Cl_2NO$	174–175	64.93	65.33	9.08	9.22	3.60	3.71	18.25	18.31
IX	*n*-Decyl	1-Nitropropyl	$C_{17}H_{35}ClN_2O_3$	173	58.18	58.50	10.05	10.10	7.98	7.91	10.10	10.63
X	*n*-Decyl	2-Phenoxyethyl	$C_{22}H_{38}ClNO_2$	250	...	...	...	...	3.57	3.68	9.04	9.14

[a] Melting points are uncorrected.

TABLE II

N-ALKYL PYRROLIDINES $(C_2H_4)_2N—R$

R	Formula	B.P. (M.P.) °C.[a]	Analysis C Calc'd	C Found	H Calc'd	H Found	N Calc'd	N Found
n-Decyl	$C_{14}H_{29}N$	111–112/1.9 mm.	79.54	79.73	13.82	13.92	6.62	6.61
n-Dodecyl[b]	$C_{16}H_{33}N$	150–152/7 mm.	80.25	80.02	13.89	13.89	5.85	5.80
n-Tetradecyl	$C_{18}H_{37}N$	150/3 mm.	80.82	80.84	13.94	13.92	5.24	5.19
n-Hexadecyl	$C_{20}H_{41}N$	160–163/3 mm. (14)	81.27	80.64	13.98	13.95	4.77	4.60
n-Octadecyl[c]	$C_{22}H_{45}N$	130–135/0.5 mm. (26–27)	81.66	81.45	14.02	13.91	4.32	4.26

[a] Boiling points and melting points are uncorrected. [b] References 4 and 6. [c] Reference 6.

TABLE III

SYMMETRICAL N,N-DIALKYL PYRROLIDINIUM ALKYL SULFATES

$[(C_2H_4)_2N(R)(R')]^+SO_4R'^-$

R	R′	Formula	M.P., °C.[a]	Analysis C Calc'd	C Found	H Calc'd	H Found	N Calc'd	N Found
n-Decyl	Methyl	$C_{15}H_{33}NO_4S$	42–43	56.95	56.72	10.45	10.07	4.15	4.20
n-Decyl	Ethyl	$C_{16}H_{35}NO_4S$	57–58	59.15	59.28	10.76	10.50	3.83	3.79
n-Dodecyl[b]	Methyl	$C_{18}H_{39}NO_4S$	55–57	59.15	59.35	10.76	10.71	3.83	3.86
n-Dodecyl	Ethyl	$C_{20}H_{43}NO_4S$	58–60	61.03	60.97	11.01	11.08	3.56	3.53
n-Tetradecyl	Methyl	$C_{23}H_{43}NO_4S$	69–70	61.03	61.02	11.01	11.17	3.56	3.60
n-Tetradecyl	Ethyl	$C_{22}H_{47}NO_4S$	79–80	62.67	62.70	11.23	11.17	3.32	3.32
n-Hexadecyl	Methyl	$C_{22}H_{47}NO_4S$	69	62.67	62.80	11.23	10.87	3.32	3.28
n-Hexadecyl	Ethyl	$C_{24}H_{51}NO_4S$	65	64.09	63.75	11.43	11.41	3.11	3.19
n-Octadecyl	Methyl	$C_{24}H_{51}NO_4S$	62–63	64.09	63.82	11.43	11.34	3.11	3.05
n-Octadecyl	Ethyl	$C_{26}H_{55}NO_4S$	67–68	65.35	65.16	11.60	11.75	2.93	2.96

[a] Melting points are uncorrected. [b] Reference 3.

toluene (Table I, compounds V through IX). The reaction mixture was refluxed until upon cooling a semi-solid waxy mass was formed. The time required varied from 4–82 hr. Compound I was formed by reaction at room temperature. Compound X required heating in an oil bath for five hours at 200° to complete the reaction.

At the end of the reaction period the solidified waxy mass was washed several times with ether, and recrystallized twice from ethyl acetate. The products are insoluble in ether and cold ethyl acetate, soluble in alcohol, and from slightly soluble to very soluble in water.

N-Alkyl pyrrolidines (Table II) were prepared by refluxing for 24 hr. 0.3 mole pyrrolidine, 0.2 mole of the alkyl bromide and 0.11 mole anhydrous potassium carbonate in a 100 ml. of methanol. The reaction mixture was filtered while hot on a sintered glass filter, and the insoluble salts were washed with two portions of boiling methanol.

The alcoholic filtrate was treated with 1 g. of decolorizing carbon and filtered while hot. The methanol and excess pyrrolidine were removed at reduced pressure and the residue was taken up in ethyl acetate and again filtered to remove a small amount of inorganic salts. The ethyl acetate was removed at reduced pressure and the N-alkyl pyrrolidine was isolated by fractional distillation *in vacuo*.

N-Alkyl pyrrolidines were also prepared by long refluxing of the appropriate primary amine with a 10% excess of 1,4-dichlorobutane in the presence of a large excess of potassium carbonate in ethyl alcohol solution. The yields obtained by this procedure were lower than those obtained by alkylation of pyrrolidine.

Symmetrical N,N-dialkyl pyrrolidinium alkyl sulfates (Table III) were prepared by reacting equimolar quantities (approximately 0.01 mole) of the N-alkyl pyrrolidine and redistilled dimethyl or diethyl sulfate in 5 g. of acetone.[3] The alkyl sulfate was added gradually with stirring to the boiling acetone solution of the *N*-alkyl pyrrolidine. The reaction mixture was allowed to cool slowly to room temperature and was then allowed to stand overnight. The *n*-decyl and *n*-dodecyl pyrrolidinium alkyl sulfates which formed as yellow oils were triturated several times with small volumes of petroleum ether and crystallized upon drying *in vacuo* over phosphorous pentoxide. The *n*-tetradecyl, *n*-hexadecyl and *n*-octadecyl pyrrolidinium alkyl sulfates formed as waxy solids. These were triturated three times with small volumes of petroleum ether, recrystallized three times from acetone or ethyl acetate, and finally dried *in vacuo* over phosphorous pentoxide. These compounds are all white, water soluble solids. The lower members of the series are hygroscopic.

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Hydrazinolysis of 1-(Alkyldithioate)-piperidine

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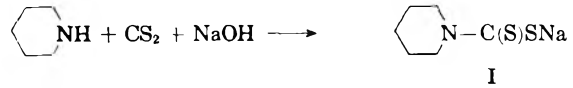
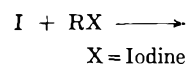
Received Aug. 17, 1956

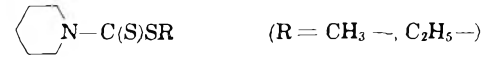
A study of the hydrazinolysis of 1-(alkyldithioate)-piperidine,[1] II, was undertaken for the purpose of preparing a thiosemicarbazide in which the fourth position embraced a reduced ring system including the nitrogen. These have not been previously described in the literature. The required II, also not previously described in the literature, were prepared by the following sequence of reactions:



I

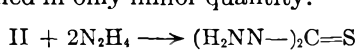


X = Iodine

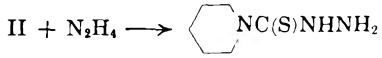


II

It was found that the I need not be isolated and that the alkylation step could be carried out in the suspension of I obtained in the initial reaction. Surprisingly, the hydrazinolysis of II (R = C_2H_5-) proceeded chiefly with the elimination of both the thioalkyl- and piperdyl-radicals, thiocarbohydrazide, III, being the major product, while the desired product, 1-(aminothiocarbamyl)-piperidine,[2] IV, was obtained in only minor quantity.



III



IV

Both III and IV were identified by analysis and conversion to benzylidene derivatives which were also analyzed. III was first described by Stolle and Bowles.[3] Its preparation by hydrazinolysis of various thiocarbonic acid derivatives has recently been reported.[4]

EXPERIMENTAL[5,6]

1-(Sodium carbodithioate)-piperidine. In a three-necked 1-l. round bottomed flask, surrounded by an ice-salt bath and fitted with mechanical stirrer, reflux condenser, thermometer, and dropping funnel were placed 82.2 g. (63 cc., 1.08 moles) carbon disulfide and a cold solution of 43.2 g. (1.08 moles) of sodium hydroxide in 96 cc. water. The mixture was cooled to 0 to 5°. While stirring, 91.8 g. (1.08 mleos) of piperidine as a cold 35% aqueous solution was added over a period of 30 minutes. Stirring was continued for two hours in order to insure complete precipitation. The product recovered by filtration weighed 178 g. (90%) and was used without further purification.

1-(Ethyl carbodithioate)-piperidine. A mixture comprising 183 g. (1 mole) of 1-(sodium carbodithioate)-piperidine, 161 g. (1 mole) ethyl iodide and 200 cc. ethanol (95%) was refluxed for two hours. At the end of this period, 200 cc. of

(1) The name for this structure is derived from the *C. A.*, 39, 5968 (1945) nomenclature for the radical-C(S)SH, carbodithioic and the 1-position of the piperidine ring.

(2) Several different names for this structure can be derived from official sources of nomenclature. The name selected was for the purpose of emphasizing that the substance is a derivative of piperidine.

(3) R. Stolle and P. E. Bowles, *Ber.*, 41, 1099 (1908).

(4) L. F. Audrieth, E. S. Scott and P. S. Kippur, *J. Org. Chem.*, 19, 733 (1954).

(5) Melting points are uncorrected.

(6) Microanalyses by Dr. C. Weiler and Dr. F. B. Strauss, Oxford, England.

water was added and the two layers separated. The bottom oil phase was washed with two 100-cc. portions of water. The combined aqueous extract was washed with two 100-cc. portions of benzene. The benzene extract, combined with the oil, was dried with sodium sulfate. After removal of the benzene the residue was vacuum fractionated at 3 mm. pressure, the product being recovered at 155–159°, n_D^{22} 1.6012, yield 123 g. (65%).

Anal. Calc'd for $C_8H_{15}NS_2$: S, 33.86. Found: S, 33.48.

1-(Methyl carbodithioate)-piperidine. Without recovering the product, an aqueous suspension of 1-(sodium carbodithioate)-piperidine was prepared from a mixture comprising 40 g. (1 mole) NaOH in 100 cc. H_2O, carbon disulfide (60 cc., 1 mole) and 85 g. (99 cc., 1 mole) piperidine in 100 cc. water. The piperidine was added in 1 hr. and the mixture allowed to stir for 30 min. The ice-salt bath was removed and 142 g. (1 mole) of methyl iodide added at once and the mixture refluxed for 1 hr. and allowed to cool to room temperature. The oil layer was recovered as described previously and after drying, vacuum fractionated at 6 mm., the product being collected over the range 171–176°.

Anal. Calc'd for $C_7H_{13}NS_2$: N, 8.00; S, 36.58. Found: N, 7.85; S, 36.30.

Thiocarbohydrazide. A mixture comprising 40 g. (0.21 mole) of 1-(ethyl carbodithioate)-piperidine, 10 cc. of 85% hydrazine hydrate (0.26 mole) and 150 cc. ethanol was refluxed for 6 hours. No precipitation of product took place after cooling at 5° for 48 hr. However, precipitation occurred after concentrating the reaction mixture by distillation of the solvent and cooling. Cooling of the mother liquor resulted in the precipitation of a crystalline solid having properties different from thiocarbohydrazide. This is described below. From the new mother liquid additional yield of thiocarbohydrazide was obtained by the addition of water. Yield, 9.4 g. (42.3%), m.p. 164–174° (Parr Block) dec.

Anal. Calc'd for CH_6N_4S: N, 52.79. Found: N, 53.0.

1-(Aminothiocarbamyl)-piperidine. The first mother liquor obtained in the above preparation yielded 1.5 g. (3.9%) of a white crystalline material which, after recrystallization from a minimum quantity of aqueous methanol, melted at 92–95°.

Anal. Calc'd for $C_6H_{13}N_3S$: N, 26.39; S, 20.48. Found: N, 26.4; S, 20.13.

1-(Benzylideneaminothiocarbamyl)-piperidine was prepared from 1 cc. benzaldehyde, 0.5 g. 1-(aminothiocarbamyl)-piperidine, 0.4 g. sodium acetate and 10 cc. ethanol by refluxing and cooling. Recrystallized from ethanol, m.p. 125–128°.

Anal. Calc'd for $C_{13}H_{17}N_3S$: N, 17.00; S, 12.98. Found: N, 17.01; S, 12.96.

Benzaldehyde 3-thiocarbohydrazone was prepared from 0.5 g. thiocarbohydrazide prepared above. M.p. 190–200° with dec.

Anal. Calc'd for $C_{15}H_{14}N_4S$: N, 19.85; S, 11.35. Found: N, 19.6; S, 11.25.

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Synthesis of 6-Nitro-2,3-dimethoxybenzaldehyde

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Received Aug. 20, 1956

In connection with the synthesis of compounds related to mescaline, it was found necessary to prepare both 5-nitro-2,3-dimethoxy benzaldehyde and 6-nitro-2,3-dimethoxybenzaldehyde. Murakami's method[2] for the synthesis of the 5-nitro compound was found to be the most satisfactory. The synthesis of 6-nitro-2,3-dimethoxybenzaldehyde recently reported by Ried and Schiller[3] however, has the disadvantage that the last step, the methylation of 6-nitro-*o*-vanillin, gave a low yield and a product that required considerable purification.

An attempt to apply Murakami's acetal procedure[2] to this methylation failed; apparently the dimethyl acetal of 6-nitro-*o*-vanillin is formed much less readily than the corresponding 5-nitro acetal. However, it was found that with methyl iodide and silver oxide, which was used by Davies[4] in the preparation of 5-nitro-2,3-dimethoxybenzaldehyde, the methylation proceeded smoothly to give 6-nitro-2,3-dimethoxybenzaldehyde of satisfactory purity in moderately good yield.

An interesting peculiarity of the 6-nitro intermediates as well as of 6-nitro-2,3-dimethoxybenzaldehyde is a considerable sensitivity to light.[3] Thus, the entire preparation from the benzenesulfonate ester of *o*-vanillin is best performed all at once and the final product stored in the dark.

EXPERIMENTAL[5]

6-Nitro-2,3-dimethoxybenzaldehyde. 6-Nitro-*o*-vanillin, freshly prepared from 63 g. (0.21 mole) of 6-nitro-*o*-vanillin benzenesulfonate ester, was used immediately after recrystallization without drying. It was refluxed in a mixture of 90 ml. of chloroform and 15 ml. of methyl iodide with 21 g. of powdered silver oxide. After filtration, the chloroform solution was washed twice with 50 ml. portions of 10 per cent sodium hydroxide, then with water, and finally evaporated to dryness. The residue after recrystallization from methanol weighed 10.5 g., m.p. 107–109°. A second recrystallization gave 8.5 g. of fine, faintly yellow needles (22 per cent overall from the nitrated ester), m.p. 109–110.5° (reported[3] 108–110°).

The 6-nitro-*o*-vanillin benzenesulfonate ester had a m.p. of 154–155°, instead of the reported[3,4] 145°.

Acknowledgment. The author is grateful to Dr. I. M. Hunsberger for his many helpful suggestions.

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(2) M. Murakami, *Ann.*, **496**, 122 (1932).
(3) W. Ried and H. Schiller, *Ber.*, **85**, 216 (1952).
(4) W. Davies, *J. Chem. Soc.*, **123**, 1575 (1923).
(5) All melting points are uncorrected.

Cleavage of Phthalylglycine by Substituted Hydrazines

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Received Aug. 20, 1956

The cleavage of N-substituted phthalimides by hydrazine, which was studied extensively by Ing

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and Manske,[2] has recently been modified by Schumann and Boissonnas,[3,4] who replaced the hydrazine of the original procedure with phenylhydrazine.

The work of the latter authors has shown that the reaction products with phthalylglycine and phenylhydrazine, using tri-*n*-butylamine as a catalyst, are glycine and N-phenylphthalhydrazide. The alternative reaction, which would result in the formation of phthalhydrazide and N-phenylglycine, does not appear to occur to any significant degree.

The use of four additional substituted hydrazines has now been studied. Of three which are derivatives of phenylhydrazine, neither 2,4-dinitrophenylhydrazine nor hydrazobenzene underwent the reaction under the usual conditions. Only 2,5-dichlorophenylhydrazine attacked phthalylglycine and gave the expected N-(2,5-dichlorophenyl)-phthalhydrazide in moderate yield.

The other compound studied, methylhydrazine, was found to enter the reaction readily to give an excellent yield of N-methylphthalhydrazide. Thus, the course of the reaction brought about by this alkylhydrazine was the same as that effected by the arylhydrazines so far reported. Unlike hydrazine itself, however, none of its derivatives appear to react at an appreciable rate in the absence of the catalyst. Whether this is due to steric or other factors has not yet been investigated.

N - (2,5 - dichlorophenyl)phthalhydrazide was found to be inactive against *M. tuberculosis* in concentrations up to 100 γ per ml. *in vitro*.

EXPERIMENTAL[5,6]

N-(2,5-Dichlorophenyl)phthalhydrazide. A solution of 1.8 g. (0.010 mole) of 2,5-dichlorophenylhydrazine, 1.03 g. (0.00500 mole) of phthalylglycine,[7] and 0.93 g. (0.005 mole) of tri-*n*-butylamine in 5 ml. of 95% ethanol was refluxed on a steam bath for 12 hr. Fifteen ml. of acetone was then added and the mixture refluxed for 15 min. more. The precipitated glycine was filtered off and the filtrate evaporated *in vacuo*, leaving a clear golden oil as residue. This was dissolved in 15 ml. of ether and treated with dry hydrogen chloride for one min. The ether was evaporated and the orange solid which remained was ground with water, filtered, and thoroughly washed with water. The dry solid weighed 1.2 g. (40%). After two recrystallizations from 95% ethanol it was faintly yellow, m.p. 204–205°.

Anal. Calc'd for $C_{14}H_8Cl_2N_2O_2$: N, 9.02; Cl, 23.09. Found: N, 8.88; Cl, 22.74, 23.03.

N-Methylphthalhydrazide. 1.03 g. (0.00500 mole) of phthalylglycine and 1.85 g. of tri-*n*-butylamine (0.0100 mole) were dissolved in 30 ml. of 95% ethanol. To this was added a solution of methylhydrazine prepared by distilling 1.44 g. (0.0100 mole) of methylhydrazine sulfate with excess alcoholic potassium hydroxide. The mixture was heated under reflux for 20 hours, after which it was evaporated to one-third its volume and 40 ml. of 2-butanone added. The mixture was refluxed for 15 min., cooled, and the glycine filtered off and washed with ether. It weighed 346 mg. (92%) and gave a benzoyl derivative, m.p. 188–190°, unchanged on mixing with authentic hippuric acid.

The filtrate and washings were evaporated to give a clear yellow oil. Forty ml. of ether and 100 ml. of pentane were added and the mixture allowed to stand overnight. The faintly yellow precipitate of N-methylphthalhydrazide was separated by filtration. It weighed 770 mg. (88%) and was insoluble in cold water, ether, and dilute hydrochloric acid, but soluble in dilute aqueous potassium hydroxide. Recrystallization from 95% ethanol gave white granular crystals, m.p. 238.5–239.5° after some sublimation above 180°. (Reported[8] m.p. 239°.) Refluxing 30 min. with acetic anhydride, followed by addition of water and sodium carbonate, gave a white crystalline precipitate, m.p. 139.5–140.5° (reported[8] for N-acetyl-N′-methylphthalhydrazide, 140°).

Acknowledgments: The author wishes to express thanks to Dr. I. M. Hunsberger for his helpful interest in this work and to Dr. M. G. Van Campen, Jr., of the Wm. S. Merrell Co., for the bacteriological tests.

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(2) H. R. Ing and R. H. F. Manske, *J. Chem. Soc.*, 2348 (1926).

(3) I. Schumann and R. A. Boissonnas, *Nature*, **169**, 154 (1952).

(4) I. Schumann and R. A. Boissonnas, *Helv. Chim. Acta*, **35**, 2235 (1952).

(5) Microchemical analyses performed by Clark Microanalytical Laboratory, Urbana, Illinois.

(6) All melting points are uncorrected.

(7) L. Reese, *Ann.*, **242**, 1 (1881); E. Drechsel, *J. prakt. Chem.*, (2) **27**, 418 (1883).

(8) J. J. Blanksma and H. A. Bakels, *Rec. trav. chim.*, 58, 497 (1939).

The Preparation of Aliphatic Propynylcarbinols[1]

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Received Aug. 20, 1956

In connection with a research program in these laboratories, it was necessary to prepare 1-propynylcyclohexanol(I) and 1-propynylcyclopentanol(II). Propynylcarbinols of the general type RR′C(OH)C≡C—CH_3 have been prepared by Iotsitch and coworkers[2] by the reaction of propynylmagnesium bromide with various ketones. Zakharova[3] has recently reported the preparation of several of these compounds by the reaction between methylacetylene and aliphatic ketones, using KOH as a condens-

(1) Paper I from the Acetylene Research Program, St. Edward's University; based in part on the B.S. thesis of James E. Kmiecik.

(2) (a) G. I. Iotsitch, *et al.*, *J. Russ. Phys. Chem. Soc.*, **39**, 652 (1907); *Bull. Soc. chim.*, **6**, 98 (1909). (b) G. I. Iotsitch, *et al.*, *J. Russ. Phys. Chem. Soc.*, **41**, 529, 540 (1909); *Bull. Soc. chim.*, **8**, 889, 890 (1910).

(3) (a) A. I. Zakharova, *J. Gen. Chem.* (*U.S.S.R.*), **17**, 686 (1947); *Chem. Abstr.*, **42**, 1871 (1948). (b) A. I. Zakharova, *J. Gen. Chem.* (*U.S.S.R.*), **19**, 83 (1949); *Chem. Abstr.*, **43**, 6153 (1949). (c) A. I. Zakharova and K. N. Dobromyslova, *J. Gen. Chem.* (*U.S.S.R.*), **20**, 2029 (1950); *Chem. Abstr.*, **45**, 5607 (1951).

TABLE I

$RR'C(OH)C{\equiv}C{-}CH_3$

R	R'	% Yield Li; NH_3	% Yield Grignard	KOH	B.P. °C.	B.P. mm.	n_D^t	t (°C.)
CH_3	CH_3	39[a]	47[b]	55[c]	133.5–134.5	750	1.4402	25
CH_3	C_2H_5	46		80[c]	149–150	750	1.4449	27
CH_3	$(CH_3)_2CH$	51			69–70	18	1.4485	25
	$-(CH_2)_4-$	0	81		99–100	30	1.4837	25
	$-(CH_2)_5-$	41[d]	41[d]		106–110	30	[e]	[e]

[a] The highest yield for several runs; the other yields determined in these experiments are for single runs. [b] Various yields have been reported by other workers; *cf.* references 2a and 3a. The indicated yield was obtained by Brother William Fitch, C.S.C., in these laboratories. [c] Reference 3. [d] Yield based on recrystallized product; the other yields are based on weight of crude distillate. [e] M.p. 48–50°.

ing agent, and McLamore and coworkers[4] report the preparation of methylvinylpropynylcarbinol in 33% yield by the reaction of lithium methylacetylide and methyl vinyl ketone in liquid ammonia.

Although ethynylcyclohexanol can be prepared conveniently and in good yield by the reaction between sodium acetylide and cyclohexanone in liquid ammonia,[5] we were unable to prepare the propynyl homolog (I) by the analogous procedure, using sodium methylacetylide. When lithium was used instead of sodium, 1-propynylcyclohexanol was obtained in 41% yield.

Attempts to prepare II by the reaction between lithium methylacetylide and cyclopentanone were unsuccessful. It is well known[6] that sodium acetylide reacts with cyclopentanone much less readily than with cyclohexanone. Compound II was subsequently prepared in good yield by the reaction of propynylmagnesium bromide with cyclopentanone.

Since methylacetylene is now commercially available,[7] considerable interest attaches to the preparation of propynylcarbinols. A brief investigation of the scope of the lithium methylacetylide reaction was undertaken, using a series of simple aliphatic ketones. The results are shown in Table I.

In most cases, the yields of propynylcarbinols by the lithium methylacetylide reaction were less than those obtained or reported by other procedures. The failure of the lithium methylacetylide procedure to yield isolable amounts of II seems indicative of the limited scope of the reaction. A single run with isobutyraldehyde also gave negative results by this method, although Iotsitch[2b] has reported the successful preparation of the corresponding propynylcarbinol by the Grignard method.

In cases where the yields are comparable, the speed and convenience of the lithium methylacetylide reaction makes it preferable to the Grignard procedure.

EXPERIMENTAL

1-Propynylcyclohexanol (I). A one-liter, 3-necked r.b. flask fitted with a mechanical stirrer and an acetylene inlet tube was charged with 750 ml. of a commercial grade of anhydrous liquid ammonia. Methylacetylene[7] was allowed to bubble through the rapidly stirring solution, while 4.9 g. (0.7 g. atom) of lithium wire[8] was added over a period of 30 min. Methylacetylene addition was continued for 15 minutes after all of the lithium had been added. A solution of 49.1 g. (0.5 mole) of cyclohexanone in 75 ml. of anhydrous ether was added during 10 min., with good stirring. The ammonia was allowed to evaporate for 6 hr., after which a solution of 40 g. of NH_4Cl in 150 ml. of water was added with stirring. One hundred ml. of ether was added, and the aqueous layer was separated and extracted with 125 ml. of ether in two portions. The combined ethereal layers were washed with two 50 ml. portions of 10% HCl saturated with brine, followed by two 75 ml. portions of brine. The solution was dried over $MgSO_4$, the ether was removed, and the product was distilled. There was a considerable forerun (*ca.* 15 g.) of cyclohexanone. The product boiling at 106–110°/30 mm. was collected. It solidified upon cooling and was recrystallized from petroleum ether; 28.5 g. (41%); m.p. 47–49°. A sample which had been recrystallized twice from petroleum ether melted 48–50°.

Anal.[9] Calc'd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 77.95; H, 10.23.

The other yields listed in column 3 of Table I were obtained by a similar procedure.

1-Propynylcyclopentanol (II). A solution of ethylmagnesium bromide (from 0.65 g. atom of magnesium and 0.65 mole of ethyl bromide) in *ca.* 350 ml. of ether was saturated with methylacetylene at room temperature, during a period of 30 min. The reaction mixture was cooled in an ice bath and stirred for 15 min. while additional methylacetylene was bubbled through it. It was allowed to warm up to room temperature slowly during 12 hours and then saturated with methylacetylene as before. After standing at room temperature for 4 hr., the solution was heated under gentle reflux for 30 min. A solution of 42 g. (0.5 mole) of cyclopentanone (Arapahoe Chemicals, Inc.) in 60 ml. of anhydrous ether was added dropwise to the reaction mixture.

(4) W. M. McLamore, M. Harfenist, A. Bavley and S. Y. P'An, *J. Org. Chem.*, 19, 570 (1954).

(5) J. H. Saunders, *Org. Syntheses*, Coll. Vol. 3, 416 (1955).

(6) G. W. Stacy and R. A. Mikulec, *J. Am. Chem. Soc.*, **76**, 525 (1954).

(7) The methylacetylene used in these experiments was obtained as a gift from the Air Reduction Company, New York.

(8) When sodium was used instead of lithium, a white solid precipitated from solution. K. N. Campbell and B. K. Campbell [*Proc. Indiana Acad. Sci.*, 50, 123 (1940); *C. A.*, **35**, 5457 (1941)] have described the use of lithium acetylide, and observed that it is more soluble than sodium acetylide in liquid ammonia.

(9) The carbon and hydrogen analyses were performed by Micro-Tech Laboratories, Skokie, Illinois.

When addition was complete (1 hr.), the reaction mixture was allowed to stand at room temperature for 4 hr., and then poured into 500 ml. of ice water containing 50 g. of NH_4Cl. The aqueous layer was separated and extracted with 60 ml. of ether. The combined ethereal layers were washed with two 100 ml. portions of 20% NH_4Cl and then with brine. After drying over $MgSO_4$, the ether was removed and the product was distilled through an 8 cm. helix-packed column. The fraction boiling 99–100°/30 mm. was collected; 50.5 g. (81%). A sample which had been redistilled twice through a 20 cm. Widmer column had the following physical properties: b.p. 99–100°/30 mm., 85–85.5°/15 mm.; n_D^{25} 1.4837; d^{25} 0.9669. The I.R. spectrum in CCl_4 solution showed strong absorption at 2.95 μ and weak absorption at 4.5 μ.

Anal. Calc'd for $C_8H_{12}O$: C, 77.37; H, 9.74. Found: C, 77.52; H, 9.80.

The other yields listed in column 4 of Table I were obtained by a similar procedure.

Acknowledgment. We are indebted to the Research Corporation for financial assistance during this investigation.

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Preparation of Alkyl Vinyl Ketones

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Received Aug. 20, 1956

In connection with another problem the need arose for some alkyl vinyl ketones. The procedure devised by McMahon *et al*[1] is unsuitable for larger scale work due to the violence of the dehydrohalogenation. Woodward[2] recommended that several small scale experiments (39 g.) be run to obtain sizable amounts of ethyl vinyl ketone.

We have found that the dehydrohalogenation of 1-chloro-3-pentanone proceeds smoothly when an intimate mixture of the haloketone and anhydrous sodium benzoate is stirred and heated. In this way it is possible to obtain the desired unsaturated ketone in 78% crude yield on mole scale runs. The two disadvantages of the method, namely, the poorer yields that resulted in the preparation of higher homologs and the mechanical difficulties in handling the cooled cement-like residues, were overcome by employing Dowtherm as a diluent in the reaction. In this way the yield of butyl vinyl ketone was increased from 30% to 58%, and the nonvolatile material remained fluid throughout.

In our preferred method we found it expedient to use the crude undistilled chloroketone. The over-all yield based on the acid chloride was at least as good as that obtained when distilled ketone was used. It was possible to obtain the higher alkyl vinyl ketones in approximately 30% over-all yield with a minimum of manipulation.

EXPERIMENTAL[3]

Ethyl vinyl ketone. A 500-ml. three-necked flask was equipped with a Hershberg stirrer and a still-head connected to a condenser set for downward distillation. The receiver, containing 0.1 g. of hydroquinone, was immersed in ice. A mixture of 90 g. of 1-chloro-3-pentanone and 0.5 g. of hydroquinone was placed in the flask and the stirrer was started. Anhydrous sodium benzoate (120 g.) was added portionwise over a 10-min. period. A second 90-g. portion of the chloroketone was added followed by a second 120-g. portion of sodium benzoate.

After the reagents were thoroughly mixed the flask was heated by means of a heating mantle. After a few minutes the contents solidified but after about 10 minutes the whole liquefied, allowing the stirrer to function. Within the next hr. and one-half the entire distillate, b.p. 100–135°, was collected.

The apparatus was dismantled while still hot and the residue immediately was emptied into a stone crock (hood). The distillate was separated from a small amount of water and dried. The crude ethyl vinyl ketone weighed 99 g. (78%).

TABLE I

ALKYL VINYL KETONES $RC(=O)CH{=}CH_2$

R	Yield[a]	B.P., °C. (mm.)	Formula	Analyses: Carbon Calc'd	Carbon Found	Hydrogen Calc'd	Hydrogen Found
n-Propyl	27	25–26 (11)	$C_6H_{10}O$	73.43	73.28	10.27	10.52
n-Butyl	34	44–45 (11)	$C_7H_{12}O$	74.95	74.50	10.79	10.66
n-Amyl	26	58–61 (11)	$C_8H_{14}O$	76.14	76.00	11.18	11.60

[a] Yield based on the acid chloride used to prepare the β-chloroketone. In the case of propyl vinyl ketone distilled 1-chloro-3-hexanone furnished the desired product in 82% yield. However there was no gain in over-all yield.

A small portion reacted with aniline to furnish 1-phenylamino-3-pentanone, m.p. 56.2–57.2° after two crystallizations from absolute ethanol. McMahon[1] reported m.p. 56.5–57°.

General method for the preparation of the alkyl vinyl ketones. One and one-half moles of the acid chloride was treated with ethylene in chloroform as described by Woodward.[2] The crude chloroketone was obtained after removal of the solvent and was weighed and used directly in the next step.

(1) E. M. McMahon, J. N. Roper, W. P. Untermohlen, R. H. Hasek, R. C. Harris and J. H. Brant, *J. Am. Chem. Soc.*, 70, 2971 (1948).

(2) R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler and W. M. McLamore, *J. Am. Chem. Soc.*, 74, 4223 (1952).

(3) Analyses were carried out by Mr. K. D. Fleischer and his staff of this Institute.

The residual haloketone, two volumes of Dowtherm, sodium benzoate (10% molar excess) and a pinch of hydroquinone were placed in a flask equipped as described above in the ethyl vinyl ketone experiment. Heating and stirring were continued until the distillation temperature reached 210°. The crude ketone was dried over Drierite and then distilled.

The contents of the flask remained fluid throughout and could be removed from the flask readily. The properties of the ketones thus prepared are described in Table I.

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Substituent Effects in the Catalytic Hydrogenation of Styrene Oxides

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Received Aug. 20, 1956

The hydrogenation of ethylene oxides is a reaction of considerable potential importance, but it has received surprisingly little systematic study. A number of monoalkyl- and arylethylene oxides have been hydrogenated,[1] and a primary alcohol has been obtained as the predominant product in every case, in the absence of added acid or base. Only a few oxides with electron-withdrawing groups have been hydrogenated, and a secondary alcohol is always produced. Glycidol,[2,3] epichlorohydrin,[3,4] and butadiene dioxide[3] are reduced to 1,2-propandiol, 1-chloro-2-propanol, and 2,3-butandiol, respectively, as the main product. Two possible factors might determine the direction of ring opening of epoxides by hydrogen, the orientation of the molecules at the catalyst surface, and the electronic effects of substituents. In the present work the electronic influences have been studied in a series of *m*- and *p*-substituted styrene oxides which presumably are similarly oriented on the platinum catalyst surface. The results appear in Table I.

TABLE I

HYDROGENATION OF SUBSTITUTED STYRENE OXIDES

Y—CH—CH_2 (O)	% Y—CH_2CH_2OH[a]	% Y—CH(OH)—CH_3
Y = *p*-CH_3-C_6H_4	100	0
C_6H_5[b]	100	0
m-CH_3O-C_6H_4[c]	88	12
p-Br-C_6H_4	82	18[d]
3,4-dichlorophenyl	35	65[e]

[a] The percentages listed refer to the composition of the material which actually underwent hydrogenation. [b] Reference 1. [c] A small amount of a low boiling substance was formed. [d] Isolated as 4-bromoethylbenzene. [e] Isolated in part as 3,4-dichloroethylbenzene.

It may be seen that the Hammett *rho* value for the reaction would be negative, as in the reaction of the same oxides with lithium borohydride.[5] The data are not considered sufficiently accurate to obtain a significant value of *rho*, because of the experimental difficulties in removing contaminants such as starting material from the desired products. The secondary alcohols 1-(4-bromophenyl)ethanol and 1-(3,4-dichlorophenyl)ethanol formed by hydrogenation of the corresponding styrene oxides, underwent hydrogenolysis to 4-bromoethylbenzene and 3,4-dichloroethylbenzene, respectively. The hydroxyl group of the primary alcohol 2-(3,4-dichlorophenyl)ethanol, as expected, did not undergo hydrogenolysis. A pure sample of the substance was hydrogenated to 2-cyclohexylethanol, although this product was not obtained from the hydrogenation of 3,4-dichlorostyrene oxide under similar conditions. It is apparent that only the secondary (benzyl) alcohols undergo hydrogenolysis to ethylbenzene derivatives, and this has been taken into account in the calculation of the amount of secondary alcohols initially formed.

The considerable substituent effect militates against a mechanism which involves the simultaneous addition of hydrogen atoms to the oxygen and carbon atoms. It is not possible to decide definitely between two alternative mechanisms[6,7] which involve the addition of a proton or hydrogen atom to the oxygen atom, with formation of a (bound) carbonium ion or radical, followed by addition of a hydride ion or a hydrogen atom to the carbon atom. It is known[8] that electron-donating substituents may facilitate both carbonium ion and radical reactions at the benzyl carbon atom, presumably by stabilization of the intermediate benzyl carbonium ion or radical.

EXPERIMENTAL[9]

Hydrogenation of the Oxides. A solution of 0.10 mole of each oxide in 100 ml. of 95% ethanol was shaken with 0.15 g. of platinum oxide catalyst for about 24 hr., or until hydrogen uptake had completely ceased. In all cases the initial pressure was about 45 lbs., and the uptake was 0.09 to 0.10 mole.

Low boiling ethylbenzene derivative and unchanged oxide were separated by fractional distillation, and the mixture of 1- and 2-arylethanol was analyzed by infrared absorption, with reference to spectra of known mixtures.[5]

(1) See, for example, O. Loehr, U. S. Patent 1,787,205; *Chem. Abstr.*, **25**, 963 (1931); M. S. Newman, G. Underwood, and M. Renoll, *J. Am. Chem. Soc.*, **71**, 3362 (1949).

(2) A. Kötz and K. Richter, *J. prakt. chem.*, [2] **111**, 373 (1925).

(3) R. Fuchs, Thesis, University of Kansas, 1953.

(4) S. Searles and C. F. Butler, *J. Am. Chem. Soc.*, **76**, 56 (1954).

(5) F. Fuchs, *J. Am. Chem. Soc.*, **78**, 5612 (1956).

(6) Mechanisms have been proposed for the hydrogenation of ethylene: L. Hernandez and F. F. Nord, *J. Colloid Sci.*, **3**, 363 (1948).

(7) R. K. Greenhalgh and M. Polanyi, *Trans. Faraday Soc.*, **35**, 520 (1939).

(8) H. H. Jaffé, *Chem. Revs.*, **53**, 191 (1953).

(9) The preparation of the oxides and the reference samples of the arylethanols was described in ref. 5.

The yield of products and recovered oxide accounted for 86 to 95% of the starting material except in the case of 4-bromostyrene oxide (55% yield) in which there was a large pot residue.

4-Bromoethylbenzene and 3,4-Dichloroethylbenzene. 4-Bromoacetophenone[10] and 3,4-dichloroacetophenone were reduced by the Clemmensen method. 3,4-Dichloroethylbenzene was distilled at 64° at 2 mm.; n_D^{25} 1.5363.

Anal. Calc'd for $C_8H_8Cl_2$: C, 54.9; H, 4.6. Found: C, C, 55.1; H, 4.6.

Hydrogenation of 2-(3,4-Dichlorophenyl)ethanol. A sample of 2-(3,4-dichlorophenyl)ethanol[5] was hydrogenated under the conditions used for the oxides. The product was 2-cyclohexylethanol, b.p. 50–57° at 0.5 mm. (reported[11] 88–90° at 7 mm.). The 3,5-dinitrobenzoate melted at 69.5–70.5° (reported[11] 70.5°).

Acknowledgment. The authors wish to thank Dr. Gilbert Ayres and Mr. Heron Peña for the infrared spectra. This project was supported by a grant from the Research Corporation.

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(10) Method of P. Karrer, E. Schlittler, K. Pfaehler, and F. Benz, *Helv. Chim. Acta*, **17**, 1516 (1934).

(11) R. C. Huston and A. H. Agett, *J. Org. Chem.*, **6**, 123 (1941).

Alkaloids from *Rauwolfia Schueli*

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Received Sept. 21, 1956

Rauwolfia schueli is the only species of this genus which grows in Argentina. It is a tree with roots of rather large diameter and the cortex of the root contains alkaloids which were found pharmacologically active in the ptosis test.[1]

An investigation of the alkaloids present in the bark revealed the presence of aricine, reserpiline, isoreserpiline, and reserpine and of the stronger base, ajmaline.

The amount of aricine found in several batches was around 0.5% of the cortex. It is very interesting to observe that the same alkaloid was found in another South American species, *Rauwolfia sellowii*,[2] but in larger amounts.

Reserpiline and isoreserpiline were both identified by Stoll, Hofmann, and Brunner[3] in the leaves of *R. canescens* and although reserpiline was first isolated from *R. serpentina* by Klohs, Draper, Keller, and Malesh,[4] the isomeric base was not found in this species.

EXPERIMENTAL

The cortex of the root was well ground and the bases were extracted with methanol. The solvent was evaporated and the residue extracted with 10% acetic acid. To the acetic acid solution 10% sodium hydroxide solution was added to bring it to *p*H 9, when most of the bases precipitated. The crude precipitate was extracted with chloroform and the solution was filtered. Practically all the sedative activity passed into the chloroform.

Ajmaline. The chloroform solution was then extracted with 10% acetic acid and the extract alkalinized to *p*H 9 and extracted with benzene. After washing with water and drying, the benzene solution was evaporated to dryness and the residue dissolved in methanol after which crystals soon appeared. Recrystallization from methanol yielded material melting at $[\alpha]_D^{21}$ +129.2° (chloroform). It was transformed into isoajmaline, m.p. 260–262°, $[\alpha]_D^{20}$ +71.4° (chloroform). These data agree substantially with the constants of ajmaline and isoajmaline.[5]

Aricine. The acid-washed chloroform solution was evaporated to dryness and the residue dissolved in ten times its weight of methanol containing 10% of acetic acid. A crystalline precipitate appeared in a few minutes. It was filtered and washed with the same solvent. Recrystallization from methanol containing 1% of acetic acid yielded rhombic plates melting at 148–149°, which contained about one mole of acetic acid.

Anal. Calcd. for $C_{22}H_{26}N_2O_4 \cdot C_2H_4O_2$: acetyl (1) 9.67. Found: 8.20.

From this acetate, aricine was prepared by shaking the crystals with a mixture of ether and dilute ammonium hydroxide, washing with water, evaporating the dried ether solution, dissolving the residue in ethanol, and seeding with a sample of the base. Recrystallization from the same solvent yielded long prisms melting at 189°. A mixed melting point with authentic aricine was unchanged. $[\alpha]_D^{25}$ −58.6 ± 1° (*c*, 0.54, ethanol). *Hydrochloride*, m.p. 255°; *hydrobromide*, m.p. 263–264°; *oxalate*, m.p. 243–245°; and *picrate*, m.p. 222–223°.

Isoreserpiline. The methanolic acetic acid solution remaining after the isolation of aricine was evaporated to dryness and the residue treated with chloroform and ammonia water, whereupon all the bases passed again into chloroform. This solution was washed, dried, and evaporated and the residue was dissolved in benzene. The solution was submitted to chromatography on a column of aluminium oxide. Elution with benzene and evaporation of the first fractions yielded a residue which was dissolved in 60% methanol. Dilute nitric acid (1:10) was added to the solution. The crystalline nitrate of the base precipitated in a few minutes. Upon recrystallization from methanol needles, m.p. 264–265° (vac.), $[\alpha]_D^{20}$ −46.3 ± 3° (*c*, 0.08, water) were obtained.

Anal. Calcd. for $C_{23}H_{28}N_2O_5 \cdot HNO_3$: C, 58.09; H, 6.15; N, 8.84. Found: C, 58.22; H, 5.93; N, 8.77.

The base was separated by dissolving the nitrate in water and adding sodium hydroxide solution to *p*H 10.5. The amorphous solid was collected, washed with water, and dried. It was dissolved in benzene-hexane and when the solution was evaporated, isoreserpiline crystallized in hexagonal plates, m.p. 208°, $[\alpha]_D^{20}$ −84.7 ± 2° (pyridine); $[\alpha]_D^{21}$ −112.0 ± 2° (chloroform); $[\alpha]_D^{21}$ −84.2 ± 2° (ethanol). Stoll *et al.*[3] give m.p. 211–212°.

(1) B. Rubin and J. C. Burke, *Federation Proc.*, **13**, 400 (1954).

(2) F. A. Hochstein, *J. Am. Chem. Soc.*, **77**, 5744 (1955); S. C. Pakrashi, C. Djerassi, R. Wassicky, and N. Neuss, *J. Am. Chem. Soc.*, **77**, 6687 (1955).

(3) A. Stoll, A. Hofmann, and R. Brunner, *Helv. Chim. Acta*, **38**, 270 (1955).

(4) M. W. Klohs, M. D. Draper, F. Keller, and W. Malesh, *Chemistry & Industry*, 1264 (1954).

(5) F. A. L. Anet, D. Chakravarti, Sir Robert Robinson, and E. Schlittler, *J. Chem. Soc.*, 1242 (1954).

Anal. Calcd. for $C_{23}H_{28}N_2O_5$: C, 66.90; H, 6.84; N, 6.79; CH_3O—(3), 22.54; CH_3—C (1); 3.6. Found: C, 67.35; H, 6.68; N, 6.62; CH_3O—, 22.84; CH_3—C, 3.26.

The infrared spectrum was identical with that of isoreserpiline.

The *hydrochloride* was prepared in the usual way. Recrystallization from absolute ethanol gave long needles, m.p. 280–281° (vac., fast heating); $[\alpha]_D^{28}$ −36.4 ± 2° (*c*, 0.37, ethanol 96%).

Anal. Calcd. for $C_{23}H_{28}N_2O_5 \cdot HCl$: C, 61.53; H, 6.51; Cl, 7.89. Found: C, 61.37; H, 6.26; Cl, 7.63.

The *methanesulfonate* prepared according to Stoll *et al.*,[3] melted at 282–283° alone and when mixed with an authentic specimen.

Reserpine. Subsequent elution of the column with benzene-acetone (2:1) gave several fractions, the first of which were pharmacologically active. They were united, evaporated to dryness in vacuum, and the residue was dissolved in boiling methanol when a spontaneous crystallization took place. After filtration and recrystallization from chloroform-methanol, needles melting 263–265° were obtained, showing no depression when mixed with pure reserpine. $[\alpha]_D^{28}$ −122 ± 3° (chloroform). By hydrolysis according to Dorfmann *et al.*,[6] *reserpic acid hydrochloride*, m.p. 255–257°, could be prepared.

Reserpiline. The mother liquors from the preparation of reserpine were evaporated, and the residue was dissolved in benzene and rechromatographed on aluminium oxide. After washing with benzene, an elution with benzene containing 0.5% of ethanol gave a small amount of reserpine.

Subsequent elution with benzene containing 1% of ethanol gave fractions which by evaporation yielded an amorphous residue. This, on solution in ethanol containing 10% of oxalic acid, gave a crystalline oxalate which was recrystallized from 70% ethanol. Long prisms, m.p. 248–250° (vac.). Klohs *et al.*[4] give m.p. 244–245°.

From the oxalate, decomposed in the usual way, the phosphate was prepared, m.p. 200–201° (vac.), $[\alpha]_D^{23}$ −50.4 ± 0.5° (water). Stoll *et al.*[3] give m.p. above 200°; $[\alpha]_D^{20}$ −52°.

The *hydrochloride*, short prisms from absolute ethanol, melted at 221–223° (vacuum, fast heating). $[\alpha]_D^{25}$ −44.7 ± 2° (ethanol 96%).

Anal. Calcd. for $C_{23}H_{28}N_2O_6 \cdot HCl$: C, 61.53; H, 6.51; N, 6.24; CH_3O (3) 20.74. Found: C, 61.58; H, 6.19; N, 5.76; CH_3O, 20.46.

The *picrate*, red needles from 50% ethanol, melted 174° (vac.).

Anal. Calcd for $C_{23}H_{28}N_2O_5 \cdot C_6H_3N_3O_7$: C, 51.32; H, 4.57. Found: C, 51.25; H, 5.29.

Acknowledgments. We wish to express our thanks to Messrs. P. Badin and M. Gutierrez for their assistance in carrying out this work; to Drs. A. Djerassi, and O. Wintersteiner for the samples of isoreserpiline methanesulfonate, aricine, and reserpine; and to Dr. J. F. Alicino and Dr. N. H. Coy, from The Squibb Institute for Medical Research (New Brunswick, N. J.), for the microanalysis and the infrared spectra.

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(6) L. Dorfmann, A. Furlenmeier, C. F. Huebner, R. Lucas, H. B. MacPhillamy, J. M. Mueller, E. Schlittler, R. Schwyzer, and A. F. St. André, *Helv. Chim. Acta*, **37**, 59 (1954).

Chemical Investigation of Roots of *Carissa Congesta*,[1] Santapau.
I. Isolation of Carissone and D-Glucoside of β-Sitosterol

D. V. JOSHI[2a] AND S. F. BOYCE[2b]

Received May 23, 1956

The plant *Carissa congesta* (Apocynaceae) has been long known in Ayurveda (Indian system of medicine) as an anthelmintic and as a bitter stomachic.[6] The only reported work on this plant is the preliminary investigation by Dymock,[7] wherein the presence of an alkaloid, based on qualitative non-specific tests, was reported. However, it was not possible to isolate any alkaloid from the roots of this plant in the present investigation.

The roots of *Carissa congesta* were collected in 1952 after the monsoon from a number of marked bushes growing on the hills of Western Ghats near Janjira, Bombay. They were sun-dried and powdered to 20 mesh. For large scale extraction the powdered roots were percolated with 96% ethyl alcohol and the extract was concentrated under reduced pressure. On working up the extract two crystalline compounds, D-glucoside of β-sitosterol (A) and carissone (B), together with a noncrystallizable bitter oil, were isolated.

Chemical investigation of (*A*). The white crystalline substance was obtained in very low yields of about 370 mg. per 180 lb. of the dry root. It was found to be insoluble in most of the organic solvents. On crystallization from glacial acetic acid it melted at 272–275°. On the basis of the carbon and hydrogen analysis and a molecular weight determination, it was assigned the molecular formula $C_{35}H_{60}O_6$. The Liebermann-Burchard test and the reduction of Fehling's solution indicated that the substance was a steroidal glucoside. From its infrared spectrum (Fig. 1)[8] and from the melting

(1) According to Cooke's Flora[3] this plant was thought to be *Carissa carandas* but later it was learned[4] that from the more recent critical studies of Santapau[5] this species should be called *Carissa congesta*. It has been pointed out that normally *Carissa carandas* has eight seeds in its fruit, whereas *Carissa congesta* has only four. There is also a difference in the shape of the leaves.

(2) (a) Department of Organic Chemistry, Institute of Science, Bombay 1, India. (b) Research Laboratories, Hindustan Antibiotics Ltd. (Govt. Penicillin Factory), Pimpri, (Poona), India.

(3) Cooke, *Flora of Bombay*, Taylor and Francis, London, 1908, iv, 124.

(4) Our sincere thanks are due to Prof. P. V. Bole of St. Xavier's College, Bombay 1, for identifying the plant.

(5) Santapau, *Botanical Survey of India*, xvi, 164 (1953).

(6) Kirtikar and Basu, *Indian Medicinal Plants*, 2nd ed., Lalit Mohan Basu, Allahabad, India, 1933, ii, 1546.

(7) Dymock, Warden, and Hooper, *Pharmacographia Indica*, London, Bombay, 1889, ii, 419.

(8) Ma and Schaffer, *Arch. Biochem. and Biophys.*, **47**, 419 (1953).

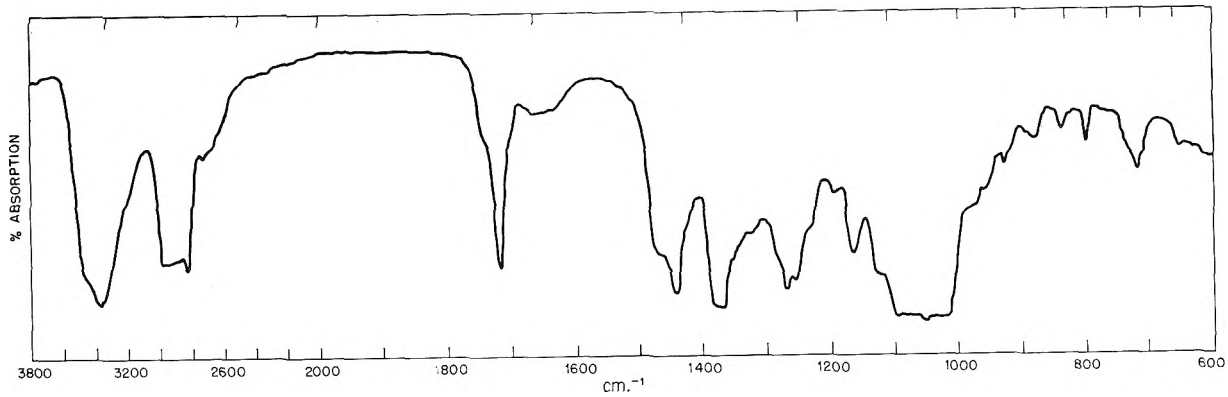
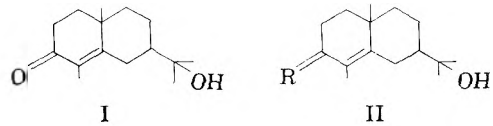


Fig. 1.—Infrared absorption spectrum of D-glucoside of β-sitosterol. Phase: Nujol mull; prism: NaCl.

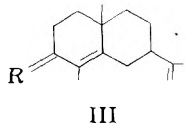
point and the rotation of its tetraacetyl derivative[9] it was identified as the D-glucoside of β-sitosterol.

Chemical investigation of (B). The isolated bitter oil was distilled under reduced pressure and on standing gave a crystalline compound, which after recrystallization melted at 77–78°. Its analysis agreed with the molecular formula $C_{15}H_{24}O_2$ and it had an α,β-unsaturated ketonic grouping. At this stage of the investigation Reichstein[10] reported the isolation of a new sesquiterpene, carissone, from *Carissa lanceolata* R. Brown. This compound had the same properties. The identity of the above substance (m.p. 77–78°) was established by a mixed melting point with carissone and the corresponding semicarbazone. Barton[11] has suggested for carissone the sesquiterpenoid structure (I) which has been confirmed by Ayer and Taylor.[12]

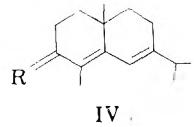


I

II



III



IV

R = :N·NH·$C_6H_3(NO_2)_2$

Later it was found that the distillation of the bitter oil was not necessary and carissone could be obtained by seeding the oil which had been rapidly passed over a short column of neutral alumina.[13]

An interesting observation was made regarding the stability of the DNP of carissone (II). When II was run through a column of neutral alumina it was dehydrated to the DNP of α-cyperone (III); this, in turn, was finally isomerized to the DNP of β-cyperone (IV) by keeping for long on a column of alumina. A similar observation of the interconversion of the DNP's was made by Barton[11] but under different conditions.

Attempts to induce the oil (left after the removal of carissone) to crystallize even through chromatography were unsuccessful. Further work is being carried out.

Bacteriological tests of the bitter oil and of carissone.[14] The bitter oil (containing a small amount of carrisone) was tested for inhibition against the following microorganisms: S. Lutea ATCC 9341, Staphaureus 209P, B. subtilis ATCC 8236, B. coli, Actinomycetes, B. protens OXK, Pyocyaneous, S. typhi TY2, S. paratyphi A, Sh. shigae, Br. obortus, and Laterospora. The activity was measured by using the cylinder-plate technique. Fish-spine beads were used as cups, and four replicates of each concentration were used (70 mg./ml. and 35 mg./ml.).

The oil showed inhibiting activity against the following: S. paratyphi A, Sh. shigae, Br. obortus, B. protens OXK, and Laterospora.

Carissone, when tried against the above microorganisms, showed no inhibition.

EXPERIMENTAL

All the melting points were taken in capillaries sealed under vacuum.

Extraction of roots of Carissa congesta, Santapau. Isolation of D-*glucoside of β-sitosterol.* Three hundred fifty lb. of the roots were collected, identified, and sun-dried for about a month to give 180 lb. of the dry roots. They were powdered to about 20 mesh and extracted with 96% ethyl alcohol. The total 250 l. of the alcohol extract was concentrated at 50° under reduced pressure to give 22.5 l. of a sticky brownish red slurry. It was acidic to litmus, easily soluble in 10% aqueous sodium hydroxide, and sparingly soluble in sodium

(9) Jantzen and Gohtes, *Biochem. Z.*, **272**, 167 (1934).

(10) Mohr, Schindler, and Reichstein, *Helv. Chim. Acta*, **37**, 462 (1954).

(11) Barton and Tarlton, *J. Chem. Soc.*, 3492 (1954).

(12) Ayer and Taylor, *J. Chem. Soc.*, 3027 (1955).

(13) Merck alumina (according to Brockmann) was neutralized with pure distilled ethyl acetate and reactivated by heating at 200 for 4 hours and subsequently cooled in the open at room temperature.

(14) The tests were carried out by Dr. P. D. Kulkarni at the Hindustan Antibiotics Ltd., Pimpri.

carbonate. Alcoholic ferric chloride gave a dirty green color. It reduced Fehling's solution and gave a positive test (thick yellow precipitate) with basic lead acetate.[15] Nitrogen, sulfur, and the halogens were found to be absent.

The crude alcohol extract (22.5 l.) was defatted with 8 l. of petroleum ether (40–60°) and then extracted with 9 l. ether in a similar manner. The ether was distilled to leave 370 g. of a residue. A 150-g. portion of the residue was dissolved in a mixture of 200 ml. methanol and 30 ml. water and again defatted three times with petroleum ether (40–60°) using 300 ml. each time. At the interphase of the petroleum ether–methanol separated 100 mg. of white crystalline substance (A). The 900 ml. of petroleum ether extract was evaporated to dryness and dissolved in 200 ml. of 70% methanol to get back the bitter portion which had gone over to petroleum ether. This was again shaken with two 250 ml. portions of petroleum ether. From this petroleum ether extract, 50 mg. more of the white crystalline substance (A) separated. The methanolic extracts, total volume 600 ml., were combined and treated as described below.

The white crystalline substance (A) (total 150 mg.) was found to be insoluble in most of the organic solvents. It was crystallized from glacial acetic acid in short white needles, m.p. 272–275°. The Liebermann-Burchard test was positive.

Anal. Calc'd for $C_{35}H_{60}O_6$: C, 72.87; H, 10.48; Mol. Wt. 576.83. Found: C, 72.17; H, 10.24; Mol. wt. 529.00.

The infrared spectrum (Fig. 1) of compound (A) agreed extremely well with that of the D-glucoside of β-sitosterol.[8]

The tetraacetyl derivative of compound A gave m.p. 167–168°; $[\alpha]_D^{28}$ −25.1 (chloroform).

Anal. Calc'd for $C_{43}H_{68}O_{10}$: C, 69.29; H, 9.20. Found: C, 69.56; H, 9.50.

Jantzen and Gohtes[9] reported m.p. 166–167° and $[\alpha]_D^{28}$ −23.0°.

Isolation of carissone from bitter oil. Six hundred ml. of the methanolic extract was concentrated to half its volume and extracted with six 200 ml. portions of chloroform. The aqueous methanolic layer did not contain any more bitter constituent and was discarded. The 1200 ml. chloroform extract was exhaustively shaken several times with a total of 5 l. of a saturated solution of sodium bicarbonate, followed by similar extraction with 3.5 l. of 5% ice cold sodium hydroxide, and finally with 1.2 l. of 5% ice cold hydrochloric acid. The chloroform extract was washed with water till neutral and concentrated under vacuum to give an oily residue.

The residue was dissolved in 200 ml. of 70% methanol and treated with freshly precipitated lead hydroxide (obtained from 70 g. lead acetate trihydrate) for 0.5 hr. The precipitate was filtered and washed with 130 ml. methanol. The lemon yellow methanolic solution was concentrated under vacuum at 50° to about 80 ml., then shaken twice with a total of 400 ml. chloroform, and finally with 100 ml. of a chloroform alcohol mixture (3:2). The last extraction yielded practically nothing.

The chloroform extract was dried over sodium sulfate and the solvent was removed under vacuum to give 14.0 g. thick yellow viscous oil. This oil was neutral to litmus and gave no coloration with alcoholic ferric chloride. Tests with Raymond reagent (violet) and Brady reagent (scarlet) were positive.

(*a*) *Distillation under high vacuum.* Five g. of the neutral bitter oil was distilled at 141° under 0.010 mm. and then redistilled twice under the same conditions. The oily distillate gave positive tests with both Raymond reagent and Brady reagent. On keeping for about a week it deposited large prismatic needles. The crystals were separated from the oil on a sintered-bed funnel and washed rapidly with a small quantity of a cold mixture of petroleum ether:ether (1:1) to remove the adhering oil. The crystals were recrystallized from the same solvent mixture to give prisms; m.p. 77–78°. Mixed m.p. with an authentic sample of carissone[10] (m.p. 77°) showed no depression.

(*b*) *Treatment over alumina.* Twenty-five g. of the undistilled neutral bitter oil was dissolved in ether and passed over a column of 250 g. of alumina. The column was washed with ether until no more of the substance was eluted. The total amount of oil eluted was 23.84 g. It gave positive tests with Raymond and Brady reagents. When this thick oil, containing a little of the solvent, was seeded with a few crystals of carissone a mass of crystals separated. They were filtered and washed as above. The yield of pure carissone was about 12 g.; m.p. 77–78°.

Anal. Calc'd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 75.94; H, 10.36.

The semicarbazone of carissone was prepared according to the method of Reichstein.[10] It was crystallized from a mixture of methanol and ether in colorless prisms, m.p. 208–215°; mixed m.p. with an authentic sample showed no depression.

Thirty mg. of carissone was dissolved in 1 ml. of alcohol and to it were added 75 mg. 2,4-dinitrophenylhydrazine dissolved in a mixture of 10 ml. alcohol and 10 drops concentrated hydrochloric acid. The contents were shaken at room temperature for about 45 min. and cooled in a refrigerator. The deep red *2,4-dinitrophenylhydrazone* which separated was recrystallized from chloroform-methanol; m.p. 172–175°. This m.p. agreed with the 2,4-dinitrophenylhydrazone of carissone prepared by Barton.[11]

Anal. Calc'd for $C_{21}H_{28}N_4O_6$: C, 60.56; H, 6.78; N, 13.45. Found: C, 60.73; H, 6.89; N, 13.20.

Instability of 2,4-dinitrophenylhydrazone. (1) The DNP of carissone, m.p. 172–175°, was dissolved in benzene and passed over neutral alumina at a rapid rate. The eluent was concentrated on the steam bath until a nearly saturated solution was obtained. The crystals which separated were crystallized from a large quantity of alcohol; m.p. 188–190°. This m.p. agreed well with that of the DNP of α-cyperone.[11]

Anal. Calc'd for $C_{21}H_{26}N_4O_4$: C, 63.30; H, 6.58; N, 14.06. Found: C, 63.10; H, 6.40; N, 14.25.

(2) The DNP of α-cyperone was dissolved in benzene and again passed over alumina. The eluted solution was concentrated and the crystals which separated were recrystallized from alcohol, m.p. 188°; a mixed m.p. with the original was undepressed.

(3) The same substance was dissolved in benzene and kept over alumina for one day and then eluted with benzene. The eluent was concentrated and the crystals which separated were recrystallized from a large quantity of alcohol in hexagonal plates; $\lambda_{max.}$ 415 mμ; (ϵ = 34860); m.p. 230°. This melting point corresponds to the m.p. of the DNP of β-cyperone.[11]

Anal. Calc'd for $C_{21}H_{26}N_4O_4$: C, 63.30; H, 6.58; N, 14.06. Found: C, 63.03; H, 6.61; N, 14.04.

Acknowledgment. We offer our best thanks to Prof. T. Reichstein for making available to us an authentic sample of carissone and for taking the trouble to compare the melting point of its semicarbazone with that of an authentic sample. We are also indebted to Mr. W. Manser of the Federal Institute of Technology, Zurich, Switzerland and to Dr. G. D. Shah of the National Chemical Laboratories, Poona, for the microanalyses and molecular weight determination. For the infrared spectra our thanks are due to Prof. R. N. Jones of the National Research Council, Ottawa, Canada.

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(15) Rosenthaler, *The Chemical Investigation of Plants*, G. Bell and Sons Ltd., London, 1930, 20.

Communications TO THE EDITOR

Ozonization of Anthracene[1]

Sir:

Badger[2] has classified ozone as a "double bond reagent" and Brown[3] has assumed that it makes a one-step attack of both reactive centers on both reactive centers of the unsaturated molecule, rather than a two-step attack. If so, it should attack anthracene at the 1,2-bond, because this bond, according to the molecular orbital theory, has the lowest "bond localization energy."[3,4]

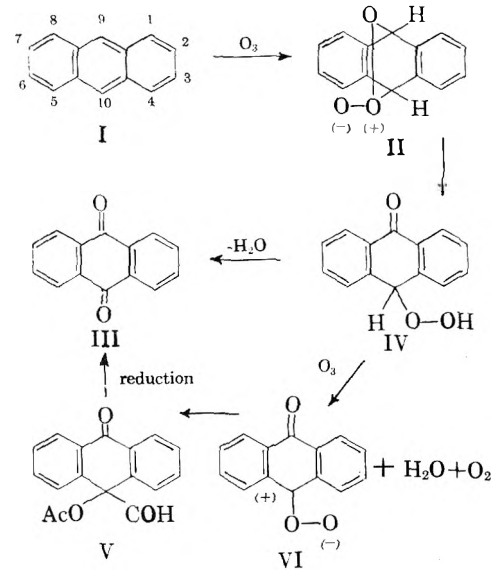
If the attack is by the two-step process, however, it should occur at the 9 and 10 positions, because these have the lowest "atom localization energies."[3,4] Diels-Alder type reagents also would attack at the 9 and 10 positions, even by a one-step mechanism, but ozone can probably be excluded from this category since it does not behave as such with ordinary conjugated systems.

The ozonization of anthracene in acetic anhydride to give anthraquinone has been reported.[5] The yield was not given, however, nor was it shown that ozone instead of oxygen actually was the reactant. We have ozonized anthracene in acetic acid at 10° with 5% ozone and have found that the ozone is readily absorbed. The reaction is complete after three moles per mole of anthracene react. Anthraquinone is produced in 69% yield. Some anthraquinone (28%) precipitates during the reaction. The remainder is produced by sodium iodide or bisulfite reduction of the peroxidic filtrate. Ozone rather than oxygen was shown to be the attacking agent not only by the fact that far more than catalytic amounts were absorbed but also by passing the same volume of 0.5–1% ozone through the reaction mixture and showing that the amount of anthraquinone produced was directly proportional to the amount of ozone employed.

These results are important for two reasons. This is the first established instance in which ozone has attacked the ends of a conjugated system rather than a specific double bond. The geometry of the system is such that the ozone molecule can reach across the ends of the system, i.e., from C-9 to C-10. Further, this is excellent evidence for the two-step mechanism and corroborates Wibaut's[6] experiments which indicate that the initial attack is electrophilic. Such can be the case only with the two-step mechanism.[3]

The following suggested mechanism for the anthracene reaction explains the essential fact that anthraquinone is produced both during the ozonolysis (presumably by decomposition of a peroxidic intermediate, e.g. IV) and by reduction of a peroxidic intermediate. Evidence for IV is the isolation of some anthrahydroquinone by sodium iodide reduction. Since anthraquinone is the principal reduction product, however, oxidation of IV to VI is proposed. This is to be expected since IV would be in equilibrium with a perhydroquinone structure.

The suggested mechanism does not explain the requirement of three moles of ozone per mole of anthracene. It seems likely that the 31% of anthracene which did not produce anthraquinone reacted by the one-step mechanism. This should result in destruction of both outer rings and account for a large portion of the total three moles of ozone.



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Received December 10, 1956

(1) Included in part in a paper presented before the International Ozone Conference, Chicago, Ill., November 28–30, 1956.

(2) Badger, *Quart. Revs.*, 5, 155 (1951).

(3) (a) Brown, *Quart. Revs.*, 6, 63 (1952). (b) Brown, *J. Chem. Soc.*, 3249 (1950).

(4) Dewar, *J. Am. Chem. Soc.*, 74, 3357 (1952).

(5) Roitt and Waters, *J. Chem. Soc.*, 3060 (1949).

(6) For leading references see Bailey, *J. Am. Chem. Soc.*, 78, 3811 (1956).

1,5-Diaryl-2,3-pyrrolidinediones. VII. Reassignment of Structure

Sir:

Since Schiff and Gigli[1] *first reported the preparation* of 1,5-diphenyl-2,3-pyrrolidinedione (Ia) a

(1) R. Schiff and L. Gigli, *Ber.*, 31, 1306 (1898).

large number of 1,5-diaryl-2,3-pyrrolidinediones has been synthesized, and several curious aspects of their chemical behavior have been studied in this laboratory.[2-6]

Previous evidence to the contrary notwithstanding,[4,7] we now wish to report conclusive proof that the structures of such compounds have been incorrectly assigned. Addition of *p*-anisidine to β-(*p*-methoxybenzoyl)-acrylic acid affords α-(*p*-anisylamino)-β-(*p*-methoxybenzoyl)-propionic acid, m.p. 144.5–145.0° dec.

Anal.[8] Calc'd for $C_{18}H_{19}NO_5$: C, 65.64; H, 5.80; N, 4.25. Found: C, 65.69; H, 5.79; N, 4.25.

Treatment of this ketoacid with sodium borohydride, followed by benzoyl chloride in pyridine yielded α-(N-benzoyl-*p*-anisylamino)-γ-*p*-anisyl-γ-butyrolactone, m.p. 164.5–165.5°.

Anal.[8] Calc'd for $C_{25}H_{23}NO_5$: C, 71.95; H, 5.55; N, 3.36. Found: C, 71.82; H, 5.53; N, 3.37.

This substance was shown by identity of infrared spectra and mixture melting point determination to be identical with the benzoyl derivative of the cyclic reduction product obtained by Vaughan and Peters[3] by catalytic hydrogenation and benzoylation of β-(*p*-anisylidine)-α-(*p*-anisylimino)-propionic acid (IIb), reacting as its proved cyclic tautomer, then presumed to be Ib, 1,5-dianisyl-2,3-pyrrolidinedione (enol form).

The absorption band in the high frequency range of the infrared spectra of substances previously held to be the enolic forms of 1,5-diaryl-2,3-pyrrolidinediones[7] is now assigned to N—H rather than O—H, since the treatment of Ia with sodium nitrite in glacial acetic acid affords an N-nitroso derivative whose infrared spectrum is transparent in the N—H region. The nitroso compound melts with decomposition at 216.0–216.5°.

Anal.[8] Calc'd for $C_{16}H_{12}N_2O_3$: C, 68.56; H, 4.32; N, 10.00. Found: C, 68.71; H, 4.17; N, 10.14.

The original substance thus has an endocyclic double bond which is evidently in the α,β-position (as in an enamine form), since the carbonyl absorption at 1736 cm.$^{-1}$ is at a lower frequency than is that for the dihydrolactone (1742 cm.$^{-1}$), whereas it would be at a higher frequency than in the dihydrolactone, if the double bond were β,γ.[9]

The present evidence for the structure of Ia and Ib coupled with the striking similarity in infrared spectra[7] and chemical behavior[2-4] as well as methods of synthesis,[7] for all previously reported and otherwise unsubstituted 1,5-diaryl-2,3-pyrrolidinediones constitutes a reasonable basis for assigning to all such compounds the 5-aryl-3-arylamino-2(5H)-furanone (V) structure.[10] Thus there is no available evidence for the existence of the otherwise unsubstituted 1,5-diaryl-2,3-pyrrolidinedione system,[11] and the previously reported reaction, I ⇄ II, becomes a special case of lacto-enoic tautomerism:[12] V ⇄ II.

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Received December 17, 1956

(2) W. R. Vaughan and L. R. Peters, *J. Org. Chem.*, 18, 393 (1953).

(3) W. R. Vaughan and L. R. Peters, *J. Org. Chem.*, 18, 405 (1953).

(4) W. R. Vaughan and D. I. McCane, *J. Org. Chem.*, 20, 143 (1955).

(5) W. R. Vaughan, *J. Org. Chem.*, 20, 1613 (1955).

(6) W. R. Vaughan, *J. Org. Chem.*, 20, 1619 (1955).

(7) W. R. Vaughan and L. R. Peters, *J. Org. Chem.*, 18, 382 (1953).

(8) Spang Microanalytical Laboratories, Ann Arbor, Michigan.

(9) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley and Sons, Inc., New York, N. Y., 1954, p. 160.

(10) This structure is the enamine form of the α-iminolactone proposed by K. Garzarolli-Thurnlackh [*Monatsh.*, 20, 480 (1899); *Ber.*, 32, 2274 (1899)] and was suggested to one of us (W.R.V.), along with a similar interpretation of our published infrared data[7] and the present type of structure proof, in 1953 by Dr. J. A. King in a private communication.

(11) It should be emphasized that this disproof of structure does not in any way apply to 2,3-pyrrolidinediones with 4-substituents or to the simpler 1-substituted compounds, for which conclusive structural evidence is available.

(12) R. P. Linstead and H. N. Rydon, *J. Chem. Soc.*, 580 (1933).

(13) National Science Foundation Predoctoral Fellow, 1954–1957.

Steroids. LXXXIV.[1] Synthesis of 6-Methyl Hormone Analogs

Sir:

The recent communication[2] describing the preparation of 6α-methyl cortical hormone analogs prompts us to announce at this time the synthesis of a number of 6-methyltestosterone and progesterone derivatives some of which possess potentiated biological activity. Perbenzoic acid oxidation of Δ^5-androstene-3β,17β-diol diacetate and reaction of the resulting 5α,6α-oxide (m.p. 165–166°, $[\alpha]_D$ −71°. Found: C, 70.65; H, 9.08[3]) with methylmagnesium bromide in ether-benzene gave 6β-methylandrostane-3β,5α,17β-triol (I)[4] (m.p. 137–138°, $[\alpha]_D$

(1) Paper LXXXIII, H. J. Ringold and G. Rosenkranz, *J. Org. Chem.*, in press.

(2) Spero, Thompson, Magerlein, Hanze, Murray, Sebek, and Hogg, *J. Am. Chem. Soc.*, 78, 6213 (1956).

(3) All melting points are uncorrected. Rotations were determined at 20° in chloroform and ultraviolet absorption spectra in 95% ethanol.

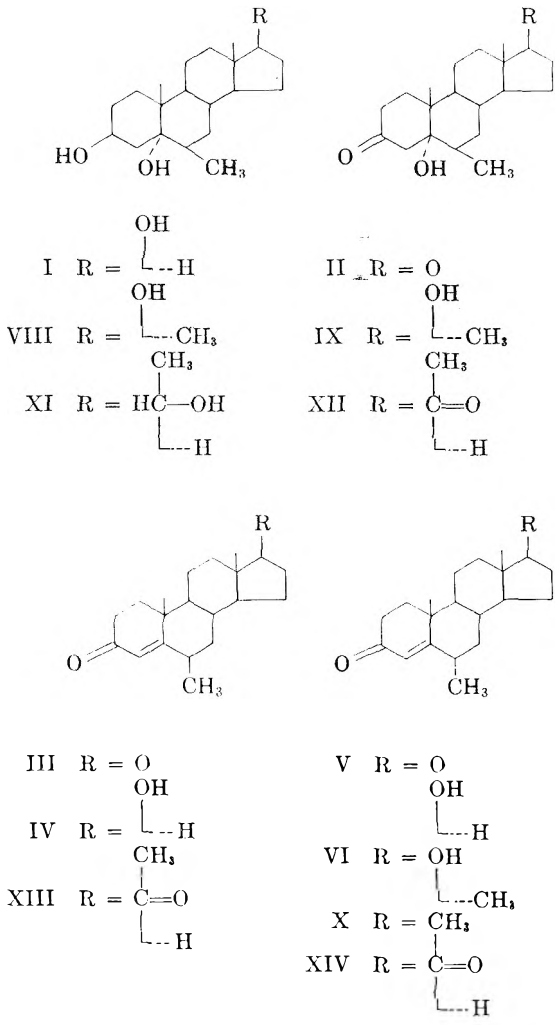
(4) Ushakov and Madaeva, *J. Gen. Chem.* (U.S.S.R.), 9, 436 (1939), first observed the opening of cholesterol α-oxide with methylmagnesium iodide. Turner, *J. Am. Chem. Soc.*, 74, 5363 (1952) investigated this reaction further and prepared 6α- and 6β-methylcholestone from the Grignard reaction product.

$-8°$)[5] which was oxidized with pyridinium chromate to 6β-methylandrostan-5α-ol-3,17-dione (II) (m.p. 228–230°, $[\alpha]_D$ +77°. Found: C, 75.16; H, 9.37). Thionyl chloride–pyridine dehydration of II at 0° yielded 6β-methyl-Δ^4-androstene-3,17-dione (III) (m.p. 175–176°, $[\alpha]_D$ +132°, λ_{max} 242 mμ, log ε 4.19. Found: C, 79.96; H, 9.52) from which 6β-methyltestosterone (IV) (m.p. 209–210°, $[\alpha]_D$ +48°, λ_{max} 242 mμ, log ε 4.19. Found: C, 79.32; H, 10.14) was derived by lithium aluminum hydride reduction followed by manganese dioxide oxidation.[6] Treatment of II with methanolic potassium hydroxide, resulting in dehydration and methyl inversion, yielded 6α-methyl-Δ^4-androstene-3,17-dione (V) (m.p. 168–170°, $[\alpha]_D$ +176°, λ_{max} 240 mμ, log ε 4.21. Found: C, 80.02; H, 9.35) which was converted to 6α-methyltestosterone (VI) (m.p. 158–159°, $[\alpha]_D$ +91°, λ_{max} 242 mμ, log ε 4.20. Found: C, 79.60; H, 10.02) by sodium borohydride reduction.[7] The latter was also readily obtained from IV by acidic or alkaline inversion of the 6β-methyl (axial) group. Catalytic hydrogenation of IV over a palladium-carbon catalyst gave almost exclusively the allo derivative 6β-methylandrostan-17β-ol-3-one (VII) (m.p. 203–205°, $[\alpha]_D$ +37°. Found: C, 79.26; H, 10.65).

Similarly, 17α-methyl-Δ^5-androstene-3β,17β-diol 3-acetate was converted to the 5,6α-oxide (m.p. 164–165°, $[\alpha]_D$ −84°. Found: C, 72.76; H, 9.09), thence to 6β,17α-dimethylandrostane-3β,5α,17β-triol (VIII) (m.p. 191–192°, $[\alpha]_D$ −45°)[5] by means of methylmagnesium bromide, to 6β,17α-dimethylandrostane-5α,17β-diol-3-one (IX) (m.p. 253–254°, $[\alpha]_D$ −26°. Found: C, 75.36; H, 10.43) by pyridinium chromate oxidation, and 6α,17α-dimethyltestosterone (X) (m.p. 136–137°, $[\alpha]_D$ +71°, λ_{max} 242 mμ, log ε 4.19. Found: C, 79.49; H, 10.09) finally derived from IX by methanolic alkali treatment.

The readily available Δ^5-pregnene-3β,20β-diol diacetate served as starting material for the preparation of 6α- and 6β-methylprogesterone by a reaction scheme essentially identical to that described above and involving the following intermediates: 5α,6α-oxidoallopregnane-3β,20β-diol diacetate (m. p. 180–181°, $[\alpha]_D$ −39°. Found: C, 71.58; H, 9.11), 6β-methylallopregnane-3β,5α,20β-triol (XI) (m.p. 236–237°, $[\alpha]_D$ −31°. Found: C, 75.22; H, 10.69), 6β-methylallopregnan-5α-ol-3,20-dione (XII) (m.p. 264–265°, $[\alpha]_D$ +75°. Found: C, 76.13; H, 9.75). Thionyl chloride-pyridine dehydration of XII led to 6β-methylprogesterone (XIII) (m.p. 170–172°, $[\alpha]_D$ +135°, λ_{max} 242 mμ, log ε 4.21. Found: C, 80.16; H, 9.65) while alkaline treatment of XII or XIII gave the stable (equatorial) isomer 6α-methylprogesterone (XIV) (m.p. 119–121°, $[\alpha]_D$ +177°, λ_{max} 242 mμ, log ε 4.21. Found: C, 80.40; H, 9.95).

In the immature castrate male rat (subcutaneous administration) 6α-methyltestosterone (VI) exhibits 0.9× the androgenic (measured by the prostate and seminal vesicles) and 4.6× the myotrophic (levator ani muscle) potency of testosterone.[8] 6β-Methyldihydrotestosterone (VII) is 3.9× as androgenic and 8.1× as myotrophic as testosterone in the same test. In the guinea pig copulatory assay[8] both 6β- and 6α-methylprogesterone (XIII and XIV) exhibit an order of activity slightly greater than the parent progesterone.



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Received January 14, 1957

(5) Satisfactory carbon-hydrogen analyses could not be obtained for I and VIII apparently due to solvent of crystallization.

(6) *Cf.* Sondheimer, Amendolla, and Rosenkranz, *J. Am. Chem. Soc.*, **75**, 5930 (1953).

(7) *Cf.* Norymberski and Woods, *J. Chem. Soc.*, 3426 (1955).

(8) Bioassays by the Endocrine Laboratories, Madison, Wis.