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Photodimerization of 2-Styrylpyridine

J. L. R. WILLIAMS

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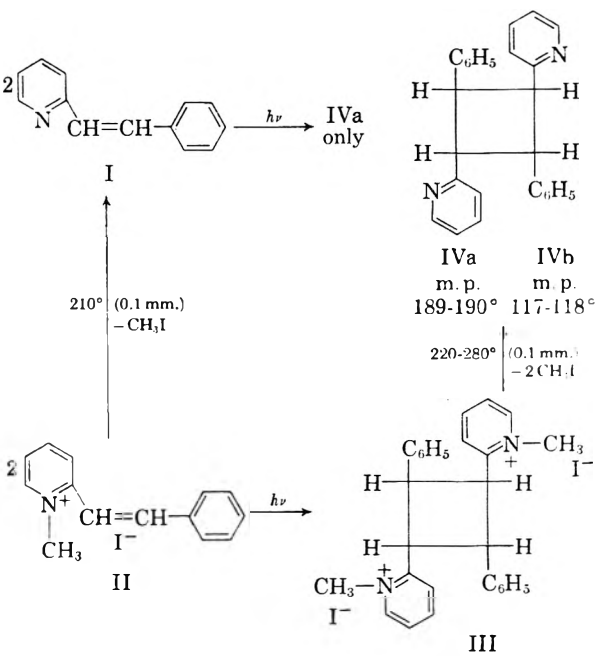
Contrary to previous reports of other investigators, 2-styrylpyridine photodimerizes, though in very low yield, owing to degradation and resinification. Irradiation of 2-styrylpyridinium methiodide produces a high yield of dimeric salt which, when sublimed *in vacuo*, gives two isomeric dimeric bases, one of which is identical with the dimer of 2-styrylpyridine.

Koller[1] reported that ultraviolet irradiation of 2,4-dichloro-3-cyano-6-styrylpyridine produced a high-melting photodimer. By molecular-weight determination and by its inert behavior toward potassium permanganate in acetone, the dimer was shown to be 1,3-bis(phenyl)-2,4-bis[2-(2,4-dichloro-3-cyano)pyridyl]cyclobutane which on pyrolysis reverted to 2,4-dichloro-3-cyano-6-styrylpyridine. Under identical conditions,[1] 2-styrylpyridine (2-stilbazole) (I) did not dimerize. Later, Henze[2] prepared a bis(2-quinolyl)bis(phenyl)-cyclobutane by irradiation of 2-styrylquinoline. It was again reported that 2-styrylpyridine (I) did not photodimerize.

During a study of the ultraviolet spectra of a group of styrylpyridinium salts, it has been found that ultraviolet irradiation of solid 2-styrylpyridinium methiodide (II), m.p. 227–228°, produced a new salt (III), m.p. 310–312°. Irradiation was accompanied by a change of color from yellow to white, with a simultaneous shift of the ultraviolet absorption of 2-styrylpyridinium methiodide (II) from 337 mμ to 265 mμ. Elemental analysis revealed that the empirical formula of the new salt was identical with that of 2-styrylpyridinium methiodide.

Sublimation of styrylpyridinium methiodides produces the corresponding styrylpyridine and methyl iodide. Accordingly, sublimation of the new salt (III) produced a free base (IV) which had elemental analyses and a molecular weight corresponding to that of a dimer of styrylpyridine. The basic dimer obtained from the sublimation melted over the range, 108° to 170°. Fractional crystallization of the basic dimer (IV) has yielded two forms (IVa and IVb) melting at 189–190° and 117–118°. The molecular weights for the two isomers are 364 and 362, respectively. Figure 1 shows that the basic dimers (IVa and IVb) and 2-(β-phenethyl)pyridine (V) are quite similar in ultraviolet spectra. 2-Styrylpyridine (I) differs vastly from both dimers in melting point and in ultraviolet absorption (λ_{max}, 309 mμ). The dimer



(1) G. Koller, *Ber.*, **60B**, 1920 (1927).
(2) M. Henze, *Ber.*, **70B**, 1273 (1937).

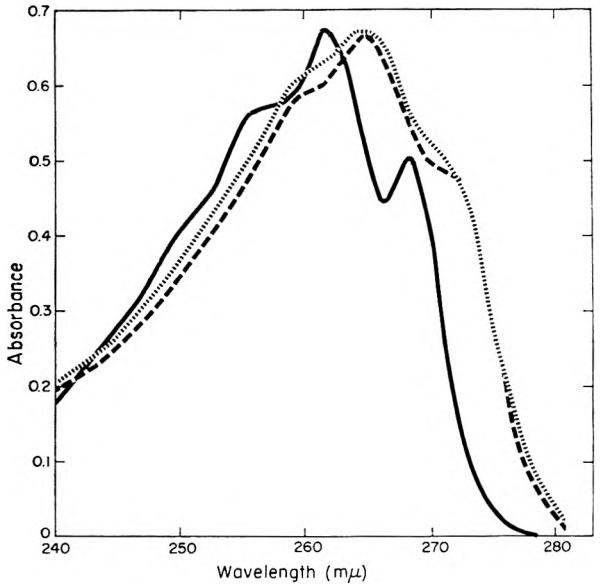


Fig. 1. Ultraviolet spectra in methanol of 2-(β-phenethyl)pyridine, (V), 2×10^{-4} molar, ———; dimer IVa, 1×10^{-4} molar, - - - - - - -; dimer IVb, 1×10^{-4} molar, ||||||||||||

salt (III) is similar in ultraviolet spectra to 2-(β-phenethyl)pyridinium methiodide (VI).

Careful repetition of the irradiation of 2-styrylpyridine (I), in the manner of Koller[1] and Henze,[2] has shown that dimerization does indeed occur, but in only 2.6% yield. The majority of 2-styrylpyridine (I) is photodegraded to a mixture of resinous and volatile products. The photodimer of 2-styrylpyridine (I) obtained is identical in physical properties with the higher melting isomer (IVa) obtained by the pyrolysis of the photodimer (III) of 2-styrylpyridinium methiodide (II).

In structures IVa, IVb, and III, no attempt is made to fix the configuration of the groups pendant to the cyclobutane ring. It appears reasonable, however, after examination of molecular models, to expect the quaternized rings to dimerize into alternate positions. This would reduce steric as well as charge interference. The configurational aspects of these tetra-substituted cyclobutanes is now under study.

EXPERIMENTAL

Photodimerization of 2-styrylpyridinium methiodide. Twenty-five g. of powdered 2-styrylpyridinium methiodide[3] was irradiated in an open dish for 80 hr. at a distance of 10 in. from a 450-watt, high-pressure, mercury-vapor lamp. The solids were mixed and crushed every 8 hr. to ensure exposure. The color of the solids changed from yellow, m.p. 227–228°, to buff, m.p. 265–269°, during irradiation. Recrystallization of the buff solid from water, after a treatment with Norit, produced a white solid, m.p. 310–312°. The yield was nearly quantitative.

Anal. Calcd. for $C_{28}H_{28}N_2I_2$: C, 51.8; H, 4.7; N, 4.4; I, 39.2. Found: C, 52.0; H, 4.5; N, 4.2; I, 39.1.

Pyrolysis of the photodimer of 2-styrylpyridinium methiodide. Two g. of the photodimer of 2-styrylpyridinium methiodide was placed in an all-glass vacuum sublimation apparatus. The solids were heated at 0.1 mm. for 2 hr. at 220°, followed by 2 hr. at 275–280°. The sublimate (1 g.) was dissolved in a boiling mixture of 100 ml. of benzene and 700 ml. of hexane. After treatment with Norit, the colorless solution was evaporated to dryness on the steam cone. The solids were boiled with 50 ml. of hexane. The undissolved solid (IVa) was separated and dried; weight, 0.2 g.; m.p. 189–190°.

Anal. Calcd. for $C_{26}H_{22}N_2$: C, 85.6; H, 6.1; N, 7.8; mol. wt., 362. Found: C, 85.1; H, 5.7; N, 7.8; mol. wt., 364. The mother liquor, when cooled to 30°, produced 0.1 g. of crystals (IVa), m.p. 185–187°. The mother liquor was then evaporated on the steam cone to 30 ml. and cooled to 30° to produce 0.1 g. of white needles (IVb), m.p. 114–115°.

Anal. Calcd. for $C_{26}H_{22}N_2$: C, 85.6; H, 6.1; N, 7.8; mol. wt., 362. Found: C, 85.7; H, 5.7; N, 7.8; mol. wt., 362.

The mother liquors yield, on evaporation to 15 ml., 0.2 g. of mixed crystals, m.p. 109 to 140°.

Photodimerization of 2-styrylpyridine. Six g. of 2-styrylpyridine[4] was irradiated for 72 hr. at a distance of 10 in. from a 450-watt, high-pressure, mercury-vapor arc. The solids were stirred periodically until they became tacky. During irradiation, a strong aromatic odor was produced. The tacky solids, weighing 4 g., were dissolved in 100 ml. of diethyl ether, and the solution was treated with Norit. The solution was evaporated to dryness, and the solids were boiled with a mixture of 50 ml. of ethyl acetate and 100 ml. of hexane. A considerable portion of the solids were sticky polymers which failed to dissolve and were then removed by filtration. The clear solution was cooled to −10°; white crystals (IVa) separated which, after filtration and drying, weighed 0.4 g., and melted at 185–188°. A sample recrystallized from (4:1) hexane–diethyl ether melted at 189–190°. A mixed melting point with (IVa) obtained from the dimer of 2-styrylpyridine methiodide (III) by pyrolysis was not depressed.

Ultraviolet absorption curves. The ultraviolet spectra were run in 1-cm. quartz cells using a Cary Model 14 instrument.

Molecular weights. Molecular-weight determinations were carried out by Dr. O. E. Schupp, of the Kodak Research Laboratories, using the elegant thermometric method of Neumayer.[5]

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(3) A. P. Phillips, *J. Org. Chem.*, 12, 333 (1947).

(4) B. D. Shaw and E. A. Wagstaff, *J. Chem. Soc.*, p. 26 (1933).

(5) J. J. Neumayer, *Anal. Chim. Acta*, 20, 519 (1959).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CORNELL UNIVERSITY]

The Preparation of 5,5-Dimethylcyclopentadiene

C. F. WILCOX, JR., AND M. MESIROV

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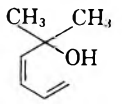
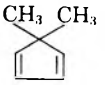
The preparation and identification of 5,5-dimethylcyclopentadiene is reported. The cyclodehydration of 2-methyl-3,5-hexadiene-2-ol is shown not to yield 5,5-dimethylcyclopentadiene.

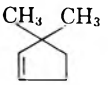
In 1939 Zonis reported that when 2-methyl-3,5-hexadiene-2-ol, I, was heated with 25% aqueous sulfuric acid for eight hours at 100° a hydrocarbon with a boiling point of 108–111° was isolated in 25% yield.[1] This hydrocarbon was assigned the structure 5,5-dimethylcyclopentadiene, II, on the basis



I



II



III

that (1) it had a molecular formula of C_7H_{10}, (2) it absorbed two equivalents of hydrogen, and (3) its molecular refractivity, 32.85, was consistent with the value of 31.40 calculated for a cyclic C_7 diene.[2] This evidence is inadequate to exclude the numerous isomeric cyclopentadiene and cyclohexadiene structures which might easily have arisen during the long exposure to hot acid. Furthermore, the reported boiling point seemed anomalous for II. As shown in Fig. 1, the boiling points of cyclopentane, cyclopentene, and cyclopentadiene decrease smoothly.[3] Similarly, the boiling points of methylcyclopentane and 3,3-dimethylcyclopentane appear to follow the same trend except for the expected elevations due to increased molecular weight. Extrapolation of the dimethyl line yields a predicted boiling point for II of 74°, *a value 35° lower than reported.*

These considerations and our interest in cyclic dienes[4] made it desirable to prepare an authentic sample of 5,5-dimethylcyclopentadiene by an independent route. A key compound in the proposed route was the known 3,3-dimethylcyclopentene, III. This compound was not prepared by one of the published sequences[5] but rather by the route shown in Fig. 2. Starting from the commercially available 2-methylcyclohexanol, the olefin, III, was prepared in 11% over-all yield. The physical properties of our III agreed closely with those reported previously.[5]

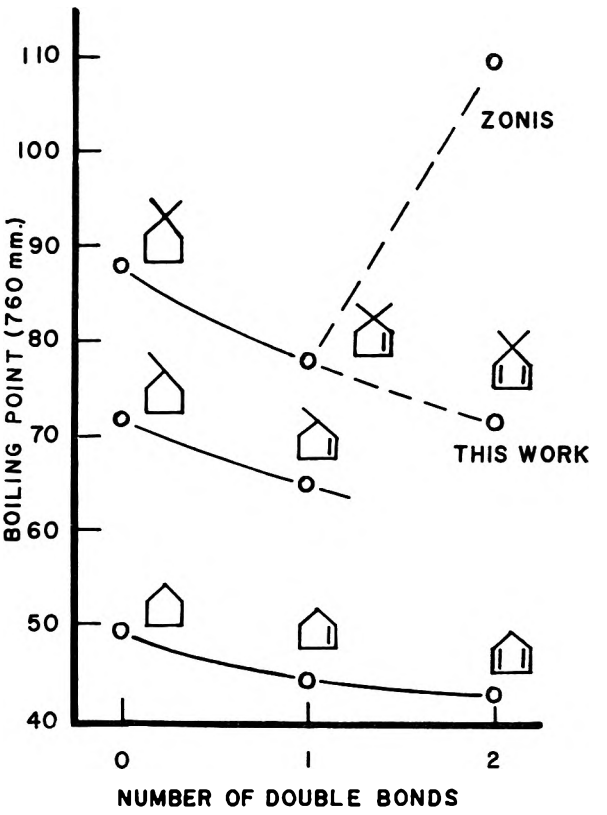


Fig. 1. The variation of boiling point of various methyl substituted cyclopentanes as a function of the number of double bonds contained in the ring

The planned scheme to convert III into II was to brominate III with *N*-bromosuccinimide and then split out a molecule of hydrogen bromide with base. Trial experiments had shown that 3-bromocyclohexene gave a 55% yield of 1,3-cyclohexadiene when heated in a 5:4 mixture of quinoline and chlorobenzene at 95° for forty-five minutes. When this reaction was applied to III by first treating it with *N*-bromosuccinimide in chlorobenzene, then adding quinoline, and heating further, the only low boiling material obtained was a 10% recovery of III.

(1) S. Zonis, *Zhur. Obscheĭ Khim.*, 9, 2191 (1939).

(2) This value is not corrected for the conjugation or *cis* nature of the double bonds. The exaltation for a cyclic conjugated diene is uncertain. K. Fajans, *Physical Methods of Organic Chemistry*, Vol. 1, A. Weissberger, ed., Interscience Publishers, Inc., New York, 1945, pp. 672–683.

(3) American Petroleum Institute Research Project 44 at the National Bureau of Standards. Selected Values of Properties of Hydrocarbons. Tables No. 6a and 18a. The boiling point given for 3,3-dimethylcyclopentene, III, appears to be in error. This value does not agree with that given by the references cited[5] nor with our own determination. It is perhaps significant that all of the physical properties given for III are identical with those given for 4,4-dimethylcyclopentene. The original value was used in preparing Fig. 1.

(4) Unpublished results of Mrs. R. Craig on spiro[4.4]-1,3-nonadiene.

(5) N. Kishner, *J. Russ. Phys. Chem. Soc.*, **40**, 994 (1908); G. Chavanne and G. Chivrdoglu, *Bull. soc. chim. Belg.*, **51**, 11 (1942).

TABLE I

PRODUCTS FROM THE CYCLODEHYDRATION OF 2-METHYL-3,5-HEXADIENE-2-OL

Fraction	B.P.	%	n_D^{25}	M_D	% Composition by Gas Chromatography[b] A	B	C	D	E
1	64–100	6.7	1.4140	23.5	10	54	36		
2	101–104.5	8.8	1.4555	33.4		25	75		
3	104.5–107	11.1	1.4660	34.4		3	96	1	
4	107–110	7.5	1.4598	32.5			77	1	22
Zonis	108–111	25	1.4580[a]	32.9			?		
I	71.3		1.4240	31.4					

[a] This value is estimated from the n_D^{20} 1.4600 actually reported by Zonis. [b] Peak C is actually two peaks; these could not be resolved completely with helium carrier gas on dinonyl phthalate at either 104° or 76°.

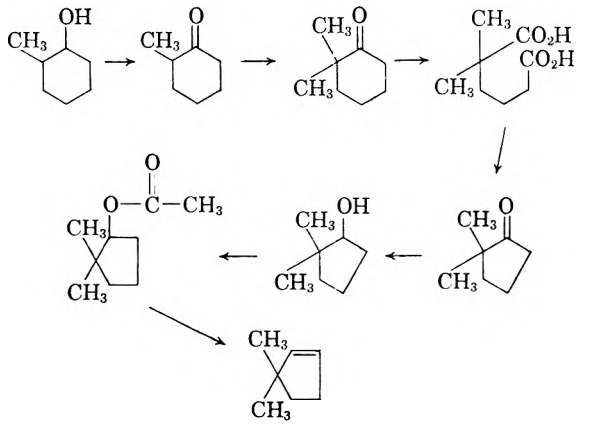


Fig. 2. Preparation of 3,3-dimethylcyclopentene

This one-step bromination-dehydrobromination was abandoned and 3,3-dimethyl-5-bromocyclopentene was prepared and isolated in 33–40% yield by use of *N*-bromosuccinimide in the lower boiling solvent, carbon tetrachloride. This easily decomposed bromide was freed of carbon tetrachloride and other gross impurities by cautious vacuum distillation at temperatures below 40°. The purified bromide was immediately heated with quinoline in such a manner that the diene distilled out of the reaction flask as it was formed. The hydrocarbon thus obtained (60%–80% yield) was shown to be 5,5-dimethylcyclopentadiene, II, by the following chain of evidence: (1) the isolated hydrocarbon was at least 99% pure as measured by vapor phase chromatography, (2) the presence of a *cis*-diene was indicated by an ultraviolet maximum at 250 mμ (log ε 3.45) which was very similar to that of spiro [4.4]-1,3-nonadiene,[4] λ_{max} (ethanol) 254 mμ, log ε 3.44, (3) it formed Diels-Alder adducts of the expected composition with maleic anhydride and *N*-phenylmaleimide, (4) the NMR showed only two types of hydrogen in a ratio of 3:2 with an unresolved vinyl peak similar to that of spiro [4.4]-1,3-nonadiene,[4] (5) under conditions where cyclopentadiene (Enjay, 95%) liberated 93% of the theoretical amount of ammonia from sodamide in dry tetrahydrofuran, this hydrocarbon liberated at most only 1%, (6) the hydrocarbon could be reduced with hydrogen to 1,1-dimethylcyclopentane, which was identical in every way with that obtained from the known 3,3-dimethylcyclopentene, III.

With an authentic sample of 5,5-dimethylcyclopentadiene, II, now available for comparison, the dehydration of I was repeated according to the recipe of Zonis[1] to see if it would provide a shorter route to II. The steam-distillable organic products thus obtained were redistilled and separated into four arbitrary fractions. The composition of these fractions as indicated by gas chromatography and their physical properties are given in Table I. The properties reported by Zonis as well as those of 5,5-dimethylcyclopentadiene are also given for reference. From these data it is difficult to be certain of the structure of the original Zonis product except that it was not 5,5-dimethylcyclopentadiene. The low boiling fraction 1 was shown to be free of 5,5-dimethylcyclopentadiene by the total absence of infrared bands at 10.55, 10.62, and 13.40 μ, which were present as medium to strong peaks in the authentic sample. Fraction 1 also failed to yield a maleic anhydride or *N*-phenylmaleimide derivative.

EXPERIMENTAL[6]

2-Methylcyclohexanone. This compound was prepared from 2-methylcyclohexanol according to the chromic acid oxidation procedure of Ouderkirk and Meinwald[7] in 83% yield; b.p. 160–162° (745 mm.), n_D^{25} 1.4508.

2,2-Dimethylcyclohexanone. The 2-methylcyclohexanone was methylated and isolated by the procedure of King, *et al.*[8] in 52% yield; b.p. 100–102° (100 mm.), n_D^{25} 1.4451; reported, b.p. 170–171° (765 mm.), $n_D^{18.5}$ 1.4492.

2,2-Dimethyladipic acid. The oxidation of 2,2-dimethylcyclohexanone was carried out by the method of Meerwein and Unkel,[9] except that only 4 ml. of concd. nitric acid was used for each gram of ketone. The recrystallized acid was obtained in 45% yield, m.p. 85–86°; reported, m.p. 86–87°.

2,2-Dimethylcyclopentanone. In a 500-ml. distilling flask was placed an intimate mixture of 6 g. of barium hydroxide and 120 g. of 2,2-dimethyladipic acid and a thermometer was inserted in the flask so that the bulb was 4 cm. from the bottom. The flask was heated gradually in a silicone oil bath to 280° and the heating was continued until only a dry residue remained (about 90 min.). The organic distillate

(6) Analyses performed by the Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

(7) J. Ouderkirk, Ph.D. dissertation, Cornell University, 1957.

(8) F. E. King, T. J. King, and J. G. Topliss, *J. Chem. Soc.*, 919 (1957).

(9) H. Meerwein and W. Unkel, *Ann.*, 376, 152 (1910).

was separated from the aqueous phase and the aqueous layer was saturated with sodium chloride and extracted once with ether. After the combined organic materials had been dried over potassium carbonate, the ether was stripped off through a short column. On distillation the residue gave 57 g. (74%) of 2,2-dimethylcyclopentanone, b.p. 140–143° (745 mm.), $n_D^{22.8}$ 1.4312; reported,[10] b.p. 143–144° (corr., $n_D^{19.5}$ 1.4322.

The 2,4-dinitrophenylhydrazone of the ketone melted at 144° (sharp); reported,[11] 141–141.5°.

Anal. Calcd. for $C_{13}H_{16}N_4O_4$: C, 53.42; H, 5.52; N, 19.17. Found: C, 53.43; H, 5.54; N, 18.68.

2,2-Dimethylcyclopentanol. The 2,2-dimethylcyclopentanone (32 g.) was reduced with a mixture of 11.1 g. of lithium aluminum hydride and 600 ml. of ether. The excess hydride was decomposed with 44 ml. of water and after the organic layer had been decanted, the salts were washed well with ether and the washings added to the organic layer. The ether solution was dried and the solvent distilled through a short column. The residue was distilled to yield 31 g. (95%) of alcohol; b.p. 151–152° (744 mm.), n_D^{20} 1.4532, reported,[12] b.p. 100° (110 mm.).

The p-nitrobenzoate of the alcohol melted at 90° (sharp).

Anal. Calcd. for $C_{14}H_{17}NO_4$: C, 63.85; H, 6.51; N, 5.32. Found: C, 63.93; H, 6.56; N, 5.49.

2,2-Dimethylcyclopentyl acetate. Ketene was bubbled into a solution of 16.1 g. of 2,2-dimethylcyclopentanol and 0.04 g. of *p*-toluenesulfonic acid in 45 ml. of ether. The complete conversion (about 3 hr.) was gauged by the disappearance of the hydroxyl peak (2.90 μ) in the infrared. After this time, the ether solution was extracted three times with 10% sodium carbonate solution and then dried over anhydrous magnesium sulfate. After the ether had been removed, the residue was vacuum distilled to yield 21 g. (95%) of the acetate; b.p. 84–86° (40 mm.) and 169–173° (744 mm.) $n_D^{24.8}$ 1.4303.

Anal. Calcd. for $C_9H_{16}O_2$: C, 69.19; H, 10.33. Found: C, 68.41, 70.07; H, 10.23, 10.44.

A sample of the acetate was hydrolyzed by refluxing it in 25% aqueous sodium hydroxide for 20 hr. The *p*-nitrobenzoate of the resulting alcohol melted at the same temperature as the previous sample and a mixed melting point showed no depression.

3,3-Dimethylcyclopentene. A Pyrex tube (37 cm. × 1.5 cm.) was packed with carborundum chips and heated to 525° in a jacket furnace. From a Hirschberg funnel equipped with a nitrogen inlet tube, 19.2 g. of the acetate was dropped onto the hot column at the rate of 0.25 g./min. The hot vapors issuing from the bottom of the column were collected in a Dry Ice trap and then neutralized first with a 30 ml. wash of 10% sodium carbonate solution and finally with solid sodium carbonate. After the organic material had been dried over anhydrous potassium carbonate, it was distilled and the material boiling from 76 to 86° collected. This fraction was redistilled to given an 88% yield of 3,3-dimethylcyclopentene which gas chromatography indicated to be at least 99% pure; b.p. 77.5-78.3° (760 mm.), n_D^{23} 1.4161, reported,[4] b.p. 77.6–78°, 78–78.5° (754 mm.), n_D^{20} 1.4190.

One gram of the olefin was dissolved in 10 ml. of diglyme and the solution hydrogenated over a prereduced platinum oxide catalyst in a Parr bomb under 30 pounds of hydrogen until there was no further uptake (0.95 equiv.). The catalyst was removed and the 1,1-dimethylcyclopentane was distilled from the solvent through a 12-cm. glass helices packed column. Only the low boiling fraction was collected to give about a 50% yield; b.p. 88.5° (capillary tube), n_D^{21} 1.4128, reported,[2] b.p. 87–88°, n_D^{20} 1.4136.

Attempted preparation of 5,5-dimethylcyclopentadiene. A solution of 5 g. of 3,3-dimethylcyclopentene and 9.7 g. of *N*-bromosuccinimide in 20 ml. of chlorobenzene was heated for 90 min. at 75–85° and then for an additional 45 min. at 95°. The reaction flask was cooled in an ice bath and the succinimide filtered. To the filtrate was added 25 ml. of quinoline and this solution was then heated to 220° and kept at this temperature until no more volatile material distilled (about 40 min.).

The only low boiling material thus obtained was 0.5 g. of starting olefin.

Under identical dehydrobromination conditions, 3-bromocyclohexene gave a 55% yield of 1,3-cyclohexadiene.

3,3-Dimethyl-5-bromocyclopentene. A solution of 9.3 g. of *N*-bromosuccinimide and 5 g. of 3,3-dimethylcyclopentene in 36 ml. of carbon tetrachloride was refluxed for 4 hr. After the reaction mixture had been cooled and the precipitated succinimide removed, the solvent was removed under vacuum (with a nitrogen bubbler) at 40°. The pressure was lowered and the 3,3-dimethyl-5-bromocyclopentene distilled at temperatures below 40° quickly to give a 33% yield of a slightly yellow liquid. This material was then redistilled; b.p. 39.5–40° (8.2 mm.) n_D^{27} 1.4877, d_4^{27} 1.27 g./ml., M_D (calcd. for $C_7H_{11}Br$, 1 F) 39.6, M_D (obs.) 39.8.

5,5-Dimethylcyclopentadiene. The dehydrobromination of the bromide above was carried out in a flask equipped with a cold finger filled with ethanol. In this flask was placed 4.8 g. of the bromide and 15 g. of quinoline and the solution was heated to 150° and maintained at this temperature until no more material distilled (about 15 min.). The temperature was then raised to 220° and kept there for 30 min. The product was distilled on a vacuum line at 10 mm. pressure to give a 60% yield of pure hydrocarbon, b.p. 71.3° (760 mm.), n_D^{25} 1.4240, d_4^{25} 0.7660 g./ml., λ_{max} 250 mμ (ethanol), ϵ 2,900, λ_{min} 221 mμ, ϵ 85. A gas phase infrared spectrum showed medium to strong bands at 3.27, 3.36, 3.51, 6.07, 6.80, 7.31, 7.35, 8.84, 9.25, 10.55, 10.62, 12.57, and 13.40 μ. A vapor phase chromatogram indicated that this sample of diene was at least 99% pure. The NMR spectrum (40 mc.) of the pure liquid showed two peaks in the ratio of 2.9 to 2.0 at +3.95 p.p.m. and −0.93 p.p.m. relative to methylene chloride as an internal standard. All attempts to resolve the pairs of vinyl hydrogens failed.

A sample of the diene was reduced under the same conditions used for the reduction of 3,3-dimethylcyclopentene. The hydrocarbon was identical with that obtained previously and its infrared spectrum was essentially identical with that reported in the A.P.I. tables.[3]

One fifth of a milliliter of the diene liberated less than 0.1 ml. of ammonia gas when injected into a mixture of sodamide in dry tetrahydrofuran. This corresponds to less than 0.25 mole % active hydrogen. Under these same conditions freshly cracked cyclopentadiene (95%-Enjay) liberated 93% of the theoretical amount based on the sample being pure diene.

The *N*-phenylmaleimide adduct, *7,7-dimethyl-N-phenylbicyclo[2.2.1]-5-heptene-2,3 dicarboximide*, melted at 174–175°.

Anal. Calcd. for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.51; H, 6.28; N, 5.05.

A maleic anhydride adduct, *7,7-dimethyl-bicyclo[2.2.1]-5-heptene-2,3-dicarboxylic anhydride*, melted at 91–92°.

Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68.73; H, 6.30. Found: C, 68.57; H, 6.45.

2-Methyl-5-hexen-3-yn-2-ol. This compound was prepared by the method of Croxall and Van Hook[13] except that commercial sodamide was used instead of preparing it directly in liquid ammonia. The alcohol was obtained in 58% yield, b.p. 56–60° (13 mm.), n_D^{27} 1.4752.

2-Methyl-3,5-pentadien-2-ol. This compound was prepared

(10) A. Haller and R. Cornubert, *Compt. rend.*, **179**, 315 (1924); see also: M. Blanc, *Bull. soc. chim.*, [4] **3**, 780 (1908) and P. Bartlett and A. Bavley, *J. Am. Chem. Soc.*, **60**, 2416 (1936) and reference 11.

(11) P. Seifert and H. Schinz, *Helv. Chim. Acta.*, **34**, 728 (1951).

(12) A. Eschenmoser and A. Frey, *Helv. Chim. Acta*, **35**, 1660 (1952).

(13) W. Croxall and J. Van Hook, *J. Am. Chem. Soc.*, **76**, 1700 (1954).

by the selective hydrogenation over Lindlar's catalyst of the triple bond of 2-methyl-5-hexen-3-yn-2-ol. The alcohol was obtained in 83% yield, b.p. 47–52° (8 mm.), n_D^{21} 1.4560; reported: 78–80° (12 mm.), n_D^{20} 1.4566.

Cyclization of 2-methyl-3,5-pentadien-2-ol. The cyclization was carried out according to the method of Zonis.[1] In a 1-l. flask was heated for 10 hr. at 100° a solution of 2-methyl-3,5-hexadiene-2-ol and 120 ml. of 25% sulfuric acid. The reaction mixture was then distilled until only a clear aqueous phase was collected. The distillate was neutralized with 10% sodium carbonate solution and the organic material separated and dried over potassium carbonate. This product was then distilled and separated into four fractions shown in Table I. This table also lists the gas chromatographic analysis and physical properties of these fractions. Fractions 1 and 3 did not show active hydrogen by the sodamide method nor did they yield maleic anhydride or *N*-phenylmaleimide derivatives.

ITHACA, N. Y.

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, NORTHWESTERN UNIVERSITY]

peri-Substituted Naphthalenes. IV. The Tetrahydro-8-isopropyl-1-naphthoic Acids[1]

ROBERT L. LETSINGER AND WILLIAM J. VULLO[2]

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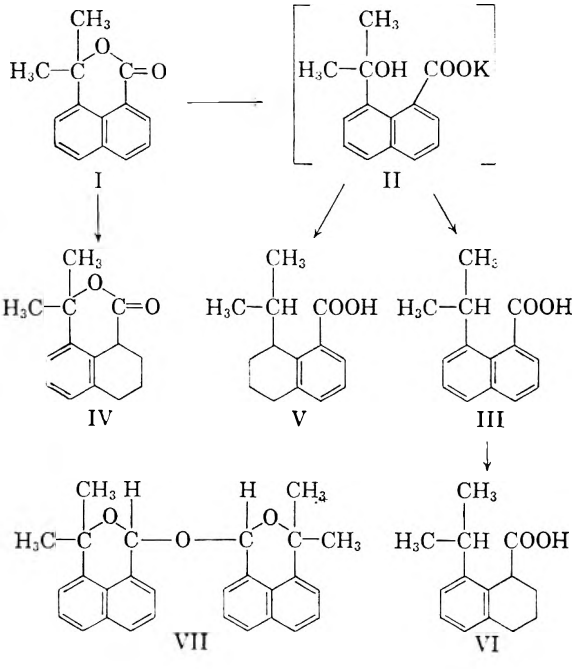
3,3-Dimethyl-1,8-naphthalide may be reduced by appropriate use of nickel-aluminum alloy and sodium metal to give tetrahydro-3,3-dimethyl-1,8-naphthalide (IV), 8-isopropyl-1-naphthoic acid (III), 5,6,7,8-tetrahydro-8-isopropyl-1-naphthoic acid (V), or 1,2,3,4-tetrahydro-8-isopropyl-1-naphthoic acid (VI). A nickel-aluminum alloy reduction was also employed in a simplified synthesis of 2-isobutylbenzoic acid. Tetrahydro acid V isomerized readily in sulfuric acid or liquid hydrogen fluoride to a neutral aldol-type product. Neither 5,6,7,8-tetrahydro-1-naphthoic acid nor 2-isobutylbenzoic acid underwent a transformation of this type under comparable conditions. The unusual lability of compound V is ascribed to the particular geometrical relationship existing between the carboxyl group and the alkyl side chain in compound V.

It has been shown that 8-isopropyl-1-naphthoic acid (III) yields an aldal (VII) when treated with sulfuric acid or hydrogen fluoride.[1] This reaction involves a hydrogen transfer from the isopropyl group to the neighboring carbonyl group. The present paper concerns the preparation and acid treatment of three related compounds—5,6,7,8-tetrahydro-8-isopropyl-1-naphthoic acid (V), 1,2,3,4-tetrahydro-8-isopropyl-1-naphthoic acid (VI), and 2-isobutylbenzoic acid (IX)—in which the relative positions of the carboxyl and isopropyl groups are similar to that in 8-isopropyl-1-naphthoic acid.

Synthesis and structure. Acids V and VI, as well as acid III and lactone IV, could be obtained by appropriate reduction of 3,3-dimethyl-1,8-naphthalide (I). The direct action of a coarse, granular grade of Raney nickel-aluminum alloy[3] on an alkaline ethanol-water solution of lactone I afforded (10%) the tetrahydrolactone (IV). This lactone was also formed, and in somewhat better yield (31%) when an ethanol solution of I was treated with sodium. By saponifying compound I with potassium hydroxide in triethylene glycol prior to addition of the alloy the course of the reaction could be altered. In this case reduction with the granular grade of alloy yielded isopropylnaphthoic acid III[1] (16–29%) and a small amount of V. When the



saponification product was similarly treated with the more active, finely powdered nickel-aluminum alloy[4] in place of the granular alloy, tetrahydro acid V was the principal product (48%). Tetrahydro acid VI was prepared (57%) by reduction of acid III with sodium and boiling amyl alcohol. The isomeric tetrahydroisopropylnaphthoic acids melted at the same temperature; however, the mixture

(1) For the previous paper in this series see R. L. Letsinger, W. J. Vullo, and A. S. Hussey, *J. Am. Chem. Soc.*, **81**, 1965 (1959).

(2) Standard Oil Company of Indiana Fellow, 1957–1958. Sinclair Oil Company Harvey Fellow, 1956–1957.

(3) Procured from the Gilman Paint and Varnish Co., Chattanooga, Tenn.

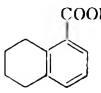
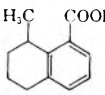
(4) Procured from the Raney Catalyst Co., Chattanooga, Tenn.

melting point was markedly depressed and their spectra differed in many respects.

The positions of the reduced rings in IV, V, and VI were established by means of the ultraviolet spectra. Pertinent information is summarized in Table I.

TABLE I

ULTRAVIOLET SPECTRAL DATA[a]

Compound	λ_{max}	log ϵ	λ_{max}	log ϵ
	236	3.6	282	3.0
 [b]	233	3.6	281	3.1
V	236	3.7	283	3.0
	264	2.6	272	2.6
VI	263	2.6	—	—
IV	267	2.32	274	2.64

[a] Ultraviolet spectra were taken with a DK-2 Beckman instrument with 95% ethanol as a solvent. [b] See ref. 5.

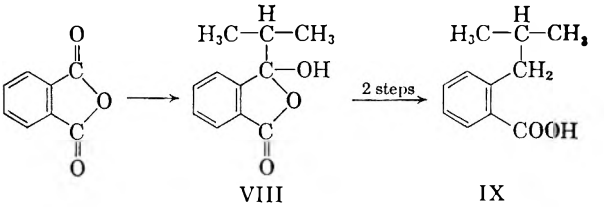
The similarity of the spectra of V and 5,6,7,8-tetrahydro-1-naphthoic acid on the one hand, and of VI and 1,2,3,4-tetrahydro-1-naphthoic acid on the other, permits an unambiguous structural assignment of the two new acids. Also, the data in Table I suggest that the carbonyl group in lactone IV is joined to the nonaromatic ring. In support of this conclusion, IV absorbs at 5.8 μ in the infrared, as expected for a compound with non-conjugated lactone carbonyl, whereas the related aromatic compound, I, absorbs at 5.9 μ.

Cason and Wordie[5] previously used the ultraviolet spectra of the tetrahydronaphthoic acids as references for establishing the structure of 5,6,7,8-tetrahydro-8-methyl-1-naphthoic acid, one of the products of a catalytic reduction of 1,8-naphthalic anhydride. The excellent agreement between the spectrum of their product and that of compound V further supports the structural assignments.

Independent evidence for the structure of acid VI may be derived from the mode of its formation. A search of the literature reveals that all cases of reduction of naphthoic acid or the substituted naphthoic acids by sodium in the presence of hydroxylic solvents are reported to afford the 1,2,3,4-tetrahydro-1- or 2-naphthoic acids; *i.e.*, the reduction occurred in the ring bearing the carboxyl group. These cases included the reduction of 1-naphthoic acid,[6,7] 2-naphthoic acid,[6] 1-methyl-2-naphthoic acid,[8] 4-ethoxy-1-naphthoic acid,[9] and naphthostyril.[10] Thus reduction of 8-isopropyl-1-naphthoic acid by sodium in amyl alcohol would be expected to yield the 1,2,3,4-tetrahydro isomer, a conclusion in agreement with that drawn from the ultraviolet spectral data.

In contrast to the sodium reductions, the course of the nickel-aluminum alloy reductions cannot at present be reliably predicted. Thus, although the reduction of potassium 8-hydroxyisopropyl-1-naphthoate (II) by the alloy yielded principally the 5,6,7,8-tetrahydro acid (V), the reduction of potassium 1-naphthoate under similar conditions produced the 1,2,3,4- and the 5,6,7,8-tetrahydro-1-naphthoic acid in yields of 44% and 16%, respectively. Furthermore, the reduction of 1,8-naphthalide by the same type of reagent gave 1,2,3,4-tetrahydro-8-methyl-1-naphthoic acid as the only reported isolated reduction product.[5,11]

2-Isobutylbenzoic acid has been described by Mann and Stewart, who prepared it incidently in connection with some studies on the chemistry of 2-methoxymethylaniline.[12] As their procedure involved seven steps from 2-bromobenzyl bromide, another shorter synthesis was developed.



VIII IX

The reaction of diisopropylcadmium with phthalic anhydride afforded (37%) a monoisopropyl adduct (VIII), which is formulated as the hydroxyphthalide rather than the keto acid, as the infrared spectrum of the solid contained a band at 3.0 μ (O—H) and a single band at 5.72 μ in the carbonyl region. A Clemmensen reduction converted VIII to 3-isopropylphthalide in 76% yield. The same transformation was also accomplished in 61% yield by heating VIII with an alkaline suspension of nickel-aluminum alloy. Reduction of the phthalide to isobutylbenzoic acid (IX) was accomplished (36%) by saponifying the phthalide of triethylene glycol at 160–170° and reducing with nickel-aluminum alloy.

Acid treatment. Tetrahydro-acid V proved to be more sensitive than 8-isopropyl-1-naphthoic acid

(5) J. Cason and J. D. Wordie, *J. Org. Chem.*, **15**, 608 (1950).

(6) W. V. Sowinski, *Ber.*, **24**, 2358 (1891).

(7) W. Kay and A. Morton, *J. Chem. Soc.*, **105**, 1565 (1914).

(8) K. v. Auwers, *Ber.*, **58**, 151 (1925). K. v. Auwers and K. Moller, *J. prakt. Chem.*, **109**, 124, 143 (1925).

(9) O. Kamm, H. B. McClugage, and A. W. Landstrom, *J. Am. Chem. Soc.*, **39**, 1247 (1925).

(10) G. Schroeter and H. Rossler, *Ber.*, **35**, 4218 (1902).

(11) R. C. Fuson and G. Munn, *J. Am. Chem. Soc.*, **71**, 1870 (1949).

(12) F. G. Mann and F. H. C. Stewart, *J. Chem. Soc.*, 4127 (1954). See F. G. Mann and F. H. C. Stewart, *J. Chem. Soc.*, 2819 (1954) and F. C. Holliman and F. G. Mann, *J. Chem. Soc.*, 1634 (1947) for preparation of the intermediates.

to the action of sulfuric acid. Indeed, concentrated sulfuric acid rapidly converted V to water soluble products. In 94.7% sulfuric acid at room temperature, however, compound V reacted to give a neutral, water insoluble oil(X) in 51–61% yield. The same material (identical infrared spectrum) was obtained quantitatively when V was treated with liquid hydrogen fluoride. This product showed no carbonyl or hydroxyl absorption in the infrared; however, it reacted readily with 2,4-dinitrophenylhydrazine in acidic solution to give an orange-red hydrazone derivative, the analysis of which agreed with the formula $C_{20}H_{22}O_5N_4$. Dehydrogenation of the oil at 250–270° in the presence of palladium afforded a low yield of 3,3-dimethyl-1,8-naphthalide (I). It therefore seems plausible, although it has not been proved, that the neutral product is an aldal analogous in structure to compound VII.

The reaction of V is particularly striking when one considers the behavior of 5,6,7,8-tetrahydro-1-naphthoic acid and 2-isobutylbenzoic acid. The former differs from V only in having hydrogen in place of the isopropyl group at the 8-position; the latter possesses an alkyl group which, with respect to the carboxyl group, is equivalent to the side chain in V except for the greater rotational freedom. Yet neither the tetrahydronaphthoic acid nor the isobutylbenzoic acid were altered by sulfuric acid under the conditions which transformed V to XI. It is therefore apparent that the isopropyl group is directly involved in the reaction of V and that it must be held in a particular position with respect to the neighboring carboxyl group in order for the hydrogen transfer to take place. The situation is similar to that for the 1,5-aryl migrations, for 8-benzhydryl-1-naphthoic acid readily isomerizes to 1-phenylhydroxymethyl-8-benzoylnaphthalene hemiketal,[13] whereas no evidence of a phenyl shift could be found with the more flexible system, 2-benzhydrylphenylacetic acid.[14]

Both 1,2,3,4-tetrahydro-8-isopropylnaphthoic acid and 1,2,3,4-tetrahydro-1-naphthoic acid reacted readily with sulfuric acid. As no water insoluble products were obtained, however, no conclusions concerning hydrogen transfer reactions can be drawn for these substances.

EXPERIMENTAL[15]

Tetrahydro-3,3-dimethyl-1,8-naphthalide (IV). (*a*) *Nickel aluminum alloy reduction.* 3,3-Dimethyl-1,8-naphthalide[1] (1.0 g.) was dissolved in a hot solution of 9 g. of potassium hydroxide in 40 ml. of ethanol and 30 ml. of water. While the solution was rapidly stirred at 58–70°, 5.0 g. of granular Raney nickel-aluminum catalyst[3] was slowly dropped in. It was necessary to add more ethanol to keep the lactone in solution. The mixture was heated at 70–75° for an additional 45 min., then filtered while hot (the filter cake was pyrophoric when dry). The filtrate was added to concd. hydrochloric acid, the resulting suspension extracted with ether, and the ether layer washed with aqueous sodium hydroxide, dried, and evaporated. The residual solid, m.p. 103–112°, was recrystallized first from hexane, then from methanol-water, yielding 0.102 g. (10%) of tetrahydro-3,3-dimethyl-1,8-naphthalide (IV); m.p. 122–123°. The analytical sample, obtained by further recrystallization, melted at 125–125.5°. No carboxylic acid was obtained as a product of this reduction

Anal. Calcd. for $C_{14}H_{16}O_2$: C, 77.47; H, 7.46. Found: C, 77.37; H, 7.31.

(*b*) *Sodium amalgam reduction.* To a refluxing solution of the lactone (0.636 g.) in 50 ml. of ethanol and 5 ml. of water was slowly added (2 hr.) 34 g. of 2% sodium amalgam. The reaction mixture was kept slightly acidic by portionwise addition of sulfuric acid (2 g. sulfuric acid in 10 ml. of water). Stirring and refluxing were continued for an additional 2 hr.; then the supernatant solution was decanted into water and extracted with ether. From this was isolated 0.200 g. (31%) of dimethyltetrahydronaphthalide, IV; m.p. 119–121°; the infrared absorption was the same as for the product from procedure (a), and a mixture melting point showed no depression.

5,6,7,8-Tetrahydro-8-isopropyl-1-naphthoic acid (V). Lactone I (6.00 g.) was saponified by heating overnight at 145° in 450 g. of triethylene glycol containing 60 g. of potassium hydroxide. Additional alkali (48 g. of potassium hydroxide in 100 ml. of water) was added; then, with the temperature at 95–97° and good stirring, 24 g. of powdered Raney nickel-aluminum alloy[4] was added in portions. Small amounts of capryl alcohol were occasionally added to reduce foaming. After standing overnight at room temperature the mixture was warmed, filtered, and the filtrate poured into concd. hydrochloric acid. The mixture was extracted with ether and the ether layer extracted with several portions of sodium carbonate solution. The acids obtained upon acidification were separated by crystallization from petroleum hexane into two portions: (a) 5,6,7,8-tetrahydro-8-isopropyl-1-naphthoic acid, 1.45 g., m.p. 113.5–114.2°, and (b) a low melting mixture, 2.6 g. Portion (b) was dissolved in 100 ml. of 12% potassium hydroxide solution and subjected to the action of 6.15 g. of powdered nickel-aluminum alloy at steam bath temperature. From this second reduction was obtained 1.5 g. of pure tetrahydro acid, making a total of 2.95 g. (48%) of this product. The analytical sample melted at 114.5–115.2°; infrared absorption, 3.4 (strong) 3.8, 5.95 (strong), 6.3, 6.86, 7.7, 7.86 (strong), 8.66, 10.54, 12.75, 13.12 (strong) μ.

Anal. Calcd. for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31; neut. equiv. 214. Found: C, 76.79; H, 8.11; neut. equiv. 215.

This tetrahydro acid was converted to the acid chloride with thionyl chloride, and the acid chloride was treated with concd. ammonium hydroxide to give the tetrahydroisopropylnaphthamide, m.p. 116–117°; infrared absorption, 3.0, 3.1, 3.4, 6.0, 6.13, 6.85 μ.

Anal. Calcd. for $C_{14}H_{19}NO$: C, 77.38; H, 8.81. Found: C, 77.08; H, 8.82.

1,2,3,4-Tetrahydro-8-isopropyl-1-naphthoic acid (VI). Sodium (3 g.), in small pieces, was dropped into a refluxing solution of 600 mg. of 8-isopropyl-1-naphthoic acid in 50 ml. of dry amyl alcohol. After all the sodium had dissolved, the mixture was poured into water. The two layers were separated and the aqueous phase, after thorough washing with ether, was acidified and extracted with ether. From this extract was obtained a solid which, after recrystallization (treatment with charcoal), was colorless and melted at 114–115°. The purified sample weighed 350 mg. (57%). When the reaction was carried out in ethanol in place of amyl alcohol the yield was only 15%. Like acid V, VI did not decolorize permanganate or bromine in carbon tetrachloride, indicating the absence of any dihydro compounds.

(13) R. L. Letsinger and P. T. Lansbury, *J. Am. Chem. Soc.*, 81, 940 (1959).

(14) R. L. Letsinger, J. D. Jamison, and A. S. Hussey, *J. Org. Chem.*, in press.

(15) The microanalyses were performed by Miss H. Beck.

That V and VI were different compounds was shown by the mixture melting point (melting started at 90°) and the distinctly different infrared spectrum; VI absorbed strongly at 3.42, 5.90, 8.21, and 12.75 μ and no bands occurred in the 12.8–13.4 μ region where V absorbed. Conversely, V had only a very weak band (8.28 μ) in the 7.9–8.4 μ region.

Anal. Calcd. for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.66; H, 8.31.

The tetrahydronaphthoic acids. In order to learn more about the course of the alloy reductions, 1-naphthoic acid was used as a substrate. In this case a solution made up with 3.8 g. of 1-naphthoic acid, 21 g. of potassium hydroxide, and 160 ml. of water was treated, at 80°, with 11.4 g. of the finely powdered Raney nickel-aluminum alloy, added in small portions. On working up the reaction mixture in the usual way 3.2 g. of an acid mixture, m.p. 69–75°, was obtained. Chromatography of a 1.0 g. sample on silica gel with a chloroform-benzene solvent yielded two substances; (a) 0.20 g., m.p. 147–149° (eluent solvent, 20% chloroform) and (b) 0.54 g., m.p. 79–81° (eluent solvent, 50% chloroform). Recrystallization of these two fractions from petroleum hexane gave 5,6,7,8-tetrahydro-1-naphthoic acid, m.p. 149.5–150°, lit.,[16] m.p. 150° and 1,2,3,4-tetrahydro-1-naphthoic acid, m.p. 84°, lit.,[17] m.p. 85°, respectively.

A sample (0.0300 g.) of 5,6,7,8-tetrahydro-1-naphthoic acid was dissolved in 3 ml. of sulfuric acid (prepared from 49 g. of concd. sulfuric acid and 1 ml. of water) and allowed to stand for 2 hr. at 22°. The solution was pale tan in color. On pouring onto ice 0.0266 g. of the tetrahydro acid, m.p. 149–150°, was recovered. A similar sulfuric acid solution of 1,2,3,4-tetrahydro-1-naphthoic acid was a rich yellow color. It yielded no precipitate when diluted.

Acid induced rearrangement of 5,6,7,8-tetrahydro-8-isopropyl-1-naphthoic acid (Product X). (a) Use of hydrogen fluoride. Tetrahydro acid V (0.60 g.) was allowed to stand at ice temperature in 20 g. of liquid hydrogen fluoride for 45 min. and then at room temperature for 45 min. The dark red solution was then poured onto ice and the resulting solution extracted with benzene. Extraction of the benzene layer with alkali and acidification yielded no organic acids, showing that the tetrahydroisopropylnaphthoic acid had reacted completely. Evaporation of the benzene layer left 0.6 g. of a neutral oil (X) which could not be induced to crystallize. Chromatographic separation gave only a series of oils, all of which gave positive tests with 2,4-dinitrophenylhydrazine. The infrared spectra of all fractions were essentially the same and had no bands characteristic of hydroxyl, carboxyl, or carbonyl groups or carbon-carbon double bonds; there was strong absorption at 9.1, 9.3, 9.7, and 10.0 μ, suggestive of ether type bonds. A 2,4-dinitrophenylhydrazone derivative melted after several recrystallizations from ethanol at 176.5–177.5°.

Anal. Calcd. for $C_{20}H_{22}O_5N_4$: N, 14.06. Found: N, 14.28.

After several further recrystallizations the sample melted at 180–183°. The existence of stereoisomers may account for the difficulty of obtaining a sharp melting derivative as well as for the oily nature of X.

Anal. Calcd. for $C_{20}H_{22}O_5N_4$: C, 60.29; H, 5.57. Found: C, 59.80, 60.64; H, 5.59, 5.61.

(b) Use of sulfuric acid. Tetrahydro acid V (0.50 g.) was added to a solution of 1.0 g. of water in 49 g. of sulfuric acid. The acid slowly dissolved, giving a dark red solution. After the mixture had stood for 2 hr. at room temperature, it was poured onto ice and worked up as in the hydrogen fluoride experiment. The neutral oil (X) weighed 0.292 g. (61%) and no starting acid could be recovered. The infrared spectrum of the oil was the same as the spectrum for the product from the hydrogen fluoride experiment.

The use of concd. sulfuric resulted in water soluble products. Thus, from a 1 hr. reaction of 200 mg. of V in 25 ml. of concd. sulfuric acid at 0° was obtained 66 mg. of starting material (V) and only a trace of neutral organic product. Longer reaction times or higher temperatures resulted in lower recoveries of V.

In contrast to the reactivity of Compound V in strong acids, the acid chloride was stable when treated with stannic chloride in carbon disulfide, and a high yield of the acid was recovered on hydrolysis.

Dehydrogenation of product X. The aldal type product (X) from the sulfuric acid reaction (0.244 g.) was heated at 250–270° with a mixture of 25 mg. of palladium black and 25 mg. of 10% palladium on charcoal. Within 3 hr. 10.3 ml. of hydrogen had been evolved and hydrogen evolution had ceased. The gummy products were taken up in ether, filtered to remove palladium, and the ether evaporated. The residual oil partially crystallized overnight in the form of long needles, which after recrystallization melted at 110–111.5° (11 mg.). This product was identified as 3,3-dimethyl-1,8-naphthalide by its spectrum and a mixture melting point determination.

3-Hydroxy-3-isopropylphthalide (VIII). This compound was prepared by the general procedure of de Benneville,[18] the quantities of reagents being 92 g. of isopropyl bromide, 18.5 g. of magnesium, 60.5 g. of anhydrous calcium chloride, and 89 g. of finely powdered phthalic anhydride. A 37.5% yield (based on phthalic anhydride) was obtained; m.p. 121.5–122.5°; lit.,[19] m.p. 120–121°; neut. equiv. found, 196; neut. equiv. calcd., 192.

A sample of the hydroxyphthalide was dissolved in concd. sulfuric acid, allowed to stand in solution 2 hr., and poured onto chopped ice. A quantitative yield of 3-isopropenylphthalide, m.p. 95–96° (lit.[19] m.p. 96°) was obtained.

Anal. Calcd. for $C_{11}H_{10}O$: C, 75.84; H, 5.79. Found: C, 76.15; H, 5.82.

2-Isobutylbenzoic acid. Concentrated hydrochloric acid (150 ml.) was added over an 8-hr. period to a refluxing, well stirred mixture of hydroxylactone VIII (5.7 g.), acetic acid (25 ml.), hydrochloric acid (25 ml.), and zinc amalgam (prepared from 50 g. of 20 mesh zinc and 5 g. of mercuric chloride). After an additional 16 hr. of reflux the liquid was decanted and extracted with benzene. From the benzene extract was obtained a neutral oil (none of the alkyl benzoic acid was isolated), tentatively identified as 3-isopropylphthalide because it absorbed at 5.69 μ (chloroform solvent) and did not absorb in the hydroxyl region. This same (by infrared) product was obtained in 61% yield by heating an aqueous solution of hydroxyphthalide (VIII) with 20 g. of potassium hydroxide to 75–85° and then adding 15 g. of the granular nickel-aluminum alloy[3] over an hour period. Filtration, acidification of the filtrate and ether extraction yielded the lactone (2.8 g.).

The isopropylphthalide (2.2 g.) was saponified by heating at 160–170° for 18 hr. with 66 g. of triethylene glycol and 8.8 g. of potassium hydroxide; then 60 ml. of water and 7.5 g. of potassium hydroxide were added, the mixture was heated to 95°, and 8.8 g. of finely powdered Raney nickel-aluminum alloy[4] was added (90-min. period) to the well stirred solution. After 3 hr. of additional stirring the mixture was allowed to cool to room temperature and to stand overnight. It was then worked up as the preparation for tetrahydro acid V to give 0.80 g. (36%) of 2-isobutylbenzoic acid, m.p. 62–63.3°; melting point after recrystallization from hexane-ether, 64–65°; lit.,[12] m.p. 64–65°.

A solution of 2-isobutylbenzoic acid (0.600 g.) in concd. sulfuric acid was allowed to stand for 2 hr. at room temperature and then poured onto ice; 0.550 g. (92%) of the isobutylbenzoic acid was recovered, m.p. 63.4–64°. From a solution of 0.75 g. of the acid in 20 g. of liquid hydrogen fluoride which had stood 45 min. at 0° and then 45 min. at room temperature was recovered 0.60 g. (80%) of isobutyl-

(16) J. v. Braun, *Ann.*, **451**, 29 (1927).
(17) A. Baeyer, *Ann.*, **266**, 184 (1891).
(18) P. L. de Benneville, *J. Org. Chem.*, **6**, 462 (1941).
(19) W. Roser, *Ber.*, **17**, 2777 (1884).

benzoic acid, m.p. 63.5–64°. A trace of a neutral oil was isolated from this reaction but it failed to give a test with 2,4-dinitrophenylhydrazine reagent.

In connection with the preparation of isobutylbenzoic acid it may be noted that an attempt to reduce 7.06 g. of 3-hydroxy-3-isopropylphthalide with hydrazine hydrate (5 ml.) and sodium hydroxide (5 g.) in diethylene glycol (80 ml.) by the Huang-Minlon procedure[20] yielded, instead of a reduction product, 6 g. (87%) of a crystalline solid, m.p. 154–156°; melting point after recrystallization from benzene-hexane, 158–159°; infrared absorption, 3.14, 3.28, 3.34, 6.04 (very strong), 12.68, 13.28 μ. The analysis, mode of formation, and spectrum indicate that this product is 4-isopropylphthalazone.

Anal. Calcd. for $C_{11}H_{12}ON_2$: C, 70.19; H, 6.43; N, 14.89. Found: C, 69.57; H, 6.36; N, 14.93.

(20) Huang-Minlon, *J. Am. Chem. Soc.*, **68**, 2487 (1946).

EVANSTON, ILL.

[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, THE HEBREW UNIVERSITY]

Experiments in the 4-Arylcycloalk-2-en-1-one Series. V[1]

ERNST D. BERGMANN AND S. YAROSLAVSKY

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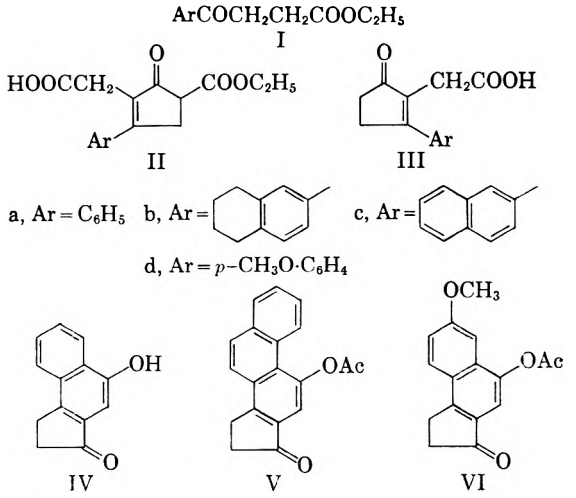
Some new cases are reported, in which the Stobbe reaction of γ-keto esters leads to cyclopent-2-enone derivatives.

Recently, it has been reported[2] that the Stobbe condensation of ethyl 3-benzoylpropionate (Ia) with diethyl succinate leads unexpectedly to 4-carbethoxy-5-oxo-2-phenylcyclopent-1-enylacetic acid (IIa). Elimination of the 4-carbethoxy group gave 5-oxo-2-phenylcyclopent-1-enylacetic acid (IIIa), characterized by its conversion into 4-hydroxy-3′-oxo-1,2-cyclopentenonaphthalene (IV), which had been prepared before by a different route.

It had escaped our attention that Turner[3] had observed the analogous reaction with methyl β-(5,6,7,8-tetrahydro-2-naphthoyl)propionate (Ib), yielding 5-oxo-2-(5,6,7,8-tetrahydro-2-naphthyl)cyclopent-1-enylacetic acid (IIIb).[4,5] In fact, the reaction seems to be general for esters of 3-aroylpropionic acids. Thus, ethyl 3-(2-naphthoyl)propionate (Ic) gave with diethyl succinate in the presence of sodium hydride an oily acidic product, to which according to the spectrum formula (IIc) was assigned. It could not be isolated in pure form, but was converted, by treatment with boiling alcoholic sulfuric acid, into ethyl 2-(2-naphthyl)-5-oxocyclopent-1-enylacetate and, by subsequent hydrolysis, to the corresponding acid (IIIc) which had the same melting point as a product which Robinson[6] had obtained by a different route and to which he assigned formula (IIIc). This was confirmed by conversion of the compound into 4-acetoxy-3′-oxo-1,2-cyclopentenophenanthrene (V), a compound possessing the steroid skeleton. The oily product obtained from ethyl 3-(*p*-anisoyl)propionate (Id) and diethyl succinate was obviously 4-carbethoxy-2-(*p*-methoxyphenyl)-5-oxocyclopent-1-enylacetic acid (IId), as it could be converted into ethyl 2-(*p*-methoxyphenyl)-5-oxocyclopent-1-enylacetate and the corresponding acid (IIId) which had been prepared before by Turner by a different route.[7] It was cyclized by boiling acetic anhydride to 4-acetoxy-6-methoxy-3′-oxo-1,2-cyclopentenonaphthalene (VI).



In Table I, the ultraviolet spectra of compounds IIIa, c, and d, of their 2,4-dinitrophenylhydrazones, and of IV, V, and VI are compared. In III, the naphthyl and even more the *p*-methoxyphenyl

(1) Part IV. E. D. Bergmann and S. Yaroslavsky, *Tetrahedron*, **82**, in press.

(2) E. D. Bergmann, S. Yaroslavsky, and H. Weiler-Feilchenfeld, *J. Am. Chem. Soc.*, **81**, 2775 (1959).

(3) D. L. Turner, *J. Am. Chem. Soc.*, **75**, 1257 (1953).

(4) We are indebted to Dr. D. L. Turner, Jefferson Medical College, Philadelphia, for drawing our attention to his paper.

(5) Another example which—at least formally—belongs to this group is the Stobbe reaction of 2-carbethoxymethyl-1-hydrindone. B. P. Sen, A. Chatterjee, S. K. Gupta, and B. K. Bhattacharyya, *J. Indian Chem. Soc.*, **35**, 751 (1958) [*Chem. Abstr.*, **53**, 16086 (1959)].

(6) R. Robinson, *J. Chem. Soc.*, 1390 (1938).

(7) D. L. Turner, *J. Am. Chem. Soc.*, **71**, 612 (1949). The same acid has recently been described by G. S. Grinenko and V. I. Maksimov [*Zhur. Obshcheĭ Khim.*, **28**, 528 (1958); *Chem. Abstr.*, **52**, 14544 (1958)], m.p. 146°. Turner and we both observed a melting point of 132°.

groups cause a bathochromic effect, corresponding to the extension of the absorbing conjugated system. On the other hand, V absorbs at longer wave lengths than IV and VI; this effect could also be expected.

TABLE I

Compound	Ultraviolet Spectra,[a] mμ (log ε)
IIIa[b]	278 (4.26)
IIIc	215 (4.65); 267 (4.57); 295 (4.28)
IIId	225 (4.43); 301 (4.43)
DPN of IIIa ethyl ester	268 (4.36); 300 (4.08); 393 (4.53)
DNP of IIIc ethyl ester	262 (4.40); 315 (4.10); 400 (4.56)
V	263 (4.89); 288 (4.51); 302 (4.29); 339 (3.28); 356 (3.46); 375 (3.51)
VI	215 (4.39); 232 (4.30); 250 (4.62); 260 (4.71); 297 (4.05); 305 (4.15); 311 (4.13); 330 (3.87); 345 (3.75)
IV	222 (4.45); 262 (4.54); 290 (3.65); 366 (3.76)

[a] In ethanol. [b] See ref. 2.

EXPERIMENTAL

3-(2-Naphthoyl)propionic acid,[8] m.p. 171°, was converted into its *ethyl ester* (Ic) with ethanol and sulfuric acid in a yield of 80%. The ester boiled at 178° (0.5 mm.) and solidified slowly on standing.

Ethyl 2-(2-naphthyl)-5-oxocyclopent-1-enylacetate (as IIIc). When a mixture of 64 g. of ethyl 3-(2-naphthoyl)propionate (Ic), 11 g. of sodium hydride, 130 g. of diethyl succinate, 250 ml. of benzene, and 2.5 ml. of ethanol was stirred at room temperature, a slow reaction took place which quickened gradually and reached after 30 min. its maximum rate, indicated by a temperature rise to 40–50°. When the temperature of the reaction had returned to normal, the stirring was continued for 2 hr. and the product treated with 50 ml. of glacial acetic acid. Addition of water and ether, separation of the organic layer, extraction with sodium carbonate solution, and acidification of the alkaline extract gave an oil (58 g., 69%) which did not crystallize. It had the spectrum expected for 4-carbethoxy-2-(2-naphthyl)-5-oxocyclopent-1-enylacetic acid (IIc). [$\lambda_{max}^{C_2H_5OH}$ 220 (4.66); 268 (4.30); 304 mμ (4.00)] and was directly treated as follows:

The product (54 g.) was refluxed for 8 hr. with 200 ml. of anhydrous alcohol, containing 1 g. of concd. sulfuric acid. The solution was concentrated, diluted with water, and extracted with ether. The extract was washed with sodium carbonate solution and water, dried, and distilled; b.p. 220° (1 mm.); yield, 18 g. (38%). In spite of the sharp boiling point, the 4-carbethoxy group had not been completely eliminated, as the analysis indicated. However, the spectrum showed the expected bands and an analytically pure 2,4-dinitrophenylhydrazone could easily be prepared. $\lambda_{max}^{C_2H_5OH}$ 215 (4.72); 268 (4.58); 302 mμ (4.74).

The *2,4-dinitrophenylhydrazone* formed, after recrystallization from nitromethane, red crystals, m.p. 235–236°; $\lambda_{max}^{CHCl_3}$ 262 (4.40); 315 (4.10); 400 mμ (4.56).

Anal. Calcd. for $C_{25}H_{22}N_4O_6$: C, 63.3; H, 4.6. Found: C, 62.9; H, 4.6.

2-(2-Naphthyl)-5-oxocyclopent-1-enylacetic acid (IIIc). A mixture of 10 g. of the foregoing ester, 10 g. of sodium hydroxide, and 100 ml. of water was refluxed for 5 hr. Acidification of the filtered solution with hydrochloric acid at ice temperature gave 8 g. (90%) of the acid which was recrystallized from dilute acetic acid and benzene and formed yellowish crystals, m.p. 169–170° (lit.[6], m.p. 170°). $\lambda_{max}^{C_2H_5OH}$ 215 (4.65); 267 (4.57); 295 mμ (4.28); $\tilde{\nu}_{max}^{KBr}$ 1725 cm^{-1}.

Anal. Calcd. for $C_{17}H_{14}O_3$: C, 76.7; H, 5.3. Found: C, 76.9; H, 5.5.[9] The *2,4-dinitrophenylhydrazone* formed red crystals, m.p. 320° (after recrystallization from nitrobenzene).

Anal. Calcd. for $C_{23}H_{18}N_4O_6$: C, 61.9; II, 4.0. Found: C, 62.0; H, 4.1.

4-Acetoxy-3'-oxo-1,2-cyclopentenophenanthrene (V). When 1 g. of the foregoing acid had been refluxed for 30 min. with 10 ml. of acetic anhydride, a solid substance began to separate upon cooling. The solid was filtered after addition of much water and recrystallized from butanol. It formed slightly brownish leaflets, m.p. 207° (lit.,[6] m.p. 207°), Yield, 1 g. (90%).

$\lambda_{max}^{C_2H_5OH}$ 263 (4.89); 288 (4.51); 302 (4.29); 339 (3.28); 356 (3.46); 375 mμ (3.51). $\tilde{\nu}_{max}^{KBr}$ 1700, 1757 cm^{-1}.

Anal. Calcd. for $C_{19}H_{14}O_3$: C, 78.6; H, 4.8. Found: C, 78.4; H, 5.0.

Ethyl 3-(p-anisoyl)propionate (Id). 3-(*p*-Anisoyl)propionic acid was prepared from anisol and succinic anhydride[10] and recrystallized from ethanol, m.p. 147° (lit.,[10] m.p. 147°); yield, 50%. The *ethyl ester*, obtained in 80% yield, boiled at 160° (0.04 mm.).

Ethyl 2-(p-methoxyphenyl)-5-oxocyclopent-1-enylacetate (as IIId). The reaction between 85 g. of the foregoing ester, 187 g. of diethyl succinate, 26 g. of sodium hydride in 360 ml. of benzene, and 3 ml. of anhydrous ethanol was carried out as described for the analogous 2-naphthyl compound. The acidic product (67 g.; 60%) obtained was an oil which absorbed at 223 (4.30) and 301 mμ (4.14) and was directly heated for 8 hr. with 300 ml. of anhydrous ethanol, containing 1 g. of concd. sulfuric acid. The neutral product (34 g., 58%) boiled at 200° (1 mm.), but was not analytically pure, a small part of the carbethoxy group not having been eliminated. However, the *2,4-dinitrophenylhydrazone* could be obtained in pure form, as red crystals, m.p. 210° (from butanol).

Anal. Calcd. for $C_{22}H_{22}N_4O_7$: C, 58.2; H, 4.8. Found: C, 58.4; H, 4.7.

2-(p-Methoxyphenyl)-5-oxocyclopent-1-enylacetic acid (IIId). A mixture of 20 g. of the ester, 20 g. of sodium hydroxide, and 400 ml. of water was refluxed for 5 hr. and the filtered solution acidified with cold dilute hydrochloric acid. The product (16 g.; 90%) was recrystallized from water and benzene and formed slightly yellowish crystals, m.p. 132° (lit.[7] m.p. 132°). $\lambda_{max}^{C_2H_5OH}$ 225 (4.43); 301 mμ (4.43). $\tilde{\nu}_{max}^{KBr}$ 1700 cm^{-1}.

Anal. Calcd. for $C_{14}H_{14}O_4$: C, 68.3; H, 5.7. Found: C, 68.8; H, 5.2. The *2,4-dinitrophenylhydrazone* of IIId was recrystallized from a mixture (1:1) of glacial acetic acid and ethyl acetate and formed red crystals, m.p. 252–253°.

Anal. Calcd. for $C_{20}H_{18}N_4O_7$: C, 56.4; H, 4.2. Found: C, 56.0; H, 4.5. The *semicarbazone of* (IIId) was recrystallized from aqueous alcohol and formed yellowish crystals, m.p. 225°.

Anal. Calcd. for $C_{15}H_{17}N_3O_4$: C, 59.4; H, 5.6. Found: C, 59.3; H, 5.6.

4-Acetoxy-6-methoxy-3'-oxo-1,2-cyclopentenonaphthalene (VI). A solution of 1 g. of the foregoing acid in 7 ml. of acetic anhydride was refluxed for 30 min., cooled, and treated with an excess of water. The precipitate was filtered and recrystallized from butanol; it formed leaflets, m.p. 193°; yield, 0.9 g. (82%). $\lambda_{max}^{C_2H_5OH}$ 215 (4.39); 232 (4.30); 250 (4.62); 260 (4.71); 297 (4.05); 305 (4.15); 311 (4.13); 330 (3.87); 345 mμ (3.75). ν_{max}^{KBr} 1700, 1757 cm^{-1}.

Anal. Calcd. for $C_{16}H_{14}O_4$: C, 71.2; H, 5.2. Found: C, 71.3; H, 5.4.

JERUSALEM, ISRAEL

(8) W. E. Bachmann and W. S. Struve, *J. Org. Chem.*, **4**, 472 (1939). *Cf.* M. S. Newman, R. B. Taylor, T. Hodgson, and A. B. Garrett, *J. Am. Chem. Soc.*, **69**, 1784 (1947).

(9) Good analytical figures were only obtained when the acid was dried at 100° in a vacuum of 1 mm. for 48 hr.

(10) O. Poppenberg, *Ber.*, **34**, 3257 (1901).

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

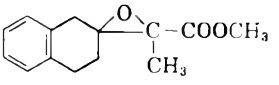
1,2,3,4-Tetrahydro-2-hydroxy-α-methyl-1-naphthylideneacetic Acid γ-Lactone from the Condensation of β-Tetralone with Methyl α-Chloropropionate

ROBERT A. CLEMENT AND TSU-CHIA SHIEH

Received April 25, 1960

An attempted Darzens glycidic ester synthesis with β-tetralone and methyl α-chloropropionate yielded 1,2,3,4-tetrahydro-2-hydroxy-α-methyl-1-naphthylideneacetic acid γ-lactone (II) as the only readily-isolable product. The structure of II was proved by dehydrogenation to 2-hydroxy-α-methyl-1-naphthaleneacetic acid γ-lactone which was synthesized for comparison by an alternative route. Reduction of II yielded a new isomer of 1,2,3,4-tetrahydro-2-hydroxy-α-methyl-1-naphthaleneacetic acid γ-lactone (III) which could be isomerized to a known isomer. Configurations are proposed for the three known isomers of III.

For a study in progress in this laboratory, we required various 1-substituted 1-(β-naphthyl)-ethanes and we considered, briefly, the possibility of using the glycidic ester I as an intermediate in their preparation. To this end, we attempted a



I

Darzens condensation between β-tetralone and methyl α-chloropropionate. The only readily-isolable product of the reaction, however, was not I but a lactone, the structure proof for which, along with ancillary observations on some structures derived therefrom, constitutes the subject of this paper. Some of the transformations involved are summarized in Fig. 1.

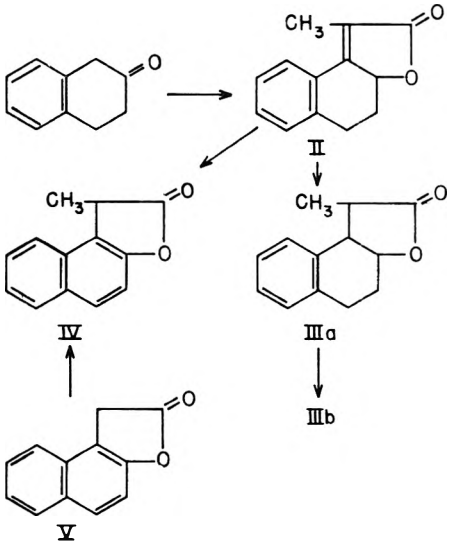


Fig. 1. Some reactions deriving from the condensation of β-tetralone with methyl α-chloropropionate

With sodium hydride as the condensing agent and benzene as the solvent, reaction between β-tetralone and methyl α-chloropropionate occurred readily, and there was isolated a crystalline substance, m.p. 153–154.5°, which obviously was not I. This substance had the elemental composition $C_{13}H_{12}O_2$, was neutral, but dissolved in hot alkali to yield a saponification equivalent of 196; within experimental error of that implied by its empirical formula. In the infrared, it exhibited carbonyl absorption at 1731 cm.$^{-1}$ and intense absorption at 1648 cm.$^{-1}$ which suggested carbonyl-conjugated unsaturation.[1] It possessed an ultraviolet spectrum remarkably similar to that of *trans*-cinnamic acid, with λ_{max} 272 mμ and λ_{min} 235 mμ. It readily added one mole of hydrogen to form a liquid dihydro derivative (IIIa) which exhibited carbonyl absorption in the infrared at 1756 cm.$^{-1}$ and possessed the ultraviolet spectrum of a simple benzene chromophore with λ_{max} 265 and 272 mμ, λ_{min} 238 and 269 mμ. On the bases of these observations and mechanistic consideration, the condensation product was tentatively identified as 1,2,3,4-tetrahydro-2-hydroxy-α-methyl-1-naphthylideneacetic acid γ-lactone (II).

When the condensation product was dehydrogenated with sulfur, there was obtained a compound, m.p. 121–124°, whose properties were in accord with the structure IV expected. It had the correct empirical formula, exhibited the high-frequency carbonyl absorption (1790 cm.$^{-1}$) associated with β,γ-unsaturated γ-lactones,[2] and possessed an ultraviolet spectrum similar to that of β-naphthol, with λ_{max} 227.5, 270.0, 280.0, 291.5, 315.0, 324.0, and 330.0 mμ. This compound proved to be identical with that prepared by methylation of the known[3,4] 2-hydroxy-1-naphthaleneacetic

(1) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley and Sons, Inc., New York, N. Y., 1958, p. 42.

(2) Ref. 1, p. 187.

(3) M. Julia and M. Baillarge, *Bull. soc. chim. France*, 640 (1953).

(4) D. S. Tarbell and B. Wargotz, *J. Am. Chem. Soc.*, **76**, 5761 (1954).

acid γ-lactone (V), making unambiguous the structural assignments II and IV.

The formation of II by reaction of β-tetralone and methyl α-chloropropionate may be rationalized as outlined in Fig. 2 with the first step, *alkylation*

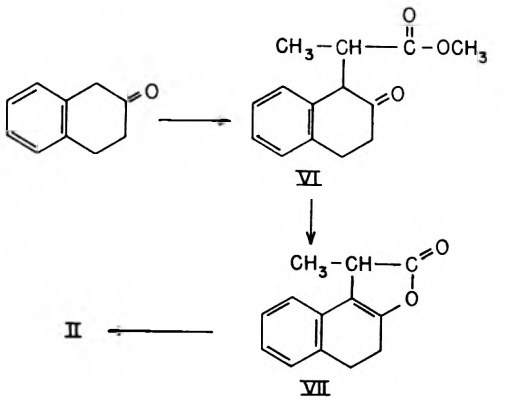


Fig. 2. A possible reaction path for the condensation of β-tetralone with methyl α-chloropropionate

of β-tetralone at the 1-position by methyl α-chloropropionate, defining the unexpected course of the reaction. Although formation of the 1-enolate from β-tetralone should be facile, we had anticipated little difficulty from side reactions involving this enolate ion since β-tetralone has been successfully employed as the ketone component in a Reformatsky condensation.[5] Obviously, however, II was derived from just such a reaction and, surprisingly, the reaction involved alkylation by the secondary (although activated) chloride function rather than acylation by the methyl ester function. The remaining steps in the sequence of Fig. 2 are straightforward and require only a catalytic amount of base which was present as sodium hydride and sodium methoxide. VII would be formed by *O*-acylation of the enolate ion derived from the 1-position of VI, and would be converted to II by simple prototropy.

As noted above, hydrogenation of II produced a liquid dihydro derivative IIIa which must be formulated as a 1,2,3,4-tetrahydro-2-hydroxy-α-methyl-1-naphthaleneacetic acid γ-lactone. Of the four racemates possible with this structure, two have been described[6]; IIIb, m.p. 121–121.5°, and IIIc, m.p. 152.5–153.5°. Although the configurations of the methyl groups were in doubt, the assignments of a *cis* ring fusion to IIIb and a *trans* ring fusion to IIIc were certainly correct. When our γ-lactone IIIa was treated with sodium ethoxide in ethanol it was converted into an isomeric γ-lactone, m.p. 118.0–119.5°, apparently the γ-lactone IIIb described by the previous workers.[6] The assumptions that hydrogenation of II involved *cis*-addition of hydrogen to the less hindered side of the double bond and that the all-*cis* isomer of III is less stable than the alternative *cis*-fused isomer lead to the configurations IIIa and IIIb as represented in Fig. 3. On the assumption that the acid treatment utilized for the isomerization of IIIc to IIIb[6] did not affect configuration at the position α to the acyl function,[7] the configuration of IIIc is that represented in Fig. 3.

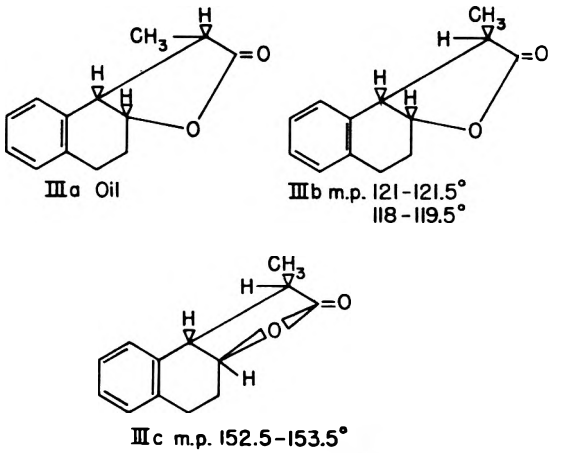


Fig. 3. Configurations of the three known 1,2,3,4-tetrahydro-2-hydroxy-α-methyl-1-naphthaleneacetic acid γ-lactones

Preparation of lactone V has been described in the literature,[3] but we employed a more direct route which is recorded in the Experimental section. Methylation of lactone V was not quantitative. In addition to the desired methyl lactone IV, we obtained comparable quantities of unchanged V and the dimethyl lactone VIII, 1,2,3,4-tetrahydro-2-hydroxy-α,α-dimethyl-1-naphthaleneacetic acid γ-lactone.

The yield of lactone II from the condensation of β-tetralone and methyl α-chloropropionate was not high, and it is possible that a significant quantity of the desired glycidic ester I was present in the reaction mixture. However, isolation of I, if present, appeared to be a difficult task not readily amenable to large-scale operations, and we abandoned this approach to the preparation of 1-substituted-1-(β-naphthyl)ethanes.

EXPERIMENTAL[8]

The condensation of β-tetralone with methyl α-chloropropionate. 1,2,3,4-Tetrahydro-2-hydroxy-α-methyl-1-naphthyldeneacetic acid γ-lactone (II). To a solution of β-tetralone[9] [14.6 g., 0.100 mole, b.p. 119° (8 mm.)], methyl α-chloropropionate (12.3 g., 0.100 mole) and dry benzene (150 ml.)

(5) W. G. Dauben and R. Teranishi, *J. Org. Chem.*, 16, 550 (1951).

(6) E. E. van Tamelin, G. Van Zyl, and G. D. Zuidema, *J. Am. Chem. Soc.*, 72, 488 (1950).

(7) This assumption seems warranted in view of the paucity of examples of acid-catalyzed racemizations about asymmetric centers α to ester functions. The same structural assignment follows from consideration of steric interactions in transition states likely for ring closure to the lactone IIIc and, on the basis of steric interactions, appears to be the more stable of the two *trans*-fused isomers.

in a 500-ml. flask which was kept under a nitrogen atmosphere and cooled in an ice bath, was added 50% sodium hydride dispersion in paraffin oil[10] (4.8 g., 0.100 mole). The reaction mixture was stirred magnetically for 3 hr. at 0° and then was permitted to warm to room temperature. When hydrogen evolution had ceased, the reaction mixture was poured into 200 ml. of 0.05*N* hydrochloric acid and the organic layer was separated and dried over magnesium sulfate. After filtration and removal of solvent under reduced pressure, there was obtained an orange paste which was triturated with three 25-ml. portions of petroleum ether (b.p. 60–68°), each portion of petroleum ether being decanted after being cooled to 0°. The solid residue was crystallized from 95% ethanol to give II (6.12 g., 31%) as a light orange solid, m.p. 151–154°. The analytical sample, prepared by recrystallization from ethanol-water and sublimation, was a white solid, m.p. 153.0–154.5°.

Anal. Calcd. for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04; sapon. equiv., 200. Found: C, 77.71; H, 6.05; sapon. equiv., 196.

In the infrared (5% in chloroform), II exhibited absorption at 1731 (lactone carbonyl) and 1648 (carbonyl-conjugated unsaturation) cm.$^{-1}$. In the ultraviolet (95% ethanol), II had λ_{max} 272 (ϵ, 20,800) mμ and λ_{min} 235 (ϵ, 3,200) mμ.

2-Hydroxy-α-methyl-1-naphthaleneacetic acid γ-lactone (IV) *from the dehydrogenation of* II. An intimate mixture of II (0.403 g., 2.02 mmoles) and sulfur (0.081 g., 2.53 mmoles) was heated at 240–270° until evolution of gas ceased, and the dark red, gummy residue was then chromatographed on 40 g. of silica gel. There was eluted with 40% methylene chloride in carbon tetrachloride a red solid which, after sublimation and crystallization from *n*-heptane, amounted to 0.119 g., (30%) of IV as white crystals, m.p. 116–121°. This material was identical, by the criteria of mixture melting point and infrared spectral comparison, with the analytical sample of IV described below.

2-Hydroxy-1-naphthaleneacetic acid γ-lactone (V).[3,4] A heterogeneous mixture of 2-methoxy-1-naphthaleneacetonitrile[11] (18.0 g., m.p. 110.5–112.0°) and 48% hydrobromic acid (180 ml.) was heated under reflux for 12 hr. and then cooled and filtered. The precipitate was taken up in benzene (250 ml.), filtered to remove some insoluble red material, washed with three 100-ml. portions of 10% aqueous potassium bicarbonate and dried over magnesium sulfate. After filtration and removal of solvent under reduced pressure, there was obtained a yellow-green solid which was evaporatively distilled and then crystallized from *n*-heptane to yield V (12.6 g., 75%) as white crystals, m.p. 102.5–104.0° (lit.[4] m.p. 103.0–104.5°). In the infrared (5% in chloroform), V exhibited lactone-carbonyl absorption at 1796 cm.$^{-1}$.

Methylation of V. *2-Hydroxy-α-methyl-1-naphthaleneacetic acid γ-lactone* (IV) *and 2-hydroxy-α,α-dimethyl-1-naphthaleneacetic acid γ-lactone* (VIII). To a solution of V (3.68 g., 20 mmoles) and methyl iodide (14.0 g., 99 mmoles) in freshly-distilled tetrahydrofuran (100 ml.) contained in a 250 ml. flask under a nitrogen atmosphere and stirred magnetically, was added 50% sodium hydride dispersion in paraffin oil[10] (0.96 g., 20 mmoles). Hydrogen evolution was rapid and complete within 10 min. as the reaction mixture became warm. The reaction mixture was stirred at ambient temperature for 1.5 hr. and then volatile material was removed by evaporation under reduced pressure and the pale-green, pasty residue was chromatographed on 140 g. of silica gel. Fractions A and B were eluted, in order, with 40% methylene chloride in carbon tetrachloride, and fraction C was eluted with 40% carbon tetrachloride in methylene chloride.

Fraction A, after one crystallization from pentane, amounted to 0.91 g. (21% on lactone V) of *2-hydroxy-α,α-dimethyl-1-naphthaleneacetic acid γ-lactone* (VIII) as long white crystals, m.p. 98–99°. The analytical sample was prepared by recrystallization from pentane and sublimation, m.p. 97–100°, and exhibited lactone-carbonyl absorption in the infrared (5% in chloroform) at 1790 cm.$^{-1}$.

Anal. Calcd. for $C_{14}H_{12}O_2$: C, 79.22; H, 5.70. Found: C, 79.30; H, 5.90.

Fraction B, after one crystallization from *n*-heptane, amounted to 0.72 g. (18% on lactone V) of *2-hydroxy-α-methyl-1-naphthaleneacetic acid γ-lactone* (IV) as pale orange crystals, m.p. 117–121°. The analytical sample was obtained as stout white crystals, m.p. 121–124°, by two recrystallizations from *n*-heptane followed by sublimation. In the infrared (5% in chloroform), it exhibited lactone-carbonyl absorption at 1790 cm.$^{-1}$ and in the ultraviolet (95% ethanol) it had λ_{max} 227.5 (ϵ, 63,000), 270.0 (ϵ, 3,800), 280.0 (ϵ, 4,800), 291.5 (ϵ, 4,000), 315.0 (ϵ, 1,600), 324.0 (ϵ, 1,500), and 330.0 (ϵ, 1,900) mμ.

Anal. Calcd. for $C_{13}H_{10}O_2$: C, 78.77; H, 5.09. Found: C, 78.52; H, 5.10.

Fraction C, after one crystallization from *n*-heptane, amounted to 0.87 g. (24% recovery) of the starting lactone V, m.p. 103–104°.

Hydrogenation of II. *1,2,3,4-Tetrahydro-2-hydroxy-α-methyl-1-naphthaleneacetic acid γ-lactone* (IIIa). A solution of II (0.667 g.) in glacial acetic acid (45 ml.) was hydrogenated at atmospheric pressure and 28° in the presence of 10% palladium/charcoal catalyst (0.10 g.). Hydrogen uptake ceased after 20 min. when 101% of theory for saturation of one double bond had been absorbed. The solution was filtered and acetic acid was removed by evaporation on the steam bath at the water aspirator. The residue was evaporatively distilled to yield IIIa (0.600 g., 89%) as a colorless, viscous liquid which exhibited lactone-carbonyl absorption in the infrared (5% in chloroform) at 1756 cm.$^{-1}$ and had, in the ultraviolet (95% ethanol), λ_{max} 265 (ϵ, 390) and 272 (ϵ, 390) mμ and λ_{min} 238 (ϵ, 71) and 269 (ϵ, 250) mμ.

Anal. Calcd. for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 76.90; H, 6.97.

Isomerization of IIIa *to* IIIb. To a solution of IIIa (0.151 g.) in absolute ethanol (25 ml.) was added 2*M* sodium ethoxide in ethanol (0.20 ml.) and the homogeneous mixture was permitted to remain at room temperature for 19 hr. Ammonium chloride (0.10 g.) was then added and the mixture was evaporated to dryness under reduced pressure. The residue was taken up in boiling benzene (50 ml.), filtered from inorganic salts, and evaporated to dryness under reduced pressure. The pale yellow solid thus obtained was sublimed and then crystallized from methanol-water to yield IIIb (0.100 g., 66%) as long white needles, m.p. 118.5–119.5° (lit.[6] m.p. 121.0–121.5°). The analytical sample was obtained by sublimation, m.p. 118–119.5°, and exhibited lactone-carbonyl absorption in the infrared (5% in chloroform) at 1756 cm.$^{-1}$. In the ultraviolet (95% ethanol), it had λ_{max} 265 (ϵ, 370) and 272 (ϵ, 340) mμ and λ_{min} 237 (ϵ, 60) and 269 (ϵ, 230) mμ.

Anal. Calcd. for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.35; H, 7.18.

Acknowledgment. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

CHICAGO 37, ILL.

(8) We are indebted to Mr. William Saschek of this Department for the elemental analyses. Infrared spectra were taken on a Perkin-Elmer Model 21 infrared spectrophotometer and ultraviolet spectra on a Beckman DU spectrophotometer. Melting points were determined on a calibrated Fisher-Johns melting point apparatus.

(9) A. J. Birch, *J. Chem. Soc.*, 430 (1944).

(10) Metal Hydrides Inc.

(11) A. H. Cook, J. Downer, and B. Hornung, *J. Chem. Soc.*, 502 (1941).

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

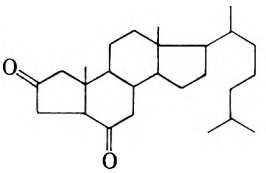
Base Catalyzed Autoxidation of Cyclic 1,4-Diketones to Enediones

WILLIAM G. DAUBEN, GEORGE A. BOSWELL,[1] AND WILLIAM TEMPLETON

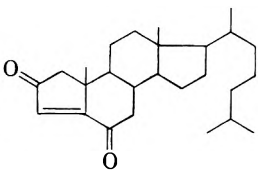
Received May 5, 1960

When an alkaline alcoholic solution of a cyclic 1,4-diketone is shaken with air, the compound is transformed in good yield to the corresponding enedione. The autoxidation most likely proceeds *via* an anion radical intermediate.

During the course of a study on the chemistry of A-norsteroids, the thermodynamic stability of A-norcoprostane-2,6-dione (I)[2] was investigated.

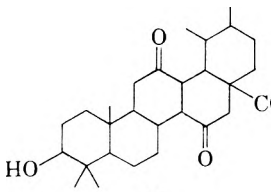


I

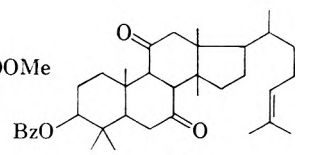


II

When the dione I was warmed for about five minutes in 0.5*N* ethanolic potassium hydroxide, a deep blue color developed. Upon standing at room temperature in a closed flask the color remained, but when the blue solution was swirled in air the blue color was discharged and an orange solution resulted. Upon repetition of the process, the same color sequence was again noted, and after a few such treatments the blue color no longer formed. Upon processing the reaction mixture, A-nor-3-cholestene-2,6-dione (II) was obtained in 40% yield. Such a base catalyzed autoxidation of a saturated 1,4-diketone to an enedione system has been reported previously in two cases. In 1953, Barton and de Mayo[3] found that when methyl diketopyroquinovate (III) was heated in base in the presence of air, the dehydro derivative was obtained. In 1955, Barton, McGhie, Pradhan, and Knight[4] reported that, when 7,11-dioxoeuphanyl



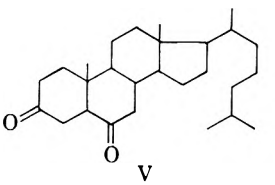
III



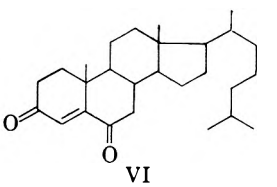
IV

benzoate (IV) was saponified, 7,11-dioxoeuphenol was obtained. In both of these latter two cases, the enedione system introduced was derived by removal of tertiary hydrogen atoms and was part of an internal ring system. In all three examples the yields of the reactions were good; in view of the simplicity of the reaction as compared to the use of such reagents as selenium dioxide for dehydrogenation, the base catalyzed autoxidation was further examined.

When an alkaline ethanolic solution of cholestane-3,6-dione (V) was warmed in air, no blue color developed as in the A-nor series but the color of the solution went from colorless to yellow to green to red. From the reaction mixture there was obtained 4-cholestene-3,6-dione (VI) in 41% yield.

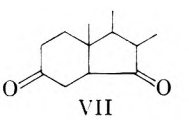


V

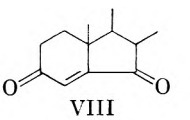


VI

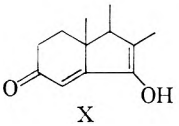
Upon similar treatment B-norcoprostane-3,6-dione (VII) did not yield the known enedione (VIII), but a new material was obtained. The pale yellow crystalline product, isolated in 62% yield, possessed the expected composition for a dehydrogenated material, but it showed no carbonyl absorption in the infrared. However, there were four bands of medium intensity in the 1650–1550 cm.$^{-1}$ region, indicating conjugated olefinic bonds, and there was a strong band at 3400 cm.$^{-1}$, characteristic of hydroxyl groups. Also, in the ultraviolet, there was a maximum at 322 mμ with an intensity of 16,300, indicating a conjugated triene system. On the basis of these data, the reaction product was assigned the structure of B-nor-2,4,6-cholestatriene-3,6-diol (IXa) or the 1,3,5-triene isomer (IXb). It has not been possible to establish the fact that no skeletal rearrangement has taken place, since when IX was allowed to react with zinc and glacial acetic acid no crystalline product could be obtained. In line with this structural assignment,



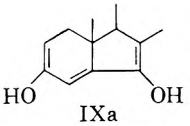
VII



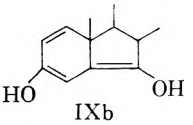
VIII



X



IXa



IXb

(1) General Electric Company Fellow in Chemistry, 1958–1959.

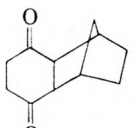
(2) A. Windaus, *Z. physiol. Chem.*, **117**, 146 (1921).

(3) D. H. R. Barton and P. de Mayo, *J. Chem. Soc.*, 3111 (1953).

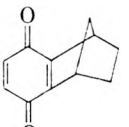
(4) D. H. R. Barton, J. F. McGhie, M. K. Pradhan, and S. A. Knight, *J. Chem. Soc.*, 876 (1955).

however, was the finding that when a sample of authentic B-nor-4-cholestene-3,6-dione (VIII) was allowed to stand in alkali, the same trienediol IX was obtained in 64% yield. Also, Rull and Ourisson[5] have reported that when B-nor-4-androstene-3,6-dione was passed through alumina, the material was transformed into an isomeric compound which possessed an ultraviolet spectrum similar to that reported above for IX. These workers postulated a dienone structure X for their material. Upon being informed of our results, they examined the infrared spectrum of their material and found no carbonyl absorption and now agree with our postulated trienediol structure.[6] In line with their work, when a solution of VIII was passed through a column of Woelm basic alumina, IX was isolated.

The generality of the base catalyzed autoxidation of a 1,4-dione to an enedione has not been widely examined but one nonsteroid case has been studied. When the dione XI[7] was subjected to the usual reaction conditions, the compound underwent dehydrogenation to yield the related quinone XII in 20% yield.



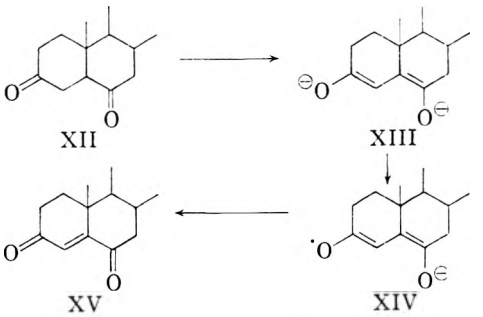
XI



XII

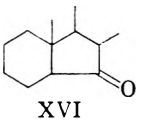
Finally some information with regard to the mechanism of the reaction has been obtained. First, it was found that when oxygen was excluded, no reaction occurred. Second, if the base concentration were sufficiently low ($\sim 0.02N$), the rate of reaction was slow and starting material was recovered after twenty-four hours. Under identical conditions, but using $0.5N$ potassium hydroxide, the dehydrogenation was complete in two hours. Third, in the A-nor case, if the blue solution were flushed free of air with nitrogen, the color remained for many weeks. These data strongly suggest a mechanism similar to that postulated by Michaelis[8] for the autoxidation of hydroquinone and which involves an anion radical intermediate. Thus, in the presence of base the diketone XII is converted to the dienolate ion XIII which reacts with oxygen to generate the blue colored anion radical XIV. Finally, XIV is oxidized further to the enedione XV.

During the course of this work, the reduction of steroidal enediones with zinc and acetic acid was studied. Recently, McKenna, Norymberski,



XII XIII XV XIV

and Stubbs[9] reported that the water content of the acetic acid had an effect on such reductions. In the present study, it was found that when 4-cholestene-3,6-dione (VI) was reduced at 100° or at reflux temperature with zinc in 90% acetic acid, random reduction of the carbonyl groups as well as the reduction of the double bond occurred. In contrast, the saturated dione (V) was obtained in high yield when the reduction was conducted in glacial acetic acid at 100°. When B-nor-4-cholestene-3,6-dione (VIII) was reduced in glacial acetic acid at 100°, B-norcoprostane-6-one (XVI) was obtained. When the reaction was conducted at



XVI

room temperature, following the procedure of McKenna, *et al.*,[9] the saturated 3,6-dione (VII) was formed. Recently, Schaefer[10] has found that amalgamated tin in ethanolic hydrochloric acid is an excellent reagent for the reduction of enediones. When this method was used in the B-nor series, an almost quantitative yield of the saturated dione could be isolated directly from the reaction mixture.

EXPERIMENTAL[11]

A-Nor-3(5)-cholestene-2,6-dione (II). A solution of 90 mg. (0.23 mmole) of A-norcoprostane-2,6-dione (I)[2] in 25 ml. of $0.5N$ methanolic potassium hydroxide was warmed in a waterbath for 5 min. The solution immediately developed a deep blue color. Upon standing overnight at room temperature, the color changed from blue to yellow-orange. The solution was diluted with water and extracted with ether. The ethereal solution was dried, the solvent evaporated, and the residue chromatographed on alumina (Act. III). Elution with petroleum ether (b.p. 30–60°)-benzene (1:1) gave 35 mg. (39%) of crystalline enedione (II), m.p. 149–152°. Recrystallization of the product from ethanol yielded A-nor-3(5)-cholestene-2,6-dione in colorless blades, m.p. 154–155°, $[\alpha]_D^{25}$ −6° (Chf), $\lambda_{max}^{ethanol}$ 244 mμ (ε 10,500), $\nu_{max}^{CS_2}$ 1700, 1708 cm^{-1}.

Anal. Calcd. for $C_{26}H_{40}O_2$ (384.58): C, 81.20; H, 10.48. Found: C, 80.75; H, 10.36.

Using $0.5N$ ethanolic potassium hydroxide, 150 mg. of anedione yielded 75 mg. (50%) of enedione.

(5) T. Rull and G. Ourisson, *Bull. soc. chim. France*, 1581 (1958).

(6) Private communication, G. Ourisson.

(7) Kindly supplied by Professor G. Wiley.

(8) L. Michaelis, *Chem. Revs.*, 16, 243 (1935); C. Walling, *Free Radicals in Solution*, John Wiley and Sons, Inc., New York, (1957), p. 457.

(9) J. McKenna, J. K. Norymberski, and R. D. Stubbs, *J. Chem. Soc.*, 2502 (1959).

(10) J. P. Schaefer, *J. Org. Chem.*, in press..

(11) Analyses by the Microanalytical Laboratory, College of Chemistry, University of California, Berkeley.

Reduction of 75 mg. of enedione II with 2 g. of zinc dust in 25 ml. of acetic acid followed by chromatography over alumina and recrystallization of the product from petroleum ether (b.p. 30–60°) yielded 55 mg. (73%) of A-norcoprostane-2,6-dione, m.p. 148–149°, identical in melting point and spectrum with authentic sample.

4-Cholestene-3,6-dione (VI). A solution of 1.0 g. (2.5 mmoles) of cholestane-3,6-dione[12] in 100 ml. of 1*N* ethanolic potassium hydroxide was warmed for 5 min. in a water bath. The color of the solution turned from colorless to yellow and then to green. The solution was allowed to stand at room temperature for 8 hr. during which time the solution turned bright red. The solution was diluted with water and extracted with ether. The ethereal extract was washed with cold 5% potassium hydroxide solution, water, dilute hydrochloric acid, water, and then saturated salt solution. Upon evaporation of the solvent there was obtained 768 mg. (77%) of semicrystalline yellow material which was chromatographed on 21 g. of alumina (Act. III). Elution with petroleum ether (b.p. 30–60°)-benzene (1:1) yielded 407 mg. (41%) of pale yellow crystals, m.p. 115–120°, which after recrystallization from methanol gave 4-cholestene-3,6-dione as pale yellow leaflets, m.p. 124–125°, $[\alpha]_D^{20}$ −38° (Chf), λ_{max}^{Chf} 252 mμ (11,600), $\nu_{max}^{CS_2}$ 1685 cm.$^{-1}$, identical in melting point and spectra with an authentic sample.[10]

B-Nor-2,4,6-cholestatriene-3,6 diol (IX). A solution of 600 mg. (1.55 mmoles) of B-norcoprostane-3,6-dione,[13] 2.8 g. of potassium hydroxide, and 50 ml. of ethanol was heated for a few minutes to effect solution. The color of the solution became yellow, then green; after standing at room temperature for 2 hr., the color was red. The solution was diluted with water and extracted with ether. The ether extracts were washed with 5% potassium hydroxide solution, then washed with water and dried. The solvent was evaporated and there was obtained 425 mg. (62%) of pale yellow crystalline material. The residue was recrystallized from ethanol to yield 400 mg. (68%) of pale yellow leaflets of B-nor-2,4,6-cholestatriene-3,6-diol, m.p. 220–225° (dec., sealed cap.), λ_{max}^{Chf} 322 mμ (16,300).

Anal. Calcd. for $C_{26}H_{40}O_2$ (384.58): C, 81.20; H, 10.48. Found: C, 81.25; H, 11.20.

When a solution of 107 mg. (0.285 mmole) of B-nor-4-cholestene-3,6-dione,[14] 1.0 g. of potassium hydroxide, and 25 ml. of ethanol was allowed to stand at room temperature for 12 hr., there was obtained, from the neutral fraction, 80 mg. (64%) of a pale yellow solid. Recrystallization of this material from ethanol yielded pale yellow leaflets of IX, identical in all respects with that prepared above.

Autoxidation of dione XI. To a solution of 200 mg. (1.1 mmoles) of dione XI[7] (m.p. 240°, ν_{max} 1710 cm.$^{-1}$) in 100 ml. of hot ethanol, there was added, with vigorous stirring, 50 mg. of potassium hydroxide. The solution turned dark red and after 2 hr. 0.5 g. of potassium hydroxide was added. The stirring was continued for a short period and the black solution was diluted with water and acidified with dilute hydrochloric acid. The mixture was extracted with ether and after evaporation of the solvent the residual dark oil was chromatographed on alumina. Elution with benzene yielded 40 mg. of the quinone XII, m.p. 125°. The ultraviolet and infrared spectra were identical with those of the authentic material.[7]

Reduction of 4-cholestene-3,6-dione (VI) *with zinc and acetic acid.* (a) *At reflux temperature.* A solution of 100 mg. (0.25 mmole) of enedione VI in 25 ml. of 90% acetic acid was refluxed with 5.0 g. of zinc dust for 4 hr. The solution was filtered, poured into water, and the aqueous suspension extracted with ether. The ethereal extract was washed with aqueous sodium bicarbonate solution and water, dried, and the solvent evaporated. The residual colorless oil crystallized as white needles (70 mg.), m.p. 74–75°. After two recrystallizations from methanol the product melts at 86–88°, ν_{max} 1700 cm.$^{-1}$

Cholestan-3-one melts at 172° and cholestane-6-one melts at 129°.

(*b*) *At 100°.* The above experiment was repeated except that the mixture was heated on a steam bath for 2 hr. The crude product melted at 72–73°.

(c) *With glacial acetic acid at 100°.* A solution of 50 mg. (0.13 mmole) of enedione VI in 25 ml. of glacial acetic acid was heated on a steam bath with 2.5 g. of zinc dust. Effervescence was vigorous at first but by the end of 1 hr. it had almost stopped. After 90 min. the reaction mixture was processed as before and the crude product melted at 110–120°. Two recrystallizations from ethanol yielded 45 mg. (90%) of white needles, m.p. 155–160°, the infrared spectrum of which was almost identical with authentic cholestane-3,6-dione.

Reduction of B-nor-4-cholestene-3,6-dione (VIII) *with zinc and acetic acid.* (*a*) *With 100% acetic acid at 100°.* A solution of 43 mg. (0.11 mmole) of enedione VIII in 12.5 ml. of glacial acetic acid containing 2 drops of acetic anhydride was heated with 2 g. of zinc dust on the steam-bath for 2.5 hr. The reaction mixture was processed as above and the resulting oil crystallized upon trituration with methanol. The white needles (24 mg.) melts at 98–100°, $[\alpha]_D$ +37° and were identical with an authentic sample of B-norcoprostane-6-one.

(*b*) *At room temperature.* To a solution of 100 mg. (0.26 mmole) of enedione VIII in 50 ml. of glacial acetic acid there was added 1.7 g. of zinc dust in four equal portions at 15-min. intervals. The mixture was shaken continuously during the additions and the shaking was continued for an additional 45 min. after the final addition of zinc. The entire procedure was conducted at room temperature. The mixture was filtered, the filtrate almost neutralized with 3*N* sodium hydroxide and then extracted with ether. The ethereal extract was washed with water, dried, the solvent evaporated, and the residue chromatographed on 5 g. of basic alumina (activity III). Elution with benzene gave white needles (50 mg.), m.p. 110–111° (from methanol), which were identified as B-norcoprostane-3,6-dione by mixed melting point and infrared spectra comparison.

Reduction of B-nor-4-cholestene 3,6 dione with tin and ethanolic hydrochloric acid. A solution of 85 mg. (0.22 mmole) of enedione VIII in 10 ml. of ethanol containing 0.1 ml. of concd. hydrochloric acid was refluxed with 1 g. of amalgamated tin and a few crystals of mercuric chloride for 30 min. The mixture was filtered, poured into water, and extracted with ether. After removal of the solvent the residue crystallized spontaneously and the pale yellow needles (80 mg.) melted from 107–110° and were identical with B-norcoprostane-3,6-dione.

Acknowledgment. This work was supported, in part, by Grant No. CY-4284, U. S. Public Health Service.

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(12) V. H. Petrow, O. Rosenheim, and W. W. Starling, *J. Chem. Soc.*, 677 (1938); W. C. J. Ross, *J. Chem. Soc.*, 737 (1946).

(13) L. F. Fieser, *J. Am. Chem. Soc.*, **75**, 4386 (1953).

(14) W. G. Dauben and G. J. Fonken, *J. Am. Chem. Soc.*, **78**, 4736 (1956).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, L. S. COLLEGE, UNIVERSITY OF BIHAR]

Succinoylation of 2-Methoxynaphthalene

MONOJIT GHOSAL

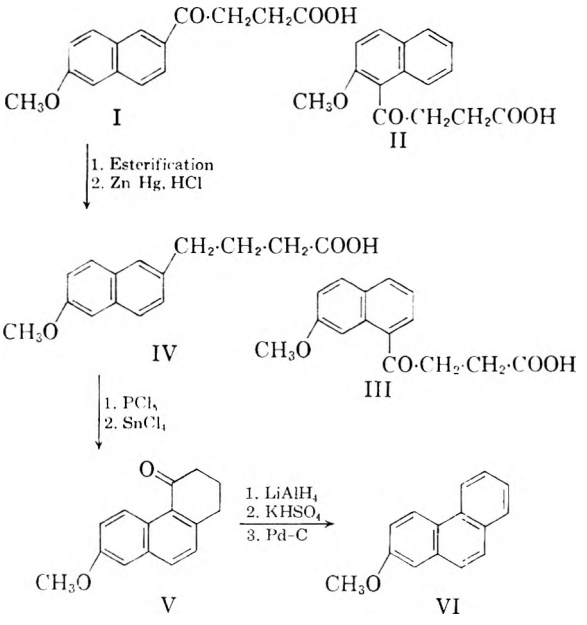
Received February 29, 1960

Succinoylation of 2-methoxynaphthalene has been studied in nitrobenzene, carbon disulfide, and tetrachloroethylene. When nitrobenzene was used as solvent, two products, β-(2-methoxy-6-naphthoyl)propionic acid (I) and β-(2-methoxy-1-naphthoyl)propionic acid (II) were obtained; in tetrachloroethylene II was the sole product; whereas, in carbon disulfide, the main compound isolated was II with traces of I. This is in close agreement to the results of Short, *et al.*[1] The reported β-(7-methoxy-1-naphthoyl)propionic acid[2] could not be obtained. This acid has been synthesized by an unambiguous route, and found different from the acids isolated by us. Additional evidence for the structure of β-(2-methoxy-6-naphthoyl)propionic acid is provided by its conversion to 2-methoxyphenanthrene. The effect of solvents on the orientation of substitution has been discussed.

The Friedel-Crafts reaction between 2-methoxynaphthalene and succinic anhydride in carbon disulfide was studied by Short, *et al.*[1] and later by Bachmann and Horton.[2] The former reported β-(2-methoxy-1-naphthoyl)propionic acid (II), m.p. 138°, as the only product. Its constitution was established by hypochlorite oxidation to the corresponding naphthoic acid. In contradiction to this report, the later workers obtained a product with m.p. 148°. They conclusively proved it to be β-(7-methoxy-1-naphthoyl)propionic acid (III), not only by hypochlorite oxidation to 7-methoxy-1-naphthoic acid, but also by reduction to γ-(7-methoxy-1-naphthyl)butyric acid, which in turn was synthesized through unambiguous routes for comparison.

In view of the above contradictory reports, the study of succinoylation of 2-methoxynaphthalene in different solvents was undertaken. In nitrobenzene, two products were isolated having m.p. 149–150° and m.p. 138° (*cf.* Short, *et al.*[1]). In tetrachloroethylene, only one acid, m.p. 138°, identical with the acid of same melting point from condensation in nitrobenzene was obtained. In carbon disulfide, again, both the acids resulted; but the higher melting acid could be isolated only in traces, the main product being the acid of m.p. 138°.

The higher melting acid was proved to be β-(2-methoxy-6-naphthoyl)propionic acid (I) by hypochlorite oxidation to 2-methoxy-6-naphthoic acid, and also by conversion to 2-methoxyphenanthrene[3] as described in accompanying formulas. Miyasaka[4] obtained 4-keto-7-methoxy-1,2,3,4-tetrahydrophenanthrene (V) using a similar procedure. Our results are at variance with those obtained by the Japanese worker. According to him, V melts at 56°, while our compound melts at 168°. Clemmensen reduction of I gave a poor yield (32%) of IV. But, when the ethyl ester of I was reduced, IV was obtained in 75.5% yield. Cyclization of IV to V was effected with stannic chloride. Reduction of V with lithium aluminum hydride, followed by dehydration and dehydrogenation gave 2-methoxyphenanthrene, which was identical with an authentic specimen kindly supplied by Dr. D. K. Banerjee of the College of Engineering and Technology, Calcutta 32, India.



Hypochlorite oxidation of the acid, m.p. 138°, afforded 2-methoxy-1-naphthoic acid, m.p. 173–175°, and was quite different from 7-methoxy-1-naphthoic acid (VII), m.p. 170.5, prepared according to the method of Fieser and Holmes[5]—a fact which was demonstrated by their mixed melting point and their Debye-Scherrer photographs. Evidence in favor of structure II for the

(1) Short, Stromberg, and Wiles, *J. Chem. Soc.*, 319 (1936).

(2) Bachmann and Horton, *J. Am. Chem. Soc.*, **69**, 58 (1947).

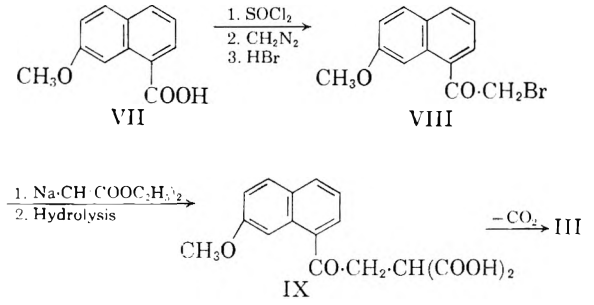
(3) Ghosal and Bagchi, *Science and Culture*, **19**, 49 (1953).

(4) Miyasaka, *J. Pharm. Soc. Japan*, **59**, 278 (1939); *C.A.* **34**, 1012 (1940).

(5) Fieser and Holmes, *J. Am. Chem. Soc.*, **58**, 2319 (1936).

acid, m.p. 138°, has already been provided by the experiments of Gilmore and Horton.[6] In no case could we isolate Bachmann and Horton's acid, m.p. 148°, although experimental conditions were varied in a number of ways such as time and temperature of reaction, order of addition of the reactants, *etc.*

For direct comparison, Bachmann and Horton's acid (III) was synthesized through the following unambiguous route from the Fieser and Holmes' acid (VII):



The final product melted at 147.5° in conformity with the observation of Bachmann and Horton.

In view of our experiences, we are forced to conclude that Bachmann and Horton's observation represents a rather unusual variation of the course of the reaction, and may be due to the presence of foreign matters in the catalyst. Instances are known in the literature[7] where employment of different Friedel-Crafts' catalysts led to different products. In fact, in the course of the present work, using different brands of anhydrous aluminum chloride for the succinoylation of 2-methoxynaphthalene in nitrobenzene, we observed variation. In some experiments, the acids (I) and (II) were obtained in the ratio 2.5:1. Subsequently, it was uniformly observed that the lower melting acid (II) was the main product (I:II:1:3). Particular care was taken to ascertain whether this was due to any other factor than the quality of the catalyst. Experiments under carefully controlled conditions compels us to believe that this may be the only reason for the variation observed.

The cutting down of the reaction time to two hours (one half hour in freezing mixture and one and a half hours at room temperature) as against 120 hours at 0° recommended by the previous workers does not materially affect the yield so long as the same grade of aluminum chloride is used. In fact, employment of shorter reaction periods facilitates the isolation of the products in purer condition. The initial supposition that β-(2-methoxy-1-naphthoyl) propionic acid may be converted into the 6-isomer in the presence of anhydrous aluminum chloride was disproved by keeping the 1-acid with aluminum chloride in nitrobenzene for 96 hours, when the 1-acid was recovered quantitatively.

DISCUSSION

Acylation of naphthalene and its derivatives are anomalous in the sense that orientation of substitution depends to a large extent on the solvent employed. It has been suggested that acylation at the β-position is favored in nitrobenzene medium, because the aluminum chloride–acyl chloride complex gets solvated to form a bulky complex.[8] As the α-position is relatively hindered, a complex with large steric requirements cannot attack this position. This simple theory is unable to explain the formation of large quantities of β-(2-methoxy-1-naphthoyl)propionic acid in nitrobenzene medium as observed by us.

It would therefore be worthwhile to try to interpret the results in terms of the more recent generalizations on the mechanism of Friedel-Crafts reaction.[9,10] It is now believed that Friedel-Crafts acylation reactions may proceed *via* two alternative mechanisms, *viz.* substitution (S) and ionic (I). The reaction proceeds primarily *via* S mechanism when the aromatic substrate is comparatively unreactive, such as benzene, toluene, *etc.*, whereas I mechanism becomes important only when a sterically hindered acyl halide is used, the aromatic substrate is reactive, or a sterically hindered position is being acylated.

The reactive hydrocarbon 2-methoxynaphthalene should undergo Friedel-Crafts substitution by the I mechanism. Acylation of this compound yields the 1- and 6-substitution products. Because the electron density at the 1-position is considerably greater than that at the 6-, a competing ionic substitution should predominantly yield the 1-substitution product. It is so when carbon disulfide and tetrachloroethylene are used as solvents. If the substitution at the 6-position is considerably large, it is highly probable that substitution at this unhindered and relatively unreactive position has taken place by the S mechanism. The preponderence of succinoylation and acetylation at the 6-position in nitrobenzene medium may be easily explained with this hypothesis.

The Friedel-Crafts complex between aluminum chloride and a succinic anhydride is practically insoluble in carbon disulfide and tetrachloroethylene. Hence, the little that goes into solution may be considered to be highly dissociated to yield acylonium ion. It is therefore reasonable to expect acylation through I mechanism, which is supported by substitution taking place exclusively at the hindered 1-position of a reactive substrate.

(6) Gilmore and Horton, *J. Am. Chem. Soc.*, **72**, 733 (1950).

(7) Gutsche and Lauck, *Chem. and Ind.*, 116 (1559).

(8) Baddeley, *J. Chem. Soc.*, 599 (1949).

(9) Brown, Pearsall, Eddy, Wallace, Grayson, and Nelson, *Ind. Eng. Chem.*, **45**, 1462 (1953).

(10) Gore, *Chem. Rev.*, **55**, 229 (1955).

The isolation of a very small quantity of the 6-isomer shows that substitution at the 6-position by I mechanism is negligible, or the simultaneous S reaction proceeds to a very limited extent. In nitrobenzene, in which the Friedel-Crafts complex is soluble, the presence of a considerable amount of undissociated complex is expected. This could lead to acylation at the 6-position (comparatively unreactive and free) through the S mechanism. This would explain the formation of a larger proportion of the 6-isomer in comparison to the product obtained by carrying out the reaction in other solvents.

2-Methoxynaphthalene is acetylated at the 6-position in nitrobenzene medium.[11,12] That no isomeric 1-derivative is formed is a sharp contrast to succinoylation of the same compound. If we compare the structures of the two Friedel-Crafts complexes, we would find that the electron releasing character of the methyl group in the case of the complex between acetyl chloride and aluminum chloride, and the electron withdrawing character of the carboxyl in the case of the complex between succinic anhydride and aluminum chloride, would respectively retard and favor the formation of the acylonium ion. We should therefore expect much less contribution of the I mechanism in the case of acetyl chloride, resulting in the acylation proceeding predominantly at the 6-position through the S-mechanism.

Results given in the literature indicate that naphthalene shows a greater tendency to be acylated at the β-position than 2-methoxynaphthalene. This may be attributed to the comparatively unreactive character of naphthalene.

It has been pointed out before that the purity of the catalyst plays a very important part in determining the course of the reaction. This may be due to the fact that minor constituents in the catalyst might to some extent promote or retard the I- and S-reaction carried out in otherwise similar conditions. In that case, the variations observed by a different set of workers for reactions carried out between the same reactants and in the same solvent may find an explanation.

EXPERIMENTAL[13]

Succinoylation of 2-methoxynaphthalene. A. *In nitrobenzene.* To a solution of aluminum chloride (29.4 g.) in nitrobenzene (98 ml.) succinic anhydride (10 g.) was added. The mixture was cooled below 0°, and 2-methoxynaphthalene (15.8 g.) was slowly added. After stirring for 0.5 hr., the cooling bath was removed; the reaction mixture was decomposed after 1.5 hr. with ice and hydrochloric acid. On working up in the usual manner, a solid acid was obtained which was methylated with 20 ml. of dimethyl sulfate. The product was then esterified with ethanol (50 ml.), benzene (75 ml.), and concd. sulfuric acid (1 ml.) for 5 hr. The benzene layer was washed with water and dilute ammonia. On removal of the solvent, the residue crystallized partially. The crystals were collected (4 g.), and washed with a little ethanol; m.p. 107°. Recrystallization from ethanol gave pure ethyl β-(2-methoxy-6-naphthoyl)propionate, m.p. 111–112°. This ester on hydrolysis with alcoholic potassium hydroxide gave a quantitative yield of β-(2-methoxy-6-naphthoyl)propionic acid, which on recrystallization from glacial acetic acid, melted at 148–149°. This acid on oxidation with sodium hypochlorite afforded 2-methoxy-6-naphthoic acid m.p. 200° (lit. 205°).

The liquid ester obtained after filtration of ethyl β-(2-methoxy-6-naphthoyl)propionate was distilled and the fraction (11.9 g.) b.p. 215–222°/4.0 mm. was collected. This on saponification gave an acid, m.p. 137–138°, not depressed by admixture with β-(2-methoxy-1-naphthoyl)-propionic acid.

Total yield of the esters was 56%.

In two experiments, aluminum chloride (58.8 g.), nitrobenzene (194 ml.), succinic anhydride (20 g.), and 2-methoxynaphthalene (31.6 g.) afforded 17.3 g. of the 6-isomer, m.p. 149°, and 6.6 g. of the 1-isomer, m.p. 139–140°. In this case, the total yield of the acids was 45%.

B. *In carbon disulfide.* Succinic anhydride (5 g.) was allowed to react with 2-methoxynaphthalene (8 g.) in carbon disulfide (30.4 g.) in the presence of anhydrous aluminum chloride (14.7 g.) under conditions identical with those described by Short, *et al.*[1] An acidic product, m.p. 108–109.5°, (4.5 g.) was obtained. This was esterified with alcoholic hydrochloric acid (9 ml., 5%) to give 3.5 g. of ester, b.p. 210–214°/3 mm. On being left for 7 days in contact with a little methanol, traces of solid, m.p. 111–112°, separated. This was removed by filtration and washed with a little methanol. Mixed melting point with ethyl β-(2-methoxy-6-naphthoyl)propionate did not show any depression. The filtrate from above was redistilled after removal of methanol when the distillate solidified on cooling, m.p. 37–38° (lit.[1] m.p. 40–41°). This was hydrolyzed with alcoholic potassium hydroxide, when 3.0 g. of solid acid were obtained. On crystallization from methanol, the first crop of β-(2-methoxy-1-naphthoyl)propionic acid (1 g.) melted at 139–140°.

Anal. Calcd. for $C_{15}H_{14}O_4$: C, 69.77; H, 5.43. Found: C, 69.61; H, 5.65.

The acid in the mother liquor was subjected to fractional crystallization, but no other product could be obtained.

The keto acid (1 g.), on oxidation with alkaline sodium hypochlorite gave 2-methoxynaphthoic acid, which was crystallized from ethyl acetate, m.p. 173–175° (lit.[1] m.p. 174–175°).

C. *In tetrachloroethylene.* Succinic anhydride (10 g.) was added to a cold suspension of aluminum chloride (29.4 g.) in tetrachloroethylene (147.8 g.). The suspension was then cooled in a freezing mixture, and 2-methoxynaphthalene (15.8 g.) was slowly added with stirring, keeping the temperature below 0°. The reaction mixture was kept below 0° for 2 hr., and then kept overnight. On working up in the usual manner, an acid was obtained which on crystallization from acetic acid gave crystals (3.5 g.) m.p. 126–127°. On recrystallization from 95% ethanol the melting point rose to 138°. Admixture with β-(2-methoxy-1-naphthoyl)propionic acid did not depress the melting point. The crude acids obtained from the mother liquor was esterified and worked up as described above, but no solid product could be isolated, demonstrating the absence of the 6-isomer.

γ-(*2-Methoxy-6-naphthyl*)*butyric acid* (IV). Amalgamated zinc (100 g.), water (16 ml.), concd. hydrochloric acid (150 ml.), toluene (175 ml.), acetic acid (75 ml.), ethanol (90 ml.), and ethyl β-(2-methoxy-6-naphthoyl)propionate (25 g.) were refluxed for 60 hr. The toluene layer was separated, washed with water. The water layer and the washings were extracted with ether, and the ether extract combined with the toluene. After removal of toluene by steam distillation, the product was methylated with 30 ml. of di-

(11) Haworth and Sheldrick, *J. Chem. Soc.*, 864 (1934).
(12) Robinson and Rydon, *J. Chem. Soc.*, 1394 (1939).
(13) All melting points are uncorrected.

methyl sulfate and alkali. The crude acid (23.5 g.) was sublimed under reduced pressure to afford a 75% yield of pale yellow solid m.p. 129–131.5°, which was crystallized from benzene-ligroin to yield shiny white crystals, m.p. 136°.

Anal. Calcd. for $C_{15}H_{16}O_3$: C, 73.78; H, 6.56. Found: C, 73.51; H, 6.62.

4-Keto-7-methoxy-1,2,3,4-tetrahydrophenanthrene (V). To γ-(2-methoxy-6-naphthyl)butyric acid (1.5 g.) suspended in 30 ml. of thiophene free benzene, phosphorus pentachloride (2.5 g.) was added. The mixture was allowed to stand for 0.5 hr. at room temperature, heated at 60° for 1 hr., and then subsequently heated for 5 min. on steam bath. The mixture was then cooled, and anhydrous stannic chloride (0.74 ml.) in thiophene free benzene (6 ml.) was added with shaking. After 10 min. the reaction mixture was decomposed with ether (9 ml.) and hydrochloric acid (9 ml.). The ether-benzene extract was washed thrice with hydrochloric acid (1:1), once with distilled water, and finally three times with dilute ammonia. On removal of the solvent, a white crystalline product, m.p. 146–152°, was obtained. Crystallization from benzene-alcohol afforded the pure ketone (0.7 g.), m.p. 168°. A 0.3-g. of sample of the impure ketone could be recovered from the mother liquor.

Anal. Calcd. for $C_{15}H_{14}O_2$: C, 79.64; H, 6.19. Found: C, 79.41; H, 6.30.

The ultraviolet absorption curve shows maxima at 216 (log ε 4.57), 251.5 (4.37), 317 (3.69), and 354 (3.52) mμ.

The oxime, m.p. 216°, was crystallized from alcohol-dioxane.

Anal. Calcd. for $C_{15}H_{15}NO_2$: N, 5.81. Found: N, 5.80.

2-Methoxyphenanthrene (VI). The above ketone (0.5 g.) in dry ether (70 ml.) was reduced with lithium aluminum hydride (0.1 g.). After decomposition with 10% sulfuric acid, the ether layer was separated and washed with water. On removal of ether, white solid m.p. 120–122° was obtained. This was heated with fused potassium hydrogen sulphate for 30 min., and the product (0.2 g.) m.p. 127–128°, was purified by sublimation. This was then dehydrogenated for 1 hr. at 300–350° with palladium-charcoal (30%, 0.2 g.). The product was purified by sublimation and crystallized from ethanol to obtain white crystals (0.1 g.), m.p. 98°; the melting point was not depressed on admixture with an authentic specimen of 2-methoxyphenanthrene.

Anal. Calcd. for $C_{15}H_{12}O$: C, 86.54; H, 5.77. Found; C, 86.31; H, 5.88.

The picrate, m.p. 125°, was crystallized from ethanol. Mixed melting point with the picrate of 2-methoxyphenanthrene was undepressed.

Anal. Calcd. for $C_{21}H_{15}N_3O_8$: N, 9.6. Found: N, 9.8.

2-Methoxy-8-bromoacetyl naphthalene (VIII). To a suspension of 7-methoxynaphthoic acid (2.6 g.) in dry thiophene free benzene (10 ml.), thionyl chloride (2.5 g.) was slowly added with shaking. After standing for 30 min., the mixture was maintained at 60° for 30 min. Then the solvent was removed with the help of a water pump. Benzene (15 ml.) was again added and removed, the operation being repeated thrice. The acid chloride was diluted with dry ether (15 ml.) and added to a cooled solution of diazomethane from nitrosomethylurea (7 g.) in ether (50 ml.), and left overnight. Hydrobromic acid (48%, 3 ml.) was added to the above solution. After the evolution of nitrogen was complete, the ethereal solution was washed first with water and then with alkali. On removal of ether, the bromoketone was obtained as solid, and was directly employed in the next step.

β-(2-Methoxy-8-naphthoyl)-α-carboxypropionic acid (IX). To a suspension of ethyl sodio malonate prepared from pulverized sodium (0.47 g.), and ethyl malonate (3.3 ml.) in dry benzene (15 ml.), the solution of the above bromoketone was added with slight cooling. The mixture was refluxed for 4.5 hr. and then decomposed with ice water. The benzene layer was separated, and the residue obtained on removal of benzene was directly hydrolyzed with methanolic potassium hydroxide (40 ml., 10%) for 3.5 hr. Crystals of the potassium salt separated on cooling. After removal of the methanol, the salt was dissolved in water and the solution carefully acidified with cooling, when precipitation took place in two distinct stages. These were separately collected. The first crop (2 g.), m.p. 107°, was found to be impure 7-methoxy-naphthoic acid. The second crop (0.9 g.), m.p. 177° dec., insoluble in benzene and chloroform, was crystallized from methanol twice to yield the pure compound, m.p. 179°.

Anal. Calcd. for $C_{16}H_{14}O_4$: C, 63.6; H, 4.6. Found: C, 64.1; H, 4.8.

β-(7-Methoxy-1-naphthoyl)propionic acid (III). The crude malonic acid IX (m.p. 177°, 0.9 g.) was decarboxylated at 180° for 30 min. The product was extracted with bicarbonate. Acidification gave a white solid (0.4 g.) m.p. 145°. After two crystallizations from methanol, colorless crystals were obtained, m.p. 147.5° (lit.[2] m.p. 148°). This acid showed depression in melting point on admixture with both I and II.

Anal. Calcd. for $C_{15}H_{14}O_4$: C, 69.76; H, 5.42. Found: C, 69.55; H, 5.45.

Acknowledgment. The author is indebted to Mr. P. Bagchi, Director of Chemical Research, East India Pharmaceutical Works Ltd., for his valuable suggestions; and to Dr. D. K. Banerjee for supplying an authentic specimen of 2-methoxyphenanthrene.

MUZAFFARPUR, INDIA

[CONTRIBUTION FROM THE ORGANIC RESEARCH LABORATORIES OF THE U. S. VITAMIN AND PHARMACEUTICAL CORP.]

Indandione Anticoagulants

SEYMOUR L. SHAPIRO, KARL GEIGER, AND LOUIS FREEDMAN

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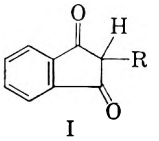
A series of 2-substituted indandiones has been synthesized and yielded compounds with considerable anticoagulant activity. High yields of arylindandiones from condensations of phthalide and the aromatic aldehyde have been obtained by employment of ethyl propionate as a solvent. The ultraviolet absorption spectra of selected compounds in this series have been reported.

An improved understanding of the coagulation process[1] and increased experience[2] have stimulated anticoagulant therapy[3] in thrombo-embolic disease. Recognition of enhanced blood coagulability[4] and increased sensitivity to alimentary lipemia[5] in atherosclerotics, and demonstration[6] that ACTH and cortisone treatment increase the incidence of thrombo-embolic manifestations, have broadened the therapeutic utility of anticoagulant drugs.

A search for more nearly ideal oral anticoagulants[7] has occupied many laboratories. Our explorations, recorded in this paper, involved indandiones of the type I.



I

R = aryl(R_1, phenyl and R_1, naphthyl)
R = long chain acyl (R_1 —CO—)

The category R = aryl was investigated as congeners of the clinically effective phenindione[8] (I, R = phenyl) and has been examined by others.[9]

The category R = long chain acyl, extended observations of shorter chain analogs,[10] diphenylacetyl,[11] and 2-halo-2-acyl derivatives of I[12] of other workers. The compounds in this category have been structurally envisioned as antimetabolites of vitamin K_1.

In addition to anticoagulant effects, compounds related to I have shown hypermetabolic activity,[14] parasiticidal effects,[15] rodenticidal,[16] analgesic,[17] antibacterial,[18] and bronchodilator[19] activity. Some of these properties have been evaluated.

For the synthesis[20] of I, R = aryl the appropriate aldehyde was condensed with phthalide under

(1) (a) F. D. Mann, *Ann. Rev. Physiol.*, **19**, 205 (1957); (b) C. L. Rose, *Research Today*, **15**, 23 (1959).

(2) (a) I. S. Wright, *Circulation*, **19**, 110 (1959); (b) R. E. Ensor and H. R. Peters, *J. Am. Med. Assoc.*, **169**, 914 (1959); (c) B. Manchester, *Ann. Internal Med.*, **47**, 1202 (1957); (d) J. H. Olwin and J. L. Koppel, *A. M. A. Arch. Internal Med.*, **100**, 842 (1957); (e) L. B. Ellis, H. L. Blumgart, D. E. Harken, H. S. Sise, and F. J. Stare, *Circulation*, **17**, 945 (1958); (f) W. B. Rawls and C. A. R. Connor, *Am. J. Cardiol.*, **4**, 470 (1959).

(3) (a) S. A. Carter, E. McDevitt, B. W. Gatje, and I. S. Wright, *Am. J. Med.*, **25**, 43 (1958); (b) W. G. Anlyan, G. D. DeLaughter, Jr., J. I. Fabrikant, J. W. Sullenberger, and W. T. Weaver, *J. Am. Med. Assoc.*, **168**, 725 (1958).

(4) J. F. Mustard, *Can. Med. Assoc. J.*, **79**, 554 (1958).

(5) J. F. Mustard, *Can. Med. Assoc. J.*, **79**, 736 (1958).

(6) G. Ungar, *Thrombosis and Embolism. I. International Conf.*, Basel, 1954, p. 421.

(7) L. S. Goodman and A. Gilman, *The Pharmacological Basis of Therapeutics*, 2nd Ed., The Macmillan Co., New York, N. Y., 1955, p. 1520.

(8) L. S. Goodman and A. Gilman, *The Pharmacological Basis of Therapeutics*, 2nd Ed., The Macmillan Co., New York, N. Y., 1955, p. 1517.

(9) (a) G. Cavallini, E. Milla, E. Grumelli, and F. Ravenna, *Farmaco (Pavia), Ed. Sci.*, **10**, 710 (1955); (b) A. Banchetti, *Farmaco (Pavia), Ed. Sci.*, **10**, 742 (1955); (c) E. Gori and L. Molteni, *Thrombosis and Embolism. I. International Conf.*, Basel, 1954, p. 223; (d) M. Furdík and P. Hrnčiar, *Chem. Zvesti*, **12**, 464 (1958); (e) M. Furdík, P. Hrnčiar, and E. Poláková, *Chem. Zvesti*, **12**, 642 (1958); (f) J. Moraux, *Therapie*, **11**, 104 (1956); (g) G. Pasero and G. Masini, *Arch. Maragliano*, **14**, 297 (1958); (h) N. Sperber, U. S. Patent **2,899,358** (Aug. 11, 1959); (i) D. Molho, French Patent **1,085,097** (Jan. 27, 1955) [*Chem. Abstr.* **53**, 3178 (1959)]; (j) G. Vanags and T. Dumpis, *Doklady Akad. Nauk, S.S.S.R.*, **125**, 549 (1959) [*Chem. Abstr.* **53**, 19991 (1959)]; (k) P. Hrnčiar, L. Krasnec, and M. Furdik, *Chem. Zvesti*, **10**, 12 (1956) [*Chem. Abstr.* **50**, 14674 (1956)]; (l) H. G. Krey, *Pharmazie*, **13**, 619 (1958).

(10) (a) L. B. Kilgore, J. H. Ford, and W. C. Wolfe, *Ind. Eng. Chem.*, **34**, 492 (1942); (b) S. R. Heisey, J. P. Saunders, and K. C. Olson, *Proc. Soc. Exp. Biol. Med.*, **91**, 86 (1956), report undesirable cardiovascular side effects with I, R = isovaleryl, and R = pivalyl.

(11) R. D. Birkenmeyer and M. E. Speeter, U. S. Patent **2,827,489** (Mar. 18, 1958).

(12) K. C. Murdock, *J. Org. Chem.*, **24**, 845 (1959). The activity of these compounds which do not bear an enolizable hydrogen in the 2-position may well be rationalized as a case of "drug latentiation,"[13] with hydrolysis to acyl indandiones *in vivo*.

(13) N. J. Harper, *J. Med. Pharm. Chem.*, **1**, 467 (1959).

(14) U. Söderberg and C. A. Wachtmeister, *J. Pharmacol. Exp. Therap.*, **117**, 298 (1956).

(15) L. W. Hazleton and W. H. Dolben, U. S. Patent **2,884,357** (Apr. 28, 1959).

(16) (a) J. T. Correll, U. S. Patent **2,900,302** (Aug. 18, 1959); (b) D. G. Crabtree and W. H. Robinson, *Pest Control*, **21**, 22 (July 1953).

(17) M. Kubovic, M. Prazic, and D. Atanackovic, *Proc. Soc. Exp. Biol. Med.*, **90**, 660 (1955).

(18) E. Gori, *Thrombosis and Embolism. I. International Conf.*, Basel, 1954, p. 271.

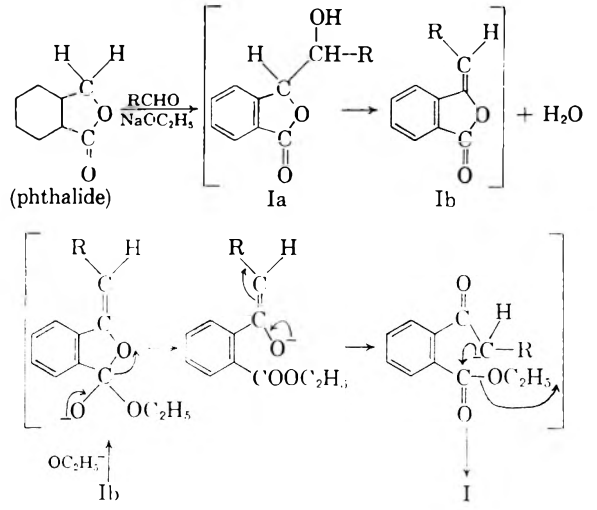
(19) H. Blumberg, H. B. Dayton, and S. M. Gordon, *Science*, **127**, 188 (1958).

(20) For an alternate synthetic route, see C. F. Koelsch, *J. Am. Chem. Soc.*, **58**, 1328 (1936). In our work, the procedure of W. Dieckmann, *Ber.*, **47**, 1439 (1914) was employed.

alkoxide catalysis to afford the required compound in moderate yield, as detailed in Scheme I.

SCHEME I

PREPARATION OF ARYLINDANDIONES



In the instance of I, R = α-naphthyl, the product was isolated in 34% yield under ethoxide catalysis as compared to 25% yield with *t*-butoxide catalysis. In addition, a compound fitting the analyses of Ia was isolated, which on treatment with ethoxide readily afforded I. The presumed intermediate Ib, α-naphthalphthalide was not isolated in the reaction, but *per se* on treatment with the ethoxide gives I.

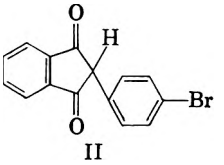
Critical to the noted yields was the formation of water (Scheme I, above) which severely restricted completion of the reaction as desired. This was overcome by employment of ethyl propionate (Method B) as the reaction solvent, along with an additional equivalent of sodium alkoxide.

The saponification of ethyl propionate served to remove the formed water of reaction and under these conditions, virtually quantitative yields of the arylindandiones were obtained. Using similar conditions, a variety of other dehydrating agents was ineffective.

The synthesis of I, R = acyl employed a modification of the procedure of Kilgore, *et al.*[10a] involving condensation of the appropriate methyl ketone with dimethyl phthalate under sodium methoxide catalysis (Method C).

The compounds prepared have been described in Table I.

The anticoagulant effects noted show that considerable enhancement of activity of I, R = phenyl is obtained with R = *p*-halophenyl, and particularly with *p*-bromophenylindandione, II.[21] The acyl compound affording the highest anticoagulant activity was compound 33, which interestingly has a sixteen carbon chain attached to the



II

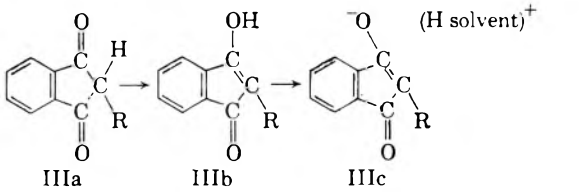
indandione nucleus, comparable to the sixteen carbon chain of the phytyl substituent in vitamin K_1.

The sodium salts of the acyl indandiones were only sparingly soluble in water, and it was established that conversion to *N*-methylglucamine salts of the enol form of such indandiones considerably enhanced water solubility. Thus, the water solubility of compound 32 was 0.1% as compared to 6.7% with compound 30.

A number of the compounds were evaluated for analgesic effect[22] (compounds 1, 15, 22, 24, 32, 35), and were inactive. Anti-bacterial studies showed complete inhibition of growth of B. *subtilis*, M. *flavus*, and S. *lutea* (compounds 27, 28, and 32) at 0.02 millimoles per liter, with no effect on E. *Coli*. Compound 33 required 2.0 millimoles per liter for similar inhibition whereas compound 34 was ineffective.

The ultraviolet absorption spectra of selected compounds of Table I have been reviewed in an effort to characterize the chromophores, and to assess whether any noted relationships between anticoagulant activity and the spectra could be found. The spectra are given in Table II.

Forms contributing to the noted pattern of absorption are:



Indandione (IIIa, R = H) has been established[23] to be in the diketo form IIIa. In this form it may be regarded as an *ortho*-substituted acetophenone[24] with stabilization in a conformation co-planar with the phenyl ring. The diffuse band in methanol at 253–259 mμ is intensified as discrete bands at about 240 and 257 mμ in sodium methoxide with formation of IIIb–c. The hyperchromic effect in isopropyl alcohol relative to methanol would suggest more enolization in the less polar solvent.[25] In aqueous alkali as well as phosphate buffer *p*H 7.5, the bands are more clearly resolved, and, hyperchromic relative to the main bands in organic

(21) This compound is currently under clinical trial under the name "Haldinone".

(22) The procedure for the analgesic test was that of C. Bianchi and J. Franceschini, *Brit. J. Pharmacol.*, **9**, 280 (1954).

(23) B. Eistert and W. Reiss, *Ber.*, **87**, 92 (1954).

(24) E. A. Braude and F. Sondheimer, *J. Chem. Soc.*, 3754 (1955).

(25) P. B. Russell, *J. Am. Chem. Soc.*, **74**, 2654 (1952).

TABLE I

INDANDIONES (SEE FORMULA I)

No.[a]	R_1	M.P.[b]	Solvent[c]	Yield,[d] %	Method[e]	Formula	Analyses[f] Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Activity[g]
	R = R_1-phenyl										
1[a1]	H	148–149	A	24	A						1+
2	NMG[h]	151–156	B	90		$C_{22}H_{27}NO_7$[h]	63.3	63.6	6.5	6.6	
3	4-F	116–117	A	17	A	$C_{15}H_9FO_2$	75.0	75.2	3.8	3.9	2+
4	2-Cl	183–184	C	20	A	$C_{15}H_9ClO_2$[i]	70.2	70.0	3.5	3.6	2+
5	3-Cl	153–155	A	30	A	$C_{15}H_9ClO_2$[i]	70.2	70.2	3.5	3.4	1+
6[a2]	4-Cl	142–144	B	15	A	$C_{15}H_9ClO_2$[i]	70.2	70.0	3.5	3.4	4+
7	2,4-diCl	143–145	B	13	A	$C_{15}H_8Cl_2O_2$	61.9	61.9	2.8	3.1	0
8[a3]	4-Br	142–146	B	74[j,k]	B	$C_{15}H_9BrO_2$	59.8	60.0	3.0	3.2	5+
9	NMG[h]	155–157	B	98		$C_{22}H_{26}BrNO_7$[l]	52.3	52.5	5.4	5.5	
10[a4]	4-I	143–144	D	89	B						
11[a5]	3,4-OCH_2O—	154–156	B	7	A	$C_{16}H_{10}O_4$	72.2	72.0	3.8	3.6	1+
12	3,4-diC_2H_5O—	155–157	A	24	A	$C_{19}H_{18}O_4$	73.5	73.8	5.9	6.0	3+
13	2-COOH	248–254	E	37	A	$C_{16}H_8O_4$	72.2	72.0	3.8	4.0	0
14	4-*i*-C_3H_7—	155–156	B	18	A	$C_{18}H_{16}O_2$	81.8	82.1	6.1	5.9	1+
	R = R_1-(α-naphthyl)										
15[a6]	H	217–218	F	83	B[m]	$C_{19}H_{12}O_2$	83.8	83.9	4.4	4.7	4+
16	NMG[h]	90–94	B			$C_{26}H_{27}NO_7$[n]	65.6	65.8	6.4	6.7	
17	2-CH_3	204–210	K		A	$C_{20}H_{14}O_2$	81.3	81.6	5.1	5.1	2+
18[a7]	4-Cl	199–201	A	4	A	$C_{19}H_{11}ClO_2$	74.4	74.0	3.6	3.6	2+
19[a8]	4-Br	203–204	G	11	A	$C_{19}H_{11}BrO_2$	65.0	65.3	3.2	3.3	3+
20[a9]	5-Br	151–153	B	20	A	$C_{19}H_{11}BrO_2$	65.0	65.3	3.2	3.0	2+
21[a10]	H[o]	173–174	A	28	A	$C_{19}H_{12}O_2$	83.8	83.9	4.4	4.5	0
	R = R_1-CO—										
22	C_3H_5—[p]	133–134	D	30	D	$C_{13}H_{10}O_3$	72.9	72.9	4.7	4.8	1+
23	CH_3COCH_2—	139–140	H	8	D	$C_{13}H_{10}O_4$	67.8	67.7	4.4	4.2	
24[a11]	*i*-C_4H_9—	68–69	B	15	D						0
25[a12]	*t*-C_4H_9—	109–115	A	19	D						
26	*n*-C_6H_{13}—[q]	258–262	I	33	C	$C_{16}H_{17}NaO_3$	68.6	68.0	6.1	6.2	
27	*n*-C_7H_{15}—[q]	266–267	I	12	C	$C_{17}H_{19}NaO_3$	69.4	69.7	6.5	7.0	4+
28	*n*-C_9H_{19}—[q]	172–175	I	13	C	$C_{19}H_{23}NaO_3$	70.8	70.7	7.2	7.1	4+
29	*n*-$C_{11}H_{23}$—	45–46	B			$C_{21}H_{28}O_3$	76.8	76.5	8.6	8.7	
30	NMG[h]	90–94	A	51		$C_{28}H_{45}NO_8$[r]	63.2	63.1	8.7	8.9	
31	DNP[s]	138–140	C	95		$C_{27}H_{32}N_4O_6$	63.7	63.9	6.3	6.4	
32	*n*-$C_{11}H_{23}$—[q]	208–209	J	26	C	$C_{21}H_{27}NaO_3$[t]	70.2	70.1	7.9	7.6	4+
33	*n*-$C_{15}H_{31}$—[q]	191–192	I	25	C	$C_{25}H_{35}NaO_3$	73.9	73.9	8.7	9.0	5+
34	*n*-$C_{17}H_{35}$—	59–61	B	22	C	$C_{27}H_{40}O_3$	78.6	78.7	9.8	9.8	5+
35	4-$CH_3C_6H_4$—	123–125	B	22	D	$C_{17}H_{12}O_3$	77.3	77.2	4.6	4.5	0
36	4-Cl—C_6H_4—	178–179	A	22	D	$C_{16}H_9ClO_3$[i]	67.5	67.6	3.2	3.4	3+
37	4-Br—C_6H_4—	174–176	C	28	D	$C_{16}H_9BrO_3$	58.4	58.9	2.8	2.6	0

[a] Compound previously reported:[a1] W. Dieckmann, *Ber.*, **47**, 1439 (1914), m.p. 146°;[a2] Ref. 9 (a), m.p. 145°,[a3] Ref. 9(a), m.p. 137–139°;[a4] Ref. 20, m.p. 145–146°;[a5] Ref. 9 (j), m.p. 159°,[a6] Ref. 9 (i), m.p. 216°;[a7] Ref. 9 (d), m.p. 212–213;[a8] Ref. 9 (d), m.p. 215–216°;[a9] Ref. 9 (k), no m.p. in abstract.[a10] Ref. 9 (i), m.p. 180°;[a11] Ref. 10 (a), m.p. 67–68°;[a12] Ref. 10 (a), m.p. 108.5–110.5°. [b] Melting points are not corrected. [c] Recrystallizing solvent: A = isopropyl alcohol, B = methanol C = ethanol, D = acetone-water, E = water-hydrochloric acid, F = methyl ethyl ketone, G = chloroform-hexane, H = acetone, I = water, J = methylal, K = acetic acid. [d] Yields are given for recrystallized products. [e] For method used, see Experimental. [f] Analyses are by Weiler and Strauss, Oxford, England. [g] The activity was established by subcutaneous injection (5 mg./kg.) of the compounds to guinea pigs. The compound was administered at 0,5 and 24 hr. and prothrombin time determined at 27 hr. The percentage depression from the normal prothrombin time of the animals was classified as 1+ (−10%); 2+ (10–19%); 3+ (20–29%); 4+ (30–39%); 5+ (over 40%). [h] *N*-methylglucamine salt of compound immediately above. [i] Acceptable halogen analyses also obtained, and omitted to save space. [j] Obtained in 38.4% yield by Method A. [k] See Experimental for different crystalline forms. [l] *Anal.* calcd. for 1/2 H_2O. Br, calcd./found: 15.8/15.7. [m] Obtained in 34% yield by Method A. [n] *Anal.* calcd. for 1/2 H_2O. N, calcd./found: 2.9/3.0. [o] β-Naphthyl rather than α-naphthyl. [p] C_3H_5— = cyclopropyl. [q] Compound isolated and characterized as sodium enolate. [r] *Anal.* calcd. for 1/2 H_2O. N, calcd./found: 2.6/2.7. [s] 2,4-Dinitrophenylhydrazone. [t] *Anal.* calcd. for 1/2 H_2O. Na, calcd./found: 6.6/6.5.

solvents, suggestive of initial formation of IIId followed by formation of IIIb[26] in aqueous systems. When the R substituent is varied as phenyl, and substituted phenyl, a variety of new bands at longer wave lengths are obtained, not noted in III, R = H, or the analogous 1,2-diketo-3-phenylhydrindene,[27] indicative of interaction between the R

(26) A. Schönberg, A. Mustafa, and W. Asker, *J. Am. Chem. Soc.*, **73**, 2876 (1951).

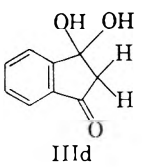
(27) C. F. Koelsch and H. Hochman, *J. Org. Chem.*, **3**, 503 (1939).

TABLE II

ULTRAVIOLET ABSORPTION SPECTRA[a]

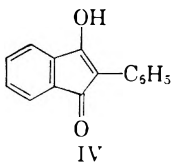
No.,[b] Solvent[c]		No.,[b] Solvent[c]	
b_1-A	253–259,[d] 10.6	6-C	273, 20.0; 310, 2.8; 322, 3.4; 336, 2.8; 354, 1.2
b_1-B	257, 28.0		
b_1-C	248, 9.9	6-D	280, 29.0; 325, 8.8; 338, 10.3; 355, 7.2
b_1-D	249, 11.9		
b_1-E	245, 10.2	6-E	291, 10.7; 347, 11.9; 361, 9.7
b_1-F	246, 32.6; 255, 30.6	6-F	285, 31.2; 331, 13.1
b_1-G	246, 25.4; 254, 24.2	6-G	286, 29.2; 330, 12.2
1-A	277, 17.8; 287, 15.8; 335, 6.2	10-A	250, 11.5; 292, 32.7; 339, 24.4; 354, 19.5
1-B	286, 35.8; 333, 14.9	10-B	250, 11.1; 292, 32.3; 339, 24.4; 353, 19.8
4-A	252, 17.8; 319, 4.3; 333, 3.5		
4-B	253, 21.2; 275, 16.9; 319, 6.3; 333, 5.0	15-A	260, 30.0
4-C	247, 12.5	15-B	252, 28.6
4-D	248, 14.5; 323, 2.5	22-A	236, 18.8; 286, 31.8; 312, 16.0; 323, 14.6
4-E	246–254,[d] 11.2		
4-F	251, 24.1; 317, 3.7	22-B	244, 17.6; 272, 27.2; 281, 44.4; 301, 12.4; 311, 18.7; 323, 19.7
4-G	251, 23.7; 300–318,[d] 3.5		
5-A	289, 31.1; 335, 17.9; 349, 14.4	25-A	238, 15.7; 285, 26.8; 312, 9.7; 322, 8.3
5-B	289, 32.2; 335, 18.5; 349, 15.3		
6-A	251, 10.7; 289, 32.8; 337, 19.0; 351, 14.9	25-B	245, 19.6; 271, 25.4; 280, 36.4; 310, 15.9; 323, 15.8
6-B	250, 10.7; 289, 33.3; 337, 18.9; 350, 15.4	29-A	246, 11.1; 274, 19.9; 282, 30.2; 310, 11.8; 322, 12.5
		29-B	244, 20.4; 282, 38.8; 310, 18.4; 322, 18.7
36-A	293, 14.5; 331, 17.4	36-E	300, 13.2; 335, 19.6
36-B	288, 14.1; 328, 16.2	36-F	291, 17.0; 330, 15.4
36-C	300, 17.3; 335, 22.4	36-G	291, 16.3; 330, 15.1
36-D	303, 16.6; 338, 23.6		

[a] The spectra were determined in a Beckman recording spectrophotometer, model DK. The data for the main absorption bands are reported as λ_{max} mμ, $\epsilon \times 10^{-3}$. [b] Numbers correspond to compound numbers in Table I;[b1] indandione, m.p. 129–131°. [c] The solvents were varied as follows: A = methanol; B = 0.1*N* sodium methoxide in methanol; C = methanol containing 1% acetic acid; D = isopropyl alcohol; E = acetonitrile containing 1% methanol; F = 0.1*N* sodium hydroxide and in the case of compounds 10 and 15, contains 1% methanol; G = 0.1*M* phosphate buffer, *p*H 7.5, containing 1% methanol. The spectra of compounds 5, 10 and 15 were established in solvents C-G and have not been reproduced to save space. [d] Shoulder, ϵ calculated at center of range.



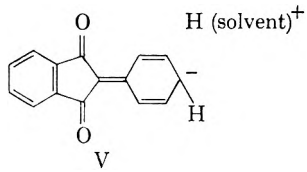
IIId

substituent and the indandione nucleus. In these structures, the *trans*-stilbene absorption characteristics are to be noted (IV).[28] The existence of a



IV

preponderance of the molecules in the enol form with I, R = *m*- or *p*-halophenyl, is reflected in the virtual identity of the spectra of these compounds in sodium methoxide and methanol. By contrast, I, R = phenyl, manifests considerable hyperchromic effect when going from methanol to sodium methoxide. An important solvating influence is also indicated in the relative hypochromicity of the spectra of the halophenyl compounds in such solvents as acetonitrile and isopropyl alcohol. Contribution of forms such as V[29] in methanol would be indicated.



V

In 1% acetic acid the longer bands disappear or diminish considerably.[30]

Of interest, and by contrast to I, R = H, the compounds, I, R = *m*- or *p*-halophenyl, are considerably less hyperchromic in aqueous alkali, relative to the spectra obtained in sodium methoxide.

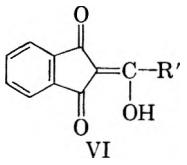
With I, R = *o*-chlorophenyl, and to some extent, R = α-naphthyl the influence of steric factors is manifest, with absorption at the longer wave lengths disappearing or being substantially diminished from steric inhibition of coplanarity of the hindered R group and the indandione system.

(28) (a) G. Berti, *Gazz. chim. ital.*, **86**, 655 (1956); (b) H. Jaffé and M. Orchin, *J. Chem. Soc.*, 1078 (1960).

(29) (a) J. Szmuszkovicz, *J. Am. Chem. Soc.*, **82**, 1180 (1960); (b) J. E. Banfield, *J. Org. Chem.*, **25**, 300 (1960).

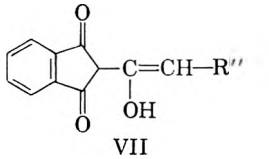
(30) L. F. Fieser and M. Fieser, *Organic Chemistry*, D. C. Heath and Co., Boston, Mass., 1944, p. 831.

With the 2-acyl indandiones studied, another allowable enolizable form[31] is VI.



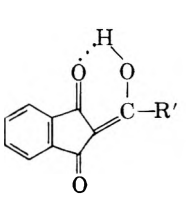
VI

The spectral characteristics of compounds in which R′ contains a methylene group *alpha* to the acyl carbonyl group (compounds 22, 29), do not permit assessment (compounds 25, 36) of the contribution to the spectra from forms such as VII.

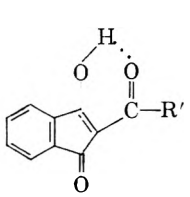


VII

The bathochromic effect with the acyl compounds relative to I, R = H, support the important contribution of forms of type VI, which parallel the V structures. Enhancement of the extinction coefficient in sodium methoxide, relative to methanol, without substantial effect on the locus of the main absorption bands would indicate that the acylated compounds are largely in the enolic form of the type corresponding to IIIb, or VI in the solvent systems inspected. Compound 36 is not vulnerable to quenching of the spectra in 1% acetic acid, and in fact, the spectra in this solvent, as well as in isopropyl alcohol are bathochromic and hyperchromic relative to those noted in methanol, which would be accountable for by chelated forms as VIIIa and VIIIb, also realizable with the other acyl derivatives.



VIIIa



VIIIb

Similar structures have been assigned for β-diketones[32-34] in other studies. It is of interest that with the diaroylmethanes[32] the extinction coefficients of the enolate ion were hypochromic relative to the ε values for the diketones *per se* in ethanol.

There is no correlation with anticoagulant activity in that virtually any of the spectral characteristics noted above are shared by compounds which are physiologically very active, or substantially inactive.

(31) J. Schieber and G. Hopfer, *Ber.*, **53**, 697 (1920).

(32) (a) G. S. Hammond, W. G. Bordius, and G. A. Guter, *J. Am. Chem. Soc.*, **81**, 4621 (1959); (b) G. A. Guter and G. S. Hammond, *J. Am. Chem. Soc.*, **81**, 4686 (1959).

(33) L. G. Van Uitert and W. C. Fernelius, *J. Am. Chem. Soc.*, **76**, 375 (1954), and previous papers in this series.

(34) A. Brandström, *Arkiv. för Kemi*, **7**, 81 (1954).

EXPERIMENTAL[35]

2-(p-Bromophenyl)indandione-1,3 (Compound 8). Method A. A mixture of 13.9 g. (0.075 mole) of *p*-bromobenzaldehyde, 10 g. (0.075 mole) of phthalide, and 5.5 g. (0.08 mole) of sodium ethoxide in 80 ml. of ethanol was heated under reflux for 1.5 hr. Water (80 ml.) was added, the alcohol removed, and the residue diluted with 500 ml. of ice water and washed with two 80-ml. portions of ether. After acidifying with hydrochloric acid the product was extracted into 100 ml. of ether, and then re-extracted with aqueous sodium bicarbonate, which was acidified with hydrochloric acid to *p*H 2. After 20 hr. the product was separated, dried, and recrystallized (methanol), 8.7 g. (38.4%) of dark red crystals, m.p. 142–146°, with the red color fading at 132°.

On recrystallization from four parts of acetic acid the white form (86%) of the product was obtained, m.p. 143–148°. On recrystallization of the white form from methanol, it reverted to the dark red crystals. The white form and red form on admixture melted 142–146° C.[36]

2-(α-Naphthyl)indandione-1,3 (Compound 15). In a manner similar to the above, and using α-naphthaldehyde, a 34.2% yield of the yellow product was obtained.

The mother liquor (from aqueous acidification and recrystallization) on concentration gave 40% of a white by-product, formulated as compound Ia (Scheme I), 3-[(α-naphthyl)hydroxymethyl]phthalide which melted 178–179° (ethanol).

Anal. Calcd. for $C_{19}H_{14}O_3$: C, 78.6; H, 4.9. Found: C, 78.4; H, 4.9.

This product, on solution in methanol and treatment with sodium methoxide, gave compound 15 in 53% yield.

The product dissolves in hot aqueous sodium hydroxide, and is recovered unchanged upon acidification.

Compound 15 is obtained in 25% yield (m.p. 213–216°) when potassium *t*-butoxide is substituted for sodium ethoxide.

α-Naphthalphthalide was prepared in 36% yield, m.p. 184–184.5°[37] (methyl ethyl ketone) following the procedure of Weiss, using α-naphthyl acetic acid and phthalic anhydride[38] On admixture with compound Ia, the m.p. was 148–156°.

2-[(α-Naphthyl)acetyl]o-benzoic acid was prepared from α-naphthalphthalide, following the procedure of Arcus and Marks[39] in 75% yield, m.p. 195–196° (ethanol). The mixed m.p. with compound Ia was 158–165°.

Anal. Calcd. for $C_{19}H_{14}O_3$: C, 78.6; H, 4.9. Found: C, 79.1; H, 4.9.

2-(α-Naphthyl)indandione-1,3. Method B.[40] A mixture of 156 g. (1 mole) of α-naphthaldehyde, 134 g. (1 mole) of phthalide, and 580 ml. of ethyl propionate was rendered anhydrous by distillation of 100 ml. of ethyl propionate from the reaction mixture (ethyl propionate–water azeotrope, b.p. 81.2°). Sodium methoxide (3 moles) in 700 ml. of methanol was added rapidly to the refluxing mixture which was maintained at about 66–68° over 4 hr. by occasional

(35) Typical procedures for the preparations given in the table are indicated.

(36) See Ref. 9 (1) for similar observations with 2-(*p*-chlorophenyl)indandione-1,3. It is of interest that compounds 4 and 7 which have an *o*-chlorophenyl substituent are obtained as colorless crystals, as is phenylindandione.

(37) E. D. Bergmann, *J. Org. Chem.*, **21**, 461 (1956) reports m.p. 179°.

(38) R. Weiss, *Org. Syntheses*, Coll. Vol. II, 61 (1943).

(39) C. L. Arcus and R. E. Marks, *J. Chem. Soc.*, 1627 (1956).

(40) A more fully detailed exploration of this method is in progress.

distillation of solvent. After removal of the volatile material the residue was dissolved in 5.5 l. of water, washed with ether, filtered, and acidified to *p*H 2, whereupon the product separated, 262 g. (96.5%), m.p. 207–211°. On recrystallization (9 parts methyl ethyl ketone) there was obtained 217 g. (83%), m.p. 217–218°.

Sodium(2-lauroyl)indandione-1,3 (Compound 32). Method C. To a suspension of 54 g. (1 mole) of sodium methoxide in 1200 ml. of benzene was added 198 g. (1 mole) of methyl undecyl ketone and 194 g. (1 mole) of dimethyl phthalate; the mixture was heated under reflux for 24 hr. with stirring. The benzene was removed, the residue suspended in a mixture of 1500 ml. of water and 200 ml. of ether, and while vigorously stirred, acidified with hydrochloric acid to *p*H 3. On extraction of the ethereal phase with 2.5 l. of 2% sodium hydroxide, the sparingly soluble sodium enolate precipitated, was separated, dried (100°), and recrystallized (methylal) to give 93.1 g. (25.9%), m.p. 208–209°.

A suspension of 30 g. (0.084 mole) of the above product in 250 ml. of water and 250 ml. of ether was acidified to *p*H 3 with hydrochloric acid. The ethereal layer was dried (magnesium sulfate), the ether removed, and the residue on recrystallization (methanol) gave 24.8 g., (88%) of 2-lauroylindandione-1,3, m.p. 45–46° (compound 29).

N-Methylglucamine salt of 2-lauroylindandione-1,3, (Compound 30). The mixture of 8 g. (0.024 mole) of 2-lauroylindandione-1,3 and 4.76 g. (0.024 mole) of *N*-methylglucamine in 15 ml. of methanol dissolved after 60 min. heating on the steam bath. The methanol was removed and the residue recrystallized (isopropyl alcohol) to give 6.5 g. (51%) of product, m.p. 90–94°.

2-(Cyclopropylketo)indandione-1,3 (*Compound 22*). *Method D.* A solution of 5.75 g. (0.25 mole) of sodium in methanol was prepared and the methanol removed. Benzene (150 ml.) was added and residual methanol removed by azeotropic distillation. After addition of 21 g. (0.25 mole) of methyl cyclopropyl ketone and 48.5 g. (0.25 mole) of dimethyl phthalate in 125 ml. of benzene, the reaction mixture was heated under reflux for 6 hr. with stirring. After steam distillation, the nonvolatile residue was diluted with one l. of water, filtered, and the product precipitated by acidification with hydrochloric acid to *p*H 3. Recrystallization (acetone-water) gave 16 g. (30%) of product, m.p. 132–134°.

Acknowledgment. The authors wish to thank Dr. G. Ungar and his staff for the pharmacological screening of the compounds, M. Blitz and R. Levinton for the antibacterial results, and D. Farkas for the ultraviolet absorption data.

YONKERS 1, N. Y.

[CONTRIBUTION FROM PLASTICS LABORATORY AND RESEARCH CENTER, MINNEAPOLIS-HONEYWELL REGULATOR CO.]

Reaction of Aniline with 3-Phenoxy-1,2-epoxypropane

LEMONT B. KIER[1] AND RAYMOND B. PENLAND[2]

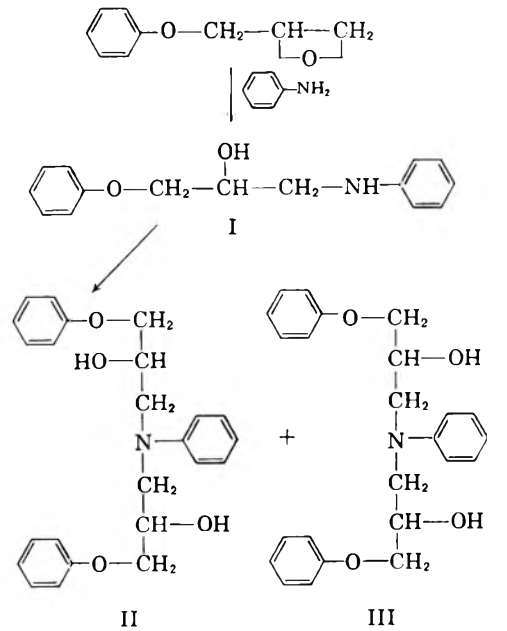
Received December 21, 1959

The products from the reaction of aniline and 3-phenoxy-1,2-epoxypropane have been characterized. One compound was shown to be a secondary amine and the other two to be the *dl* and *meso* forms of a tertiary amine. The structures were proved by independent synthesis.

In order to study the reaction between polyfunctional epoxides and polyfunctional aromatic amines in the formation of resins, a study was made of the model reaction between 3-phenoxy-1,2-epoxypropane and aniline. Fourneau[3] reported one compound from this reaction to which he assigned the structure I; however he reported no evidence for his assignment.

From the direct reaction of 3-phenoxy-1,2-epoxypropane and aniline, the authors have obtained three crystalline products, I, II, and III. Compound I proved to be a secondary amine, while II and III, not previously reported, were higher molecular weight tertiary amines. By the reaction of I with a second mole of 3-phenoxy-1,2-epoxypropane, II and III were formed, indicating that the original model reaction involved two steps.

The infrared spectrum of I indicated it to be a secondary aminoalcohol in conformance with Fourneau's assignment, and the spectra of II and III, which were identical, indicated that they were tertiary aminoalcohols, hence must be related as the *dl* and *meso* forms. The structures of I,

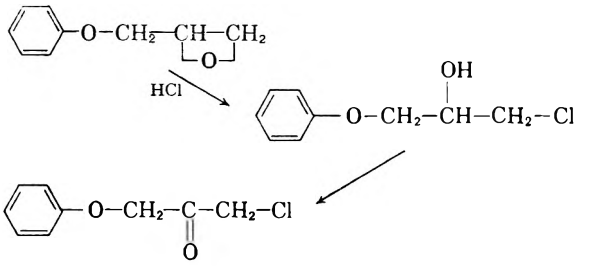


(1) Present address: College of Pharmacy, University of Florida, Gainesville, Fla.

(2) Present address: U. S. Borax Research, Anaheim, Calif.

(3) E. Fourneau, *J. Pharm. Chem.*, 1, 99 (1910).

II, and III were proven by an independent synthesis[4,5] using 3-phenoxy-2-hydroxypropyl chloride IV prepared by the reaction of 3-phenoxy-1,2-epoxypropane and hydrochloric acid. Proof of the structure of IV was made by oxidation to the haloketone V which was identified by its infrared spectrum.



The reaction of IV with aniline gave a product which proved to be identical with I. This product was treated with additional IV to give two compounds which were found to be identical with II and III. Attempts to resolve either II or III to prove which one was the *dl* were unsuccessful. A quantity of the (+) form of I was prepared by separation of the diastereoisomers formed with *d*-camphor sulphonic acid. This (+) I was treated with 3-phenoxy-1,2-epoxypropane to give two tertiary aminoalcohols, one of which was optically active. The optically active product must be a resolved form of II which is the *dl* form.

EXPERIMENTAL

Model reaction of aniline and 3-phenoxy-1,2-epoxypropane. Aniline (6.2 g., 0.067 mole) was treated with 3-phenoxy-1,2-epoxypropane (10 g., 0.067 mole) at 95° in an oven for 16 hr. The product was a dark resinous material which eventually crystallized. The crude product was fractionally crystallized from methanol-water yielding three products: I, 4.0 g., m.p. 56–57°, yield 25%; II, 3.0 g., m.p. 87–88°, III, 3.0 g., m.p. 96–97°, yields for both 23% based on 3-phenoxy-1,2-epoxypropane.

3-Phenoxy-1-anilino-propan-2-ol (I). The material for analysis was recrystallized from methanol-water four times, giving needles, m.p. 56–57°.

Anal. Calcd. for $C_{15}H_{17}NO_2$: C, 74.04; H, 7.04; N, 5.76; Mol. wt., 243. Found: C, 74.22; H, 6.98; N, 5.70; Mol. wt., 250 (Rast camphor).

The infrared spectrum (potassium bromide pellet) had a band at 7.75 μ (sec-amine C—N).

A *picrate* of I was prepared and recrystallized from ethanol as yellow plates, m.p. 127–129°.

Anal. Calcd. for $C_{21}H_{20}N_4O_9$: C, 53.39; H, 4.27; N, 11.86. Found: C, 53.53; H, 4.30; N, 11.68.

dl-N,N-Di(3-phenoxy-2-hydroxypropyl) aniline (II). The material was recrystallized several times from methanol-water to give needles, m.p. 87–88°.

Anal. Calcd. for $C_{24}H_{27}NO_4$: C, 73.26; H, 6.92; N, 3.56, Mol. wt., 394. Found: C, 73.53; H, 6.70; N, 3.68; Mol. wt., 412 (Rast camphor).

The infrared spectrum had a band at 7.40 μ (*tert*-amine C—N).

A *picrate* of II was prepared and recrystallized from ethanol as yellow needles, m.p. 125–127°.

Anal. Calcd. for $C_{30}H_{30}N_4O_{11}$: C, 57.87; H, 4.86; N, 9.00. Found: C, 57.76; H, 4.80; N, 8.83.

meso-N,N-Di(3-phenoxy-2-hydroxypropyl) aniline (III). This material was isolated from the final mother liquor and recrystallized four times from methanol-water as transparent plates, m.p. 96–97°.

Anal. Calcd. for $C_{24}H_{27}NO_4$: C, 73.26; H, 6.92; N, 3.56; Mol. wt., 394. Found: C, 73.10; H, 6.72; N, 3.62; Mol. wt., 406 (Rast camphor).

The infrared spectrum showed a band at 7.40 μ (*tert*-amine C—N).

A *picrate* derivative of III was recrystallized from ethanol as yellow needles m.p. 137–139°.

Anal. Calcd. for $C_{30}H_{30}N_4O_{11}$: C, 57.87; H, 4.86; N, 9.00. Found: C, 57.83; H, 4.91; N, 8.87.

Reaction of I *with 3-phenoxy-1,2-epoxypropane.* Compound I (6.85 g., 0.028 mole) and 3-phenoxy-1,2-epoxypropane (4.05 g., 0.027 mole) were allowed to react at 120° in an oven overnight. The resinous solid was recrystallized to give 4.7 g., 43% yield, of a compound, m.p. 96–97° and 4.7 g., 43% yield of a compound, m.p. 87–88°. Both of these compounds gave no depression in mixed melting point with their respective products II and III from the model reaction.

3-Phenoxy-2-hydroxypropyl chloride. Hydrochlorination of 3-phenoxy-1,2-epoxypropane to the corresponding chlorohydrin, 3-phenoxy-2-hydroxypropyl chloride IV, was accomplished with dry hydrogen chloride.[6,7] The conversion was almost quantitative, b.p. 136–137° (8 mm.), n_D^{24} 1.5410, d_4^{24} 1.210. Literature values[8]: b.p. 125–126° (2 mm.), n_D^{25} 1.540, d_4^{25} 1.209; and[9] b.p. 153–155° (12.5 mm.), n_D^{25} 1.542, $d_4^{23.5}$ 1.210.

Anal. Calcd. for $C_9H_{11}ClO_2$: C, 57.90; H, 5.94; Cl, 18.00. Found: C, 58.03; H, 6.11; Cl, 18.75.

Oxidation of IV *to ketone.* To prove the secondary hydroxyl of IV, it was oxidized with chromium trioxide in sulfuric acid[10] to give the corresponding ketone V, b.p. 145–146° (12 mm.). The infrared spectrum had a strong band at 5.73 μ (α-halo ketone). The absence of a band at 3.45–3.70 μ (aldehyde C—H) indicated that the 3-phenoxy-1-hydroxy-2-chloropropane isomer was not formed.

Anal. Calcd. for $C_9H_9ClO_2$: C, 58.65; H, 4.92; Cl, 19.23. Found: C, 58.48; H, 5.11, Cl, 18.95.

Independent synthesis of I. Aniline (42 g., 0.45 mole) was treated with IV (37.4 g., 0.2 mole) at 125° for 7 hr. The amines were dissolved in dilute acid, washed, then rendered alkaline to recover them. The aniline was removed by distillation and the residue recrystallized from methanol-water to give 18 g. (37% yield based on IV) of product, m.p. 56–57°. A mixed melting point with I gave no depression. A comparison of the infrared spectra of the two compounds indicated that they were identical.

Anal. Calcd. for $C_{15}H_{17}NO_2$: C, 74.04; H, 7.04; N, 5.76; Mol. wt., 243. Found: C, 73.92; H, 6.79; N, 5.94: Mol. wt., 237 (Rast camphor).

Independent synthesis of II *and* III. Compound I (48.5 g., 0.2 mole) was refluxed with IV (18.7 g., 0.1 mole) in 50 ml. of xylene at 120° for 10 hr. The reaction mixture was recrystallized from methanol-water to give 7 g. product identical with II (30% yield) and 7 g. of product identical with III (30% yield).

Anal. of product identical with II. Calcd. for $C_{24}H_{27}NO_4$: C, 73.26; H, 6.92; N, 3.56. Found: C, 72.94; H, 6.65; N, 3.59.

(4) R. T. E. Schenck, and S. Karzerman, *J. Am. Chem. Soc.*, **75**, 1636 (1953).

(5) F. G. Ponomareau, *Zhur. Obshchei Khim.*, **23**, 1638 (1953).

(6) M. Dalfe, *J. Chem. Soc.*, 1861 (1950).

(7) O. J. Stephanson, *J. Chem. Soc.*, 1571 (1954).

(8) A. Fairbourne, *J. Chem. Soc.*, 1965 (1932).

(9) E. Levas, *Compt. rend.*, **222**, 555 (1946).

(10) J. B. Conant, and O. R. Quayle, *Org. Syntheses*, Coll. Vol. I, 206 (1932).

Anal. of product identical with III. Calcd. same as above. Found: C, 73.06; H, 6.95; N, 3.52.

Both of these compounds, as well as their picrates gave no depression in melting point when compared with the corresponding compounds from the model reaction. The infrared spectra of the corresponding products were identical.

d-Camphor sulfonate of I. *d*-Camphor sulfonic acid (23.2 g., 0.1 mole) was dissolved in ethyl acetate containing I (24.3 g., 0.1 mole). From the solution, 20 g., (42% yield) of white crystalline material formed, m.p. 154.5–155.5°.

Anal. Calcd. for $C_{25}H_{33}NO_6S$: C, 63.16; H, 6.99; N, 2.95; S, 6.74. Found: C, 63.15; H, 7.13: N, 3.03; S, 6.73.

The diastereoisomer was not isolated since only one active form of I was needed.

(+) I. The *d*-camphor sulfonate salt (8 g., 0.017 mole) was dissolved in 200 ml. of benzene and refluxed with stirring with 100 ml. of 5% sodium hydroxide for 2 hr. The benzene was washed with water and concentrated to dryness. The residue was taken up in naphtha and refrigerated. Several crops of amorphous material formed totalling 2.6 g., (63.5% yield). After several recrystallizations from methanol-water a white crystalline material formed, m.p. 62–63.5°, $[\alpha]_D^{25}$ + 17.16° (c, 2.25 methanol).

Anal. Calcd. for $C_{15}H_{17}NO_2$: C, 74.04; H, 7.04; N, 5.76. Found: C, 74.10; H, 6.89; N, 5.81.

Reaction of (+) *I with 3-phenoxy-1,2-epoxypropane.* The active I (2.6 g., 0.0107 mole) was treated with 3-phenoxy-1,2-epoxypropane as before. Two products were isolated. The first, m.p. 96–97°, gave no mixed melting point depression with III and was optically inactive. The second compound, m.p. 84.5–85.5°, $[\alpha]_D^{25}$ +23.5° (*c*, 3.45 methanol) gave a marked mixed melting point depression with II.

Anal. of compound m.p. 84.5–85.5°. Calcd. for $C_{24}H_{27}NO_4$: C, 73.26; H, 6.92; N, 3.56. Found: C, 73.08; H, 6.90; N, 3.76.

Acknowledgment. We are grateful to L. L. Bolstad and P. A. Joyner for their assistance with this work.

MINNEAPOLIS, MINN.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN CO.]

Some Reactions of Mannich Bases Derived from α-Phenoxyacetophenone and α-Phenoxypropiophenone

JOHN B. WRIGHT

Received April 6, 1960

Mannich bases (I) derived from α-phenoxyacetophenone on treatment with polyphosphoric acid were converted in good yields to 2-dialkylaminomethyl-3-phenylbenzofurans (II). The carbinols (III), obtained by catalytic hydrogenation or by treatment of the Mannich bases with Grignard reagents, on treatment with polyphosphoric acid in a similar manner gave the corresponding dihydrobenzofurans (IV). The carbinols were also acylated (V) and several converted to urethanes (VI) by conventional procedures. Attempted acylation of one of the carbinols, namely 1,1-diphenyl-2-phenoxy-2-methyl-3-dimethylaminopropanol (III. R_2 = C_6H_5, R_1 = CH_3, R = CH_3) gave in good yield a nitrogen-free product which was identified as 1,1-diphenyl-2-phenoxypropene (VIII). Heating under reflux with dimethylaniline was found to be a convenient method for converting the Mannich bases (I) to α-phenoxyacrylophenones (VII).

Mannich bases (I) derived from α-phenoxyacetophenone and α-phenoxypropiophenone are prepared readily in good yield.[1,2] They are readily hydrogenated under catalytic conditions to the corresponding carbinols (III. R_2 = H).[1,3] We wish to report now on some further reactions of these compounds.

Reaction of the Mannich bases (I) with polyphosphoric acid, according to the method used by Davies and Middleton[4,5] to prepare phenylbenzofuran from α-phenoxyacetophenone, gave in good yield the corresponding 2-dialkylaminomethyl-3-phenylbenzofurans (II). These compounds, isolated as the *hydrochlorides*, are listed in Table I.

Reaction of the Mannich bases (I) with Grignard reagents gave the corresponding tertiary carbinols (III). These compounds are listed in Table II. In those cases where reaction with the Grignard reagent produced a new asymmetric carbon atom a mixture of diastereoisomers was produced and some difficulty was experienced in separating the two isomers. Treatment of several of the carbinols (III) with polyphosphoric acid in the manner described above gave the corresponding 3-phenyl-2-dialkylaminodihydrobenzofurans (IV, Table III). In the preparation of these compounds a simple dehydration of the carbinols (III. where R_1 = H) to give an isomeric substituted styrene is also possible; however, the dihydrobenzofuran structure is assigned on the basis of the ultraviolet absorption data obtained for these compounds.

The carbinols (III) when treated with acetic anhydride or propionic anhydride in the presence of pyridine gave the corresponding acylated compounds (V). Treatment of the carbinols with phenyl chlorocarbonate followed by cleavage of the resulting product with liquid ammonia gave the

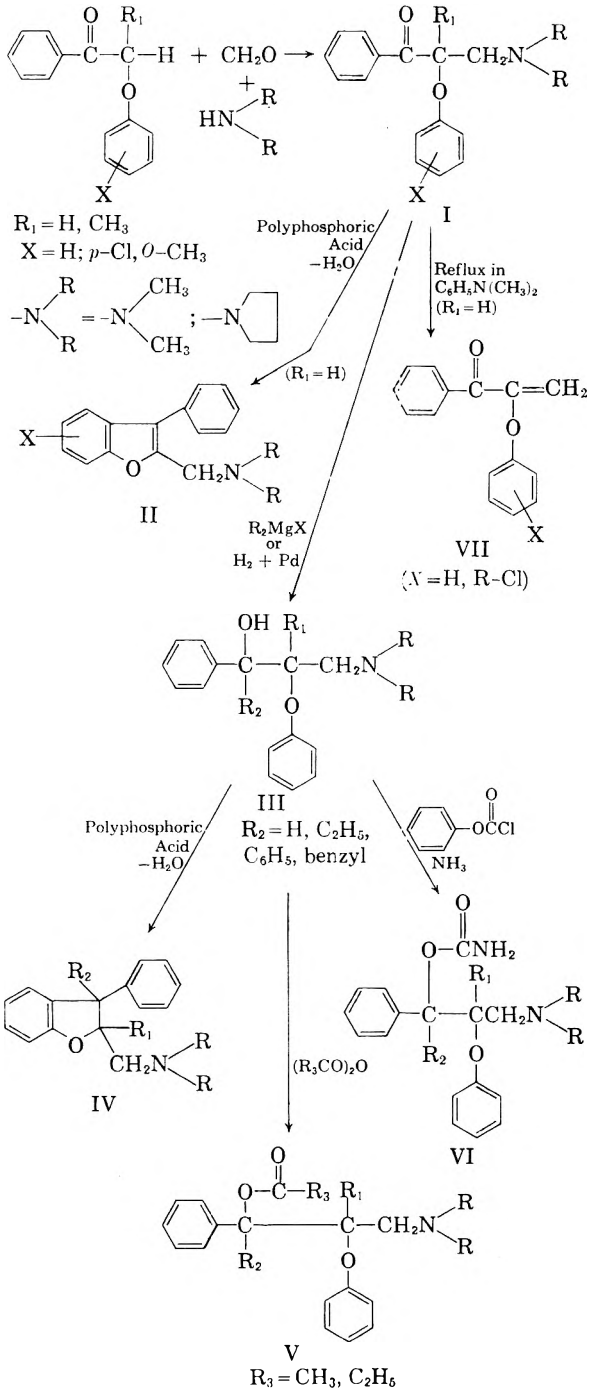
(1) J. B. Wright and E. H. Lincoln, *J. Am. Chem. Soc.*, 74, 6301 (1952).

(2) U. S. Patent 2,655,542.

(3) U. S. Patent 2,695,919.

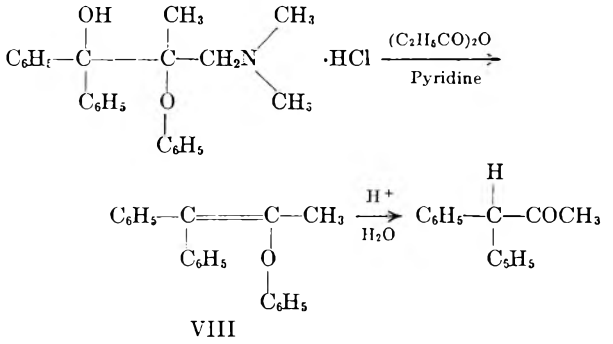
(4) W. Davies and S. Middleton, *Current Trends in Heterocyclic Chemistry*, Academic Press, Inc., New York, N.Y., 1958, p. 58.

(5) W. Davies and S. Middleton, *J. Chem. Soc.*, 822 (1958).



corresponding urethanes (VI). The compounds of the type V and VI that were prepared are listed in Table IV.

In the attempted acylation of 1,1-diphenyl-2-phenoxy-2-methyl-3-dimethylaminopropanol-1 hydrochloride (III. $R_2 = C_6H_5$, $R_1 = CH_3$, $R = CH_3$) with propionic anhydride and pyridine, according to the method that was used to prepare compounds of type V, none of the desired product was obtained but rather a *nitrogen-free* product, in very good yield. The empirical formula of this product, according to microanalysis, was $C_{21}H_{18}O$. The structure of this compound appears to be 1,1-diphenyl-2-phenoxypropene (VIII) on the basis of its infrared and ultraviolet spectra and the fact that on acid hydrolysis it gave diphenylacetone.



The nature of this reaction is not clear at the present time. However, it appears to be limited to carbinols of the type III that contain a methyl group ($R_1 = CH_3$) that may sterically block reaction at the hydroxyl grouping.

It was previously shown[1,6] that attempted distillation of β-piperidino-α-phenoxypropiophenone (I. $-N<^{R}_{R}$ = piperidino) resulted in the elimination of piperidine with the formation of α-phenoxyacrylophenone (VII. X = H). It has been found that this reaction may be carried out more conveniently and in a better yield by refluxing the Mannich base (I) in dimethylaniline for a short period of time. By means of this method α-phenoxyacrylophenone and *p*-chloro-α-phenoxyacrylophenone (VII. X = *p*-Cl) were prepared from the corresponding Mannich bases in yield of 85% and 65%, respectively.

EXPERIMENTAL[7,8]

α-Phenoxy-p-chloropropiophenone. To a stirred solution of 122.4 g. of *p*-chloropropiophenone in 500 ml. of anhydrous ether cooled in an ice bath was added dropwise 116 g. of bromine. The solution was washed with water, dried over anhydrous magnesium sulfate, and the ether removed. To the flask containing the crude bromoketone (177.5 g.; m.p. 77–80°) was added 68.5 g. of phenol, 134.3 g. of potassium carbonate, and 1450 ml. of acetone and the mixture heated under reflux for 7 hr. To the cooled reaction mixture was added 1400 ml. of water and the mixture extracted with ether. The ethereal extracts were washed with 10% sodium hydroxide, dried over anhydrous magnesium sulfate, and the ether removed. The residual solid was recrystallized from

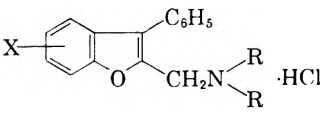
(6) J. B. Wright and E. H. Lincoln, *J. Am. Chem. Soc.*, 80, 6697 (1958).

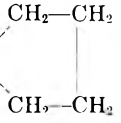
(7) All melting points reported are uncorrected and were taken in a capillary tube.

(8) We are indebted to Mr. William Struck and his coworkers of these laboratories for the microanalytical data and to Mr. Marvin Grostic and Mr. James Stafford of these laboratories for infrared and ultraviolet spectral determinations. Our thanks are due especially to Mr. Albert Lallinger for technical assistance and to Dr. Richard Heinzelman for suggestions and discussions.

TABLE I

2-DIALKYLAMINOMETHYL-3-PHENYLBENZOFURAN HYDROCHLORIDES

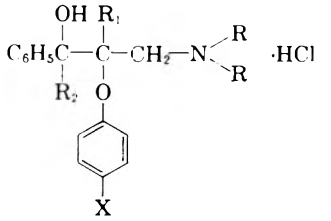


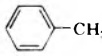
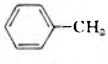
X	R	M.P.	Yield, %	Formula	Calcd. C	H	Cl	N	Found C	H	Cl	N
H[a]	$-N(CH_3)_2$[a]	187.5–188.5[a]	97	$C_{17}H_{17}NO\cdot HCl$	70.95	6.30	12.32	4.87	70.86	6.64	12.23	4.74
H	$-N(C_2H_5)_2$	158.5–159.5	87	$C_{19}H_{21}NO\cdot HCl$	72.25	7.02	11.23	4.44	72.06	7.02	11.14	4.80
H		181.5–182.5	87	$C_{19}H_{19}NO\cdot HCl$	72.71	6.42	11.30	4.46	72.78	6.21	11.20	4.74
5-Cl	$-N(CH_3)_2$	206.5–207.0	94.5	$C_{17}H_{16}ClNO\cdot HCl$	63.36	5.32	22.02		62.68	5.23	21.81	
7-CH_3O	$-N(C_2H_5)_2$	212.5–214	85	$C_{20}H_{23}NO_2\cdot HCl$	69.45	6.99	10.25	4.05	69.45	7.16	10.26	4.33

[a] The free base is a solid melting at 64.5–65.5° after recrystallization from ethanol-water (2:1). *Anal.* Calcd. for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.36; H, 7.04; N, 5.49.

TABLE II

3-AMINO-2-PHENOXY-1-PHENYLPROPANOL HYDROCHLORIDES



R_2	R_1	X—NR_2	Procedure	Yield, %	M.P. °C.	Formula	Calcd. C	H	Cl	N	Found C	H	Cl	N
C_6H_5	H	H—$N(CH_3)_2$	..	45	176–176.5	$C_{19}H_{25}NO_2\cdot HCl$	67.94	7.80	10.56	4.17	68.27	7.57	10.41	4.41
C_6H_5	H	H—$N(CH_3)_2$	A	69	100° (dec.)[a]	$C_{23}H_{25}NO_2\cdot HCl$	71.96	6.83	9.23	..	72.13	6.81	8.98	..
C_6H_5	H	Cl—$N(CH_3)_2$	A	27	92–94°[b]	$C_{23}H_{24}ClNO_2$[c]	72.34	6.33	9.28	3.67	72.17	6.23	9.66	3.48
C_6H_5	CH_3	H—$N(CH_3)_2$	A	47	126.5–127.5[b]	$C_{24}H_{27}NO_2$[c]	79.74	7.53	...	3.87	79.64	7.53	...	3.83
	H	H—$N(CH_3)_2$	A	27	233–235°	$C_{24}H_{27}NO_2\cdot HCl$[c]	72.43	7.09	8.91	3.52	72.30	7.62	9.03	3.65
	CH_3	H Pyrrolidino	A	37	231–231.5	$C_{27}H_{31}NO_2\cdot HCl$[d]	74.04	7.37	8.09	3.20	73.88	6.89	8.03	3.47

[a] The free base melted at 89.5–90.5° after recrystallization from ethanol. *Anal.* Calcd. for $C_{23}H_{25}NO_2$: C, 79.51; H, 7.25; N, 4.03. Found: C, 79.40; H, 7.17; N, 4.01. [b] Recrystallized from ethanol. These are the melting points of the free base. [c] Only the free base was prepared. [d] Recrystallized from methyl ethyl ketone–anhydrous ethanol (5:2). [e] Recrystallized from a methanol–ethyl acetate mixture (1:4).

ethanol. There was obtained 163.7 g. (87%) of colorless needles melting at 83–84°. Additional recrystallization from ethanol raised the melting point to 85–86°.

Anal. Calcd. for $C_{15}H_{13}ClO_2$: C, 69.10; H, 5.02; Cl, 13.60. Found: C, 69.20; H, 5.13; Cl, 13.31.

α-p-Chlorophenoxy-p-chloropropiophenone was prepared according to the procedure given above for α-phenoxy-*p*-chloropropiophenone, using an equivalent amount of *p*-chlorophenol; yield, 76%; m.p. 94.5–95.0° after recrystallization from ethanol.

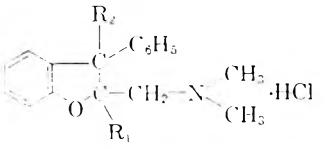
Anal. Calcd. for $C_{15}H_{12}Cl_2O_2$: C, 61.04; H, 4.10; Cl, 24.02. Found: C, 61.10; H, 4.41; Cl, 24.02.

Preparation of Mannich bases. The preparation of several of the Mannich bases used as starting materials has been described elsewhere.[1] Those that were not prepared previously are listed in Table V. The general methods described previously[1] were used for the preparation of these compounds.

N,N-Dimethyl(2-phenoxy-3-hydroxy-3-phenyl)amylamine hydrochloride. To a solution of ethylmagnesium bromide in ether, prepared from 3.65 g. (0.15 mole) of magnesium, 16.35 g. (0.15 mole) of ethyl bromide and 50 ml. of ether was added 10 ml. of dry benzene. Then, keeping the inner temperature below 0°, there was added a solution of 13.45 g. (0.05 mole) of β-dimethylamino-α-phenoxypropiophenone[1] in 40 ml. of dry benzene. Heat was applied and the ether removed until the inner temperature reached 65°. The mixture was hydrolyzed by pouring into a cold solution of 15%

TABLE III

2-DIMETHYLAMINOMETHYL-3-PHENYL-2,3-DIHYDROBENZOFURAN HYDROCHLORIDES

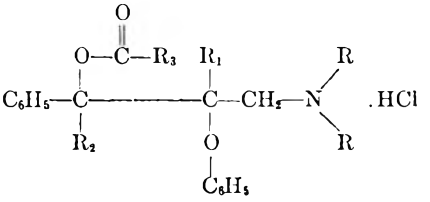


R_1	R_2	M.P.	Yield, %	Formula	Calcd. C	Calcd. H	Calcd. Cl	Calcd. N	Found C	Found H	Found Cl	Found N
H	H	216.5–217	38	$C_{17}H_{19}NO \cdot HCl$	70.46	6.96	12.23	4.83	70.25	7.27	12.24	4.84
CH_3	H	201 (dec.)	59	$C_{18}H_{21}NO \cdot HCl$[a]	71.16	7.30	11.67	..	70.48	7.35	11.41	..
H	C_6H_5	267 (dec.)[b]	69[b]	$C_{23}H_{23}NO \cdot HCl$[c]	75.50	6.61	9.69	3.83	75.52	6.47	9.68	3.84
CH_3	C_6H_5	269 (dec.)	94	$C_{24}H_{25}NO \cdot HCl$[d]	75.87	6.90	9.33	3.69	75.97	7.03	9.42	3.76

[a] Recrystallized from an ethanol–methyl ethyl ketone (1:15) mixture. [b] The free base melted at 109–109.5° after recrystallization from ethanol. *Anal.* Calcd. for $C_{23}H_{23}NO$: C, 83.86; H, 7.04; N, 4.25. Found: C, 83.90; H, 7.63; N, 4.16. [c] Recrystallized from isopropanol. [d] Recrysta.lized from an anhydrous ethanol–ethyl acetate (1:1) mixture.

TABLE IV

3-ACYLOXY-3-PHENYL-2-PHENOXYPROPYL AMINE HYDROCHLORIDES



R_3	R_2	R_1	$-N(R)(R)$	Procedure	Yield, %	M.P.	Formula	Calcd. C	Calcd. H	Calcd. Cl	Calcd. N	Found C	Found H	Found Cl	Found N
CH_3	C_6H_5	H	$-N(CH_3)_2$	B	19	179–80[a]	$C_{25}H_{27}NO_3 \cdot HCl$	—	—	8.32	3.29	—	—	8.25	3.26
NH_2	C_6H_5	H	$-N(CH_3)_2$	C	42	178 (dec.)[b]	$C_{24}H_{26}N_2O_3 \cdot HCl$	67.51	6.38	8.30	6.56	67.62	6.56	8.20	6.42
NH_2	H	H	$-N(CH_3)_2$	C[e]	45	169–170[c]	$C_{18}H_{22}N_2O_3$[d]	68.76	7.06	—	8.91	69.04	7.23	—	8.64
C_2H_5  $-CH_2$		H	$-N(CH_3)_2$	B	34	204–206.5[f]	$C_{27}H_{31}NO_3 \cdot HCl$	71.42	7.10	7.81	3.09	71.63	7.03	7.77	2.96

[a] Recrystallized from methyl ethyl ketone. [b] Recrystallized from anhydrous ethanol–ether (1:3). The free base melted at 133–135° after recrystallization from petroleum ether (b.p. 60–71°)–anhydrous ethanol (20:1). *Anal.* Calcd. for $C_{24}H_{26}N_2O_3$: C, 73.82; H, 6.71; N, 7.18. Found: C, 74.10; H, 6.45; N, 7.08. [c] Recrystallized from ethanol. This is the melting point of the free base. [d] The hydrochloride was not prepared. [e] Benzene was used in place of the ether for extraction of the compound. [f] Recrystallized from acetone.

ammonium chloride. The benzene layer was separated and the aqueous layer extracted with benzene. The benzene was removed by distillation. The residue after standing in the refrigerator for some time partially solidified. The mixture was triturated with petroleum ether (b.p. 29–38°), the solid recovered by filtration and recrystallized from methanol. There was obtained 6.78 g. (45%) of colorless prisms melting at 99.5–100.5°.

Anal. Calcd. for $C_{19}H_{25}NO_2$: N, 4.68. Found: N, 4.73.

The *hydrochloride* was prepared by adding an ethereal hydrogen chloride solution to a solution of the free base in ether. After recrystallization from methyl ethyl ketone there was obtained colorless needles melting at 176–176.5°.

Anal. Calcd. for $C_{19}H_{25}NO_2HCl$: C, 67.94; H, 7.80; Cl, 10.56; N, 4.17. Found: C, 68.27; H, 7.57; Cl, 10.41; N, 4.41.

The methanolic mother liquors from the recrystallization of the free base on long standing in the refrigerator deposited 1.47 g. of material melting at 54–55.5°. This was converted to its *hydrochloride* salt and the latter recrystallized repeatedly from ethyl acetate–methyl ethyl ketone (1:1). There was obtained 250 mg. of fine colorless needles melting at 190–191°.

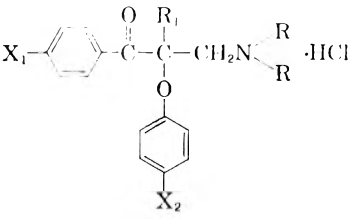
Anal. Calcd. for $C_{19}H_{25}NO_2 \cdot HCl$: Cl, 10.56; N, 4.17. Found: Cl, 10.84; N, 4.38.

Procedure A. α-(2-Dimethylamino-1-methyl-1-phenoxyethyl)benzhydrol hydrochloride. To a stirred solution of phenylmagnesium bromide (0.2 mole) in 150 ml. of ether was added dropwise a solution of 31.9 g. (0.1 mole) of α-phenoxy-β-dimethylaminopropiophenone in 100 ml. of ether. The mixture was stirred and heated under reflux for an hour and was then decomposed with 150 ml. of a 20% ammonium chloride solution. The ether layer was separated and the aqueous layer extracted with ether. The combined ethereal extracts were dried over anhydrous magnesium sulfate, the drying agent removed by filtration, and the hydrochloride precipitated by the addition of an ethereal hydrochloric acid solution.

Procedure B. 1,2-Diphenyl-3-phenoxy-4-dimethylamino-2-butylpropionate hydrochloride. A mixture of 3.98 g. (0.01 mole) of 1,2-diphenyl-3-phenoxy-4-dimethylamino-2-buta-

TABLE V

MANNICH BASE HYDROCHLORIDES



X_1	X_2	R_1	—NR_2	Yield, %	M.P.	Formula	Calcd. C	Calcd. H	Calcd. N	Calcd. Cl	Found C	Found H	Found N	Found Cl
H	H	H	pyrrolidino	—	157.5–158.0[a]	$C_{19}H_{21}NO_2 \cdot HCl$	68.77	6.68	4.22	10.68	68.88	6.60	4.32	10.65
H	H	CH_3	pyrrolidino	—	181[b]	$C_{20}H_{23}NO_2 \cdot HCl$	69.45	6.99	4.05	10.25	69.21	7.20	3.93	10.12
H	Cl	H	—$N(CH_3)_2$	77[d]	164–165[c]	$C_{17}H_{18}ClNO_2 \cdot HCl$	60.01	5.63	4.11	20.84	59.78	5.65	4.21	20.95
Cl	H	CH_3	—$N(CH_3)_2$	72[d,f]	138–139[a]	$C_{18}H_{20}ClNO_2 \cdot HCl$	61.02	5.98	3.95	20.02	60.85	6.01	4.11	19.95
Cl	Cl	CH_3	—$N(CH_3)_2$	97[d,f]	182[e]	$C_{18}H_{19}Cl_2NO_2 \cdot HCl$	55.61	5.19	3.60	27.36	55.75	5.16	3.38	27.43

[a] Recrystallized from acetone. [b] Recrystallized from methyl ethyl ketone–ethanol (3:1). [c] Recrystallized from methyl ethyl ketone–ethanol (1:1). [d] The yield is based upon the amount of propiophenone actually used in the reaction. [e] Recrystallized from ethanol. [f] Procedure B of reference 1 was employed.

nol hydrochloride, 4 ml. of propionic anhydride, and 4 ml. of pyridine was heated under reflux for 4 hr. The mixture was allowed to cool, anhydrous ether was added, and the solid removed by filtration and purified by recrystallization.

Procedure C. α-(2-Dimethylamino-1-phenoxyethyl)benzhydryl carbamate hydrochloride. To a stirred ice-cooled solution of 31.9 g. (0.09 mole) of α-(2-dimethylamino-1-phenoxyethyl)benzhydrol in 36 ml. of dry pyridine was added dropwise 14.04 g. (0.09 mole) of phenyl chlorocarbonate. This suspension was added with stirring to about 200 ml. of liquid ammonia over a period of about 0.5 hr. The mixture was stirred at reflux for 8 hr. using a Dry Ice condenser. The ammonia was allowed to evaporate overnight. Water and ether were added to the mixture. The ether layer was separated and the aqueous layer extracted with ether. The combined ethereal extracts were washed twice with a 5% sodium hydroxide solution, once with a saturated salt solution and dried over anhydrous magnesium sulfate. The ether was removed by distillation. The residual oil solidified upon standing and was purified by recrystallization. The free base was dissolved in ether and the hydrochloride precipitated by the addition of a saturated ethereal hydrogen chloride solution.

Procedure for 2-dialkylaminomethyl-3-phenylbenzofuran hydrochlorides. 2-Diethylaminomethyl-3-phenylbenzofuran hydrochloride. Into a three-necked flask was weighed 308 g. of polyphosphoric acid.[9] The flask was fitted with a stirrer and a drying tube and heated on the steam bath. To the stirred polyphosphoric acid was added 30.8 g. (one tenth of the weight of acid) of α-phenoxy-β-diethylaminopropiophenone hydrochloride.[1] Effervescence took place immediately and the mixture became red in color. The mixture was heated on the steam bath with stirring for 2.5 hr. To the reaction mixture when cool was added 150 g. of ice, with stirring, as soon as this became possible. The mixture was transferred to a large beaker, ice and water were added, and the acid neutralized by the addition of a sodium hydroxide solution. Additional water was added to make the mixture sufficiently fluid for extraction.

The mixture was extracted with ether, the ethereal extracts dried over anhydrous magnesium sulfate, the drying agent removed by filtration, and the hydrochloride precipitated by the addition of an ethereal hydrogen chloride solution. The product was purified by recrystallization from acetone.

The compounds listed in Table I were prepared by this general procedure.

Procedure for 2-dimethylaminomethyl-3-phenyl-2,3-dihydrobenzofuran hydrochlorides. 2-Dimethylaminomethyl-3-phenyl-2,3-dihydrobenzofuran hydrochloride. Ten grams of 3-dimethylamino-1-phenyl-2-phenoxypropanol-1 hydrochloride[1] was heated with ten times its weight of polyphosphoric acid according to the procedure described above for 2-diethylaminomethyl-3-phenylbenzofuran hydrochloride. Using the requisite carbinol all of the compounds listed in Table III were prepared in this general way.

Attempted preparation of 1,1-diphenyl-2-phenoxy-2-methyl-3-dimethylaminopropylpropionate hydrochloride. Preparation of 1,1-diphenyl-2-phenoxypropene. A mixture of 17.4 g. (0.046 mole) of 1,1-diphenyl-2-phenoxy-2-methyl-3-dimethylaminopropanol-1-hydrochloride (prepared by adding gaseous hydrogen chloride to an ethereal solution of the free base), 15 ml. of dry pyridine and 15 ml. of propionic anhydride was heated under reflux for 2 hr. The mixture when cool was diluted with an excess of anhydrous ether. The solution was decanted from the small amount of oil that precipitated, was washed with water, and the ether removed. The yellow solid residue was recrystallized from ethanol. There was obtained 7.27 g. (55%) of colorless prisms melting at 61–62.5°. Additional recrystallizations from ethanol raised the melting point to 64–65°.

Anal. Calcd. for $C_{21}H_{18}O$: C, 88.08; H, 6.34. Found: C, 88.33; H, 6.64.

One gram of the product was heated under reflux for 2 hr. with 1.1 ml. of concd. hydrochloric acid, 4 ml. of water, and 20 ml. of ethanol. The alcohol was removed *in vacuo*. The residue was diluted with water, made basic with a solution of sodium carbonate, and extracted with ether. The ethereal extracts were washed with a 5% sodium hydroxide solution and dried over anhydrous magnesium sulfate. The crude solid was recrystallized from petroleum ether (b.p. 60–71°). There were obtained colorless prisms melting at 58.5–59.5° which gave no depression when mixed with an authentic sample of diphenylacetone. The infrared spectrum of the compound was identical with that from diphenylacetone.

Anal. Calcd. for $C_{15}H_{14}O$: C, 85.68; H, 6.71. Found: C, 85.50; H, 6.70.

(9) Obtained from The Victor Chemical Company—115% Ortho equivalent.

α-Phenoxyacrylophenone.[1,6] A mixture of 50 g. (0.186 mole) of β dimethylamino-α-phenoxypropiophenone[1] and 50 ml. of *N,N*-dimethylaniline was heated under reflux for 1 hr. After cooling to room temperature the reaction mixture was dissolved in 300 ml. of ether and the ethereal solution extracted twice with 400 ml. of 1*N* hydrochloric acid. The ethereal solution was dried over anhydrous magnesium sulfate, the ether removed, and the residue recrystallized from ethanol. There was obtained 35.4 g. (85%) of colorless prisms melting at 100–102°.

α-p-Chlorophenoxyacrylophenone was prepared by heating β-dimethylamino-α-*p*-chlorophenoxypropiophenone under reflux with *N,N*-dimethylaniline, as described above for α-phenoxyacrylophenone. The product after recrystallization from anhydrous ethanol consisted of colorless prisms melting at 102.5–104.5°, yield, 65%.

Anal. Calcd. for $C_{15}H_{11}ClO_2$: C, 69.64; H, 4.29; Cl, 13.70. Found: C, 69.76; H, 4.17; Cl, 13.32.

KALAMAZOO, MICH.

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, FACULTY OF SCIENCE, A'IN SHAMS UNIVERSITY]

Studies on Naphthalides. III.[1] Action of Substituted Phenylacetic Acids, Quinaldine and Picolines on Naphthalic Anhydride

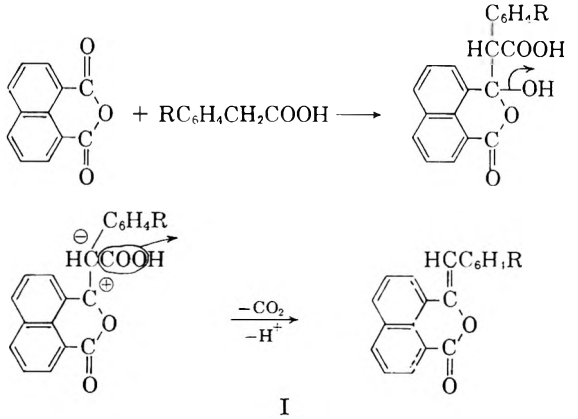
WILLIAM IBRAHIM AWAD AND OSMAN MOHAMAD ALY

Received February 18, 1960

Substituted phenylacetic acids were condensed with naphthalic anhydride, to show the effect of different groups on the products, which are 3-benzalnaphthalides (I) or β-diketones (II). Other active methylene compounds, *e.g.* quinaldine, α-picoline, and γ-picoline were allowed to condense with naphthalic anhydride to produce the corresponding pyronaphthalones.

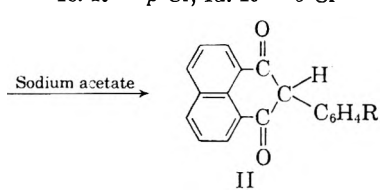
The authors[1] have already shown that naphthalic anhydride reacts with phenylacetic acid and sodium acetate to give a mixture of 8-phenyl-*peri*-naphthindan-7,9-dione (IIa) and 3-benzalnaphthalide (Ia). This work is now extended to investigate the effect of substitution in the aromatic ring of phenylacetic acid on the above Perkin condensation.

A semiquantitative study on the relative yields of the β-diketones (II) to the benzalnaphthalides (I) has been taken as a criterion for this investigation (*cf.* Table I). The following mechanism is proposed for this condensation:



I

Ia. R = H; Ib. R = *p*-OCH$_3$;
Ic. R = *p*-Cl; Id. R = *o*-Cl



II

IIa. R = H; IIb. R = OCH$_3$; IIc. R = *p*-Cl

TABLE I

RELATIVE YIELDS OF β-DIKETONES AND BENZALNAPHTHALIDES

	Benzalnaphthalide, %	β-Diketone, %	Total yield, %
Phenylacetic acid	16	50	66
p-Methoxyphenylacetic acid	22.3	40	62.3
p-Chlorophenylacetic acid	9	13	22
o-Chlorophenylacetic acid	13	—	13
p-Nitrophenylacetic acid	—	—	—

It is likely that II arises from I by the action of sodium acetate by a mechanism analogous to Scheme A (*inter alia*).

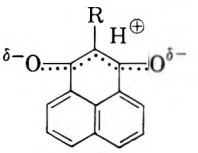
In the case of *p*-methoxyphenylacetic acid, the total yield is slightly less than that of phenylacetic acid but the ratio of the diketone is much higher. The total yields in the case of *o*- and *p*-chlorophenylacetic acids are much less when compared with the other two cases. It is also to be noticed that, in the case of the chloro derivatives, the benzal compounds (I) are predominant. No diketone was isolated in the case of *o*-chlorophenylacetic acid, perhaps because the electron attracting groups (*i.e.* Cl, −I>+T) facilitates the partial decarboxylation of such acids prior to condensation which may be responsible for the relatively poor yields in such cases. This is verified by the fact

(1) O. M. Aly, W. I. Awad, and A. M. Islam, *J. Org. Chem.*, **23**, 1624 (1958).

that *p*-nitrophenylacetic acid (NO_2, —I, —T effect) does not give any condensation product.

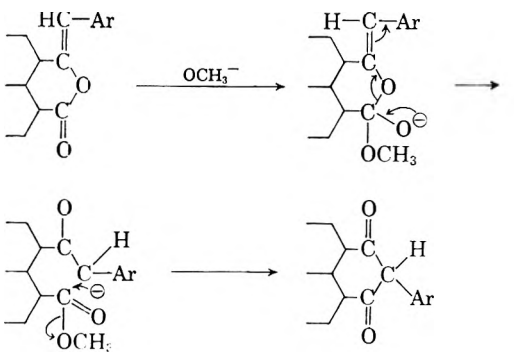
The constitution of the benzalnaphthalide (I) is based on two facts: (i) the ease of their rearrangement into the corresponding β-diketones on treatment with sodium methoxide (*cf.* Nathanson[2] and Eibner[3]), and the presence in the infrared spectra of these naphthalides of a carbonyl stretching frequency in the region of δ-unsaturated lactones[1] (*cf.* Table II). The infrared spectra of the corresponding β-diketones are also shown in the same table.

The β-diketones (II) do not show normal ketonic properties (hydrazones, oximes). They have a pronounced acidic character (soluble in dilute sodium carbonate), and no free —OH stretching frequency appears in the infrared spectra. It is thus not unreasonable that III can be considered as one of the possible unperturbed structures (*cf.* III).



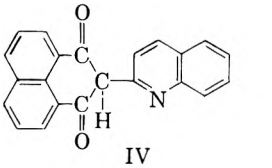
III

When 3-(*o*-chlorobenzal)naphthalide (Id) is treated with sodium methoxide in a trial to get the corresponding diketone, we obtained a yellow crystalline compound which is chlorine free; at the present time we are unable to assign any structure for it and it is still under investigation. Scheme A is proposed for the action of sodium methoxide on benzalnaphthalides to give the corresponding β-diketones:

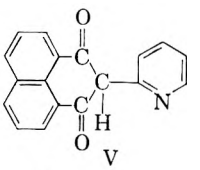


Scheme A

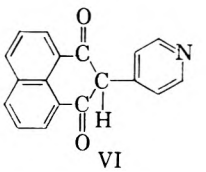
Some other active methylene compounds, namely quinaldine, α-picoline and γ-picoline have been allowed to condense with naphthalic anhydride on the hope of obtaining anticonvulsants and estrogenic antagonists.[4] In the case of quinaldine the reaction was carried out in the presence of sodium acetate or zinc chloride, while in the case of α- and γ-picolines the reaction was successful only by the use of zinc chloride in a sealed tube. In these cases only the diketones are obtained and no benzalnaphthalides. The structure of these nitrogenous diketones (IV), (V), and (VI) is based upon: (i) the stability of these compounds towards sodium methoxide, and (ii) infrared spectra (*cf.* Table II), which indicate a carbonyl stretching frequency in the region of β-diketones.[1]



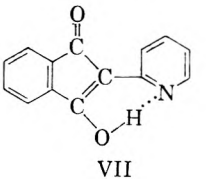
IV



V



VI



VII

TABLE II[a]

INFRARED SPECTRA

Compound	Carbonyl Stretching Frequency cm.$^{-1}$
Ib	1724
Ic	1739
Id	1745
IIb	1626
IIc	1618
IV	1639
V	1639

[a] Infrared measurements were carried out on Perkin-Elmer infracord model 137 using nujol nulls.

Manly, *et al.*[4] stated that structure VII is possible for the pyrophthalones. Such structure could not be detected in the case of the pyronaphthalones IV, V, and VI as no free nor chelated —OH groups could be observed in the infrared spectra. Structure III for the perinaphthalene derivatives seems to play a more important role.

EXPERIMENTAL[5]

Reaction of naphthalic anhydride with p-methoxyphenylacetic acid. A mixture of naphthalic anhydride (5 g.), *p*-methoxyphenylacetic acid (*p*-methoxybenzyl cyanide was prepared according to *Organic Syntheses*,[6] followed by hydrolysis in acid medium in the normal way), and fused sodium acetate (0.3 g.) was heated rapidly to 240–250° and maintained at that temperature for 1 hr. The hot melt was rubbed with 30 ml. of alcohol and allowed to cool. On filtration, a brownish orange product was obtained (6.5 g.). The crude product was extracted with 150 ml. of petroleum ether (b.p. 70–80°) in a Soxhlet extraction apparatus. The extract acquired an orange coloration. On concentration of the petroleum ether solution, an orange yellow product was ob-

(2) Nathanson, *Ber.*, **26**, 2576 (1893).

(3) Eibner, *Ber.*, **39**, 2203 (1906).

(4) D. G. Manly, A. Richardson, Jr., A. M. Stock, C. H. Tilford, and E. D. Amstutz, *J. Org. Chem.*, **23**, 373 (1958).

(5) Microanalyses were carried out by Alfred Bernhardt, im Max-Planck Institut, Mülheim (Ruhr), Germany. Melting points are not corrected.

(6) *Org. Syntheses*, **36**, 56 (1956).

tained. This product was washed with a hot solution of sodium carbonate. Recrystallization from benzene–petroleum ether (b.p. 40–60°) gave (Ib), 1.7 g., 22.3% as yellow crystals, m.p. 168–169°.

Anal. Calcd. for $C_{20}H_{14}O_3$: C, 79.45; H, 4.67. Found: C, 78.94; H, 4.69.

Ib was rearranged quantitatively to the corresponding β-diketone (IIb) on treatment with sodium methoxide solution[1] (melting point and mixture melting point).

The product which was insoluble in petroleum ether (b.p. 70–80°) was recrystallized from benzene (charcoal) to give IIb, 2.9 g., (40%); as orange needles, m.p. 220–222°.

Anal. Calcd. for: $C_{20}H_{14}O_3$: C, 79.45; H, 4.67. Found: C, 79.85; H, 4.84.

The product was soluble in a cold dilute solution of sodium hydroxide or sodium carbonate.

Reaction of naphthalic anhydride with o-chlorophenylacetic acid. A mixture of naphthalic anhydride (5 g.), *o*-chlorophenylacetic acid (4.3 g.) (prepared in a manner similar to that for *p*-fluorophenyl acetic),[7] and fused sodium acetate (0.5 g.) was treated as described before.

Recrystallization of the product extracted with petroleum ether (b.p. 70–80°) from ethyl alcohol gave Id, 1.1 g. (13%), as yellow needles, m.p. 185–186°.

Anal. Calcd. for $C_{19}H_{11}O_2Cl$: C, 74.39; H, 3.6; Cl, 10.44. Found: C, 74.09; H, 3.49; Cl, 11.21.

When Id was treated with alcoholic sodium methoxide solution a chlorine free yellow product was obtained, m.p. 195–97°.

Anal. Found: C, 83.51; H, 3.85.

The product which was insoluble in petroleum ether (b.p. 70–80°) proved to be naphthalic anhydride (melting point and mixture melting point). No β-diketone was isolated.

Reaction of naphthalic anhydride with p-chlorophenylacetic acid. A mixture of naphthalic anhydride (5 g.), *p*-chlorophenylacetic acid (*cf.* ref. 7) (4.3 g.), and fused sodium acetate (0.3 g.) was treated as described before.

Recrystallization of the product extracted with petroleum ether (b.p. 70–80°) from ethyl alcohol gave Ic, 0.7 g. (9%), as orange yellow needles, m.p. 178–79°.

Anal. Calcd. for $C_{19}H_{11}O_2Cl$: C, 74.39; H, 3.6; Cl, 10.44. Found: C, 74.32; H, 3.52; Cl, 11.16.

The product was rearranged quantitatively to the corresponding β-diketone on treatment with alcoholic sodium methoxide solution (melting point and mixture melting point).

The product which was insoluble in petroleum ether (b.p. 70–80°) was recrystallized from ethyl alcohol to give IIc, 1.0 g. (13%), as orange crystals, m.p. 272–273°.

Anal. Calcd. for $C_{19}H_{11}O_2Cl$: C, 74.39; H, 3.60; Cl, 10.44. Found: C, 73.74; H, 3.59; Cl, 10.99.

The product (IIc) was soluble in a cold dilute solution of sodium hydroxide or sodium carbonate.

Reaction of naphthalic anhydride with quinaldine. A mixture of naphthalic anhydride (1.0 g.), quinaldine (1.5 g.), and a catalytic amount of fused zinc chloride or sodium acetate (0.3 g.) was heated rapidly to 230–240° for 3 hr. The reaction mixture was then poured on cold water, whereby a dark solid mass was obtained. Recrystallization of the product so obtained from ethyl alcohol gave IV, 1 g. (62%), as deep red needles, m.p. 254–255°. The product separated from benzene solution as deep violet rosets and from concentrated benzene solution as olive green crystals.

Anal. Calcd. for $C_{22}H_{13}O_2N$: C, 81.72; H, 4.05; N, 4.33. Found: C, 81.98; H, 3.98; N, 4.50.

Reaction of naphthalic anhydride with α-picoline. A mixture of naphthalic anhydride (2 g.), α-picoline (3 ml.), and a catalytic amount of fused zinc chloride was heated in a sealed tube at 200° for 4 hr. The reaction product was poured on cold water and the solid mass so obtained was washed with a little methyl alcohol, then allowed to dry. The crude product was dissolved in dry benzene and chromatographed over silica gel. On elution with dry benzene, a colorless fraction (0.9 g.) was obtained which proved to be naphthalic anhydride (melting point and mixture melting point). An orange fraction was also obtained, which on concentration gave V, 0.8 g. (30%), as orange needles, m.p. 268–269°. It was soluble in dilute solution of sodium hydroxide or sodium carbonate.

Anal. Calcd. for $C_{18}H_{11}O_2N$: C, 79.11; H, 4.06; N, 5.13. Found: C, 79.17; H, 4.04; N, 5.10.

Reaction of naphthalic anhydride with γ-picoline. Naphthalic anhydride (2 g.), γ-picoline (3 ml.), and catalytic amount of fused zinc chloride was treated as discussed above. Naphthalic anhydride was also isolated here and VI, 0.60 g. (23%), was isolated as orange needles, m.p. 258–59°. It was soluble in a dilute solution of sodium hydroxide or sodium carbonate.

Anal. Calcd. for $C_{13}H_{11}O_2N$: N, 5.13. Found: N, 4.57.

(7) F. L. M. Patisson and B. C. Saunders, *J. Chem. Soc.*, 2745(1949).

ABBASSIA, CAIRO
EGYPT, U.A.R.

[CONTRIBUTION FROM THE YERKES RESEARCH LABORATORY, E. I. DU PONT DE NEMOURS & CO., INC., FILM DEPARTMENT]

Carbamates. IV. The Reactions of Disubstituted Carbamates with Alcohols

NORMAN G. GAYLORD[1]

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The reaction of ethyl *N,N*-disubstituted carbamates with alcohols in the presence of the sodium alkoxide of the alcohol yields either carbamates or carbonates, apparently as a function of the relative base strengths of the disubstituted amine and the alkoxide. Thus, the reactions of isobutyl alcohol with ethyl *N,N*-diethyl- and *N*-ethyl-*N*-phenylcarbamates, and benzyl alcohol with ethyl *N*-ethyl-*N*-phenylcarbamate and *N-N'*-dicarbethoxypiperazine yield the corresponding carbamates. The reaction of isobutyl alcohol with ethyl *N,N*-diphenylcarbamate yields principally diisobutyl carbonate and diphenylamine, while the reaction of benzyl alcohol with ethyl *N,N*-diphenylcarbamate yields dibenzyl ether, by decarboxylation of the carbonate, and diphenylamine.

It has previously been reported[2] that the reactions of ethyl carbamate with low boiling alcohols, *e.g.*, isobutyl alcohol, with acid catalysis, or with high boiling alcohols, *e.g.*, benzyl alcohol,

(1) Present address: The Western Petrochemical Corporation, Polymer Division, 96 Roanoke Avenue, Newark 5, N. J.

(2) N. G. Gaylord and C. E. Sroog, *J. Org. Chem.*, 18, 1632 (1953).

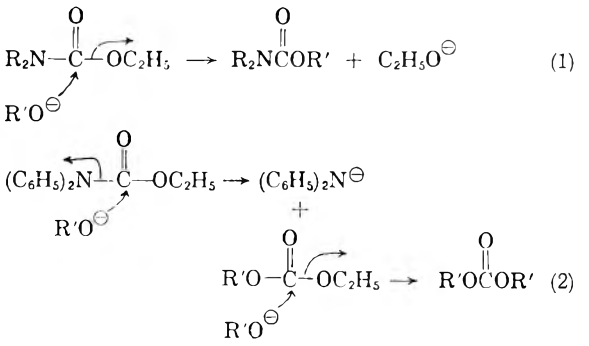
without catalysis, yield the corresponding carbamates, probably by an ester exchange mechanism. The reaction of ethyl *N*-monosubstituted carbamates with benzyl alcohol yields the corresponding benzyl carbamate by what is probably a decomposition of the initial carbamate to an isocyanate followed by reaction with benzyl alcohol. Isobutyl alcohol does not react with the monosubstituted carbamate even with acid catalysis.

Whereas the attempted reactions of isobutyl alcohol with ethyl *N*,*N*-diethyl- and *N*,*N*-diphenylcarbamates, in the presence of sulfuric acid, of benzyl alcohol with ethyl *N*,*N*-diethyl-, *N*,*N*-dibutyl- and *N*,*N*-diphenylcarbamates, in the absence of sulfuric acid, of benzyl alcohol with ethyl *N*,*N*-diphenylcarbamate, in the presence of sulfuric acid, failed to yield any ethanol,[2] it was observed that the uncatalyzed reaction of benzyl alcohol with ethyl *N*-ethyl-*N*-phenylcarbamate yielded the theoretical amount of ethanol after 125 hours, with the subsequent isolation of benzyl *N*-ethyl-*N*-phenylcarbamate in 85% yield. As no satisfactory explanation for this behavior could be set forth, the latter reaction was repeated with a new batch of purified reagents. In this case no ethanol was obtained even after refluxing for eight days. The single, irreproducible success, probably due to the presence of an impurity, indicated that an ester exchange reaction was possible with a disubstituted carbamate, and prompted an investigation of the base-catalyzed reaction of disubstituted carbamates with alcohols.

The reaction of ethyl *N*-ethyl-*N*-phenylcarbamate with benzyl alcohol in the presence of the sodium alkoxide of the alcohol gave the theoretical amount of ethanol in 2.6 hours. An 82% yield of benzyl *N*-ethyl-*N*-phenylcarbamate was obtained. The reaction with isobutyl alcohol gave a 94% yield of the isobutyl analog. This was noteworthy, as the only previously observed successful reaction with isobutyl alcohol had occurred with the unsubstituted ethyl carbamate in the presence of sulfuric acid. The reaction of ethyl *N*,*N*-diethylcarbamate with isobutyl alcohol in the presence of the alkoxide gave an 87% yield of isobutyl *N*,*N*-diethylcarbamate.

The reaction of ethyl *N*,*N*-diphenylcarbamate with isobutyl alcohol in the presence of the sodium alkoxide gave only a 5% yield of isobutyl *N*,*N*-diphenylcarbamate, accompanied by 87% of diphenylamine and 62% of diisobutyl carbonate. Similarly, reaction with benzyl alcohol gave 5% of the benzyl carbamate, 94% of diphenylamine, and 77% of dibenzyl ether. The ether undoubtedly arose through decarboxylation of dibenzyl carbonate. It has been shown[3] that at elevated temperatures α-polydecamethylene carbonate undergoes scission to give carbon dioxide and decamethylene oxide radicals which combine to form the polymeric ether.

The mechanism of the alkoxide catalyzed reactions undoubtedly involves a nucleophilic attack of the anion on the carbonyl carbon atom:



Whether the reaction follows path (1) or (2) is determined by the relative base strengths of the secondary amine and the alkoxide ion. The fact that the diethylamine and ethylaniline derivatives follow path (1) indicates that these compounds are stronger bases than the alkoxide. On the other hand, diphenylamine is a much weaker base than the other amines and probably weaker than the alkoxide ion, resulting in the elimination of the amine grouping. This is in line with the mechanism of the acetoacetic ester type of condensation which will proceed when a base is formed which is weaker than that used as the condensing agent.[4]

The reaction of *N*,*N*′-dicarbethoxypiperazine with benzyl alcohol in the presence of the alkoxide followed path (1) to yield the dicarbamate.

The attempted reactions of ethyl carbamate with isobutyl alcohol or *t*-butyl alcohol in the presence of the sodium alkoxide resulted in the recovery of ethyl carbamate.

The reaction between *N*-carbethoxyimidazole and ethanol in the absence of a catalyst is reported to give a 70% yield of diethyl carbonate.[5] *N*,*N*′-Biscarbethoxy-1,*n*-diamines are reported[6] to undergo a base-catalyzed selfcondensation to yield polyureas, ethanol, and diethyl carbonate. However, no reaction reportedly took place when bisurethanes prepared from *N*,*N*-disubstituted amines were heated under the same conditions.

EXPERIMENTAL

Reaction of ethyl N-ethyl-N-phenylcarbamate and benzyl alcohol. A. Uncatalyzed. A mixture of 38.6 g. (0.2 mole) of the carbamate was heated with 64.8 g. (0.6 mole) of benzyl alcohol under a Vigreux column topped by a partial takeoff reflux head. After 125 hr. the theoretical amount of ethanol was collected. The reaction mixture was distilled and 43.1 g. (84.6% yield) of benzyl *N*-ethyl,*N*-phenylcarbamate was

(3) J. W. Hill, *J. Am. Chem. Soc.*, **57**, 1131 (1935).

(4) C. R. Hauser and B. E. Hudson, Jr., *Org. Reactions*, I, 270 (1942).

(5) H. A. Staab, *Ann.*, **609**, 83 (1957).

(6) T. M. Laakso and D. D. Reynolds, *J. Am. Chem. Soc.*, **79**, 5717 (1957); D. D. Reynolds and T. M. Laakso, U. S. Patent 2,784,163 (March 5, 1957).

collected at 155–158° (4 mm.). On redistillation the product boiled at 130–133° (0.3 mm.), n_D^{25} 1.5545, d_4^{25} 1.0960.

Anal. Calcd. for $C_{16}H_{17}NO_2$: C, 75.29; H, 6.67; N, 5.49. Found: C, 75.20; H, 6.70; N, 5.45.

Numerous attempts to repeat this reaction have been unsuccessful.

The structure of the product was proved by hydrolysis and decarboxylation in the presence of methanolic potassium hydroxide. The carbamate, 12.7 g., was heated under reflux for 17 hr. with 14 g. of potassium hydroxide and 25 ml. of methanol. Work-up of the reaction mixture gave 2.5 g. of benzyl alcohol, identified as the 1-naphthylurethane, and 6.7 g. of *N*-ethylaniline, identified as the benzoyl derivative after purification of the base through the hydrochloride.

B. Catalyzed. Sodium metal, 0.46 g. (0.02 mole) was dissolved in 64.8 g. (0.6 mole) of benzyl alcohol and heated, under a Vigreux column topped by a partial takeoff reflux head, with 38.6 g. (0.2 mole) of ethyl *N*-ethyl,*N*-phenylcarbamate. The theoretical amount of ethanol was collected in 157 min. The reaction mixture was diluted with ether, washed with water until neutral and dried over anhydrous sodium sulfate. On distillation there was collected 41.6 g. (82%) of benzyl *N*-ethyl-*N*-phenylcarbamate, b.p. 120–125° (0.2 mm.). On redistillation the product boiled at 145–146° (0.8 mm.) and its physical constants were identical with those of the product obtained in the uncatalyzed reaction.

Reaction of ethyl N-ethyl-N-phenylcarbamate and isobutyl alcohol. Under the same conditions as above, the reaction of 38.6 g. (0.2 mole) of the carbamate with the alkoxide from 0.46 g. (0.02 mole) of sodium and 44.4 g. (0.6 mole) of isobutyl alcohol gave the theoretical amount of ethanol in 4 hr. A total of 41.4 g. (94%) of isobutyl *N*-ethyl,*N*-phenylcarbamate was collected at 80–88° (1 mm.). On redistillation the product boiled at 75–78° (0.2 mm.), n_D^{25} 1.4908, d_4^{25} 1.0062.

Anal. Calcd. for $C_{13}H_{19}NO_2$: C, 70.59; H, 8.60; N, 6.33. Found: C, 70.25; H, 8.30; N, 6.34.

Reaction of ethyl N,N-diethylcarbamate and isobutyl alcohol. The reaction of 29 g. (0.2 mole) of the carbamate with the alkoxide from 0.46 g. (0.02 mole) of sodium and 44.4 g. (0.6 mole) of isobutyl alcohol gave the theoretical amount of ethanol in 5.5 hr. A total of 31 g. (87%) of isobutyl *N,N*-diethylcarbamate was collected at 90–100° (31 mm.). On redistillation the product boiled at 95–98° (31 mm.).

Anal. Calcd. for $C_9H_{19}NO_2$: N, 8.09. Found: N, 8.27, 7.81.

Reaction of ethyl N,N-diphenylcarbamate and isobutyl alcohol. The reaction of 48.2 g. (0.2 mole) of the carbamate with the alkoxide from 0.46 g. (0.02 mole) of sodium and 44.4 g. (0.6 mole) of isobutyl alcohol gave the theoretical amount of ethanol in 3.75 hr. Ether was added to the reaction mixture and the precipitate was filtered. The precipitate was dissolved in water, acidified with dilute hydrochloric acid, made alkaline with 10% sodium hydroxide, and extracted with ether. The dried ether extract was combined with the original ether filtrate. Gaseous hydrogen chloride was bubbled through the ethereal solution and the resultant white precipitate filtered. This was repeated twice. The precipitated hydrochloride, 37.6 g., was treated with sodium hydroxide to liberate 29.4 g. (87%) of diphenylamine, m.p. 51–53° (reported[7] m.p., 54°).

Anal. Calcd. for $C_{12}H_{11}N$: N, 8.28. Found: N, 8.27.

The benzamide of diphenylamine, prepared in the usual manner, melted at 180–181° (reported[7] m.p. 180°) and showed no depression on a mixed melting point with authentic material.

The filtrate from the hydrogen chloride treatment was neutralized with solid sodium bicarbonate and dried over magnesium sulfate. Distillation gave two fractions, 21.7 g. (62%), b.p. 67–71° (10 mm.) and 2.6 g. (4.8%), b.p. 140–145° (0.6 mm.).

The lower boiling fraction on redistillation boiled at 184–186°, n_D^{25} 1.4060, d_4^{25} 0.9050, and was identified as diisobutyl carbonate by analysis and by the liberation of carbon dioxide on heating a methanol solution in the presence of concd. hydrochloric acid.

Anal. Calcd. for $C_9H_{18}O_3$: C, 62.07; H, 10.35. Found: C, 62.11; H, 10.44.

The higher boiling fraction, isobutyl *N,N*-diphenylcarbamate, had n_D^{29} 1.5538 and after standing for several months solidified to m.p. 50–50.5°.

Anal. Calcd. for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.63; H, 7.00; N, 5.32.

Reaction of ethyl N,N-diphenylcarbamate and benzyl alcohol. The reaction of 0.2 mole of the carbamate with 0.6 mole of benzyl alcohol in the presence of 0.02 mole of sodium gave the theoretical amount of ethanol in 2 hr. and 52 min. The reaction mixture was worked up and treated with gaseous hydrogen chloride as above to yield 38.5 g. (94%) of diphenylamine hydrochloride, m.p. 174–175°, which was converted to the free base, m.p. 51–53°, in quantitative yield.

The filtrate from the hydrogen chloride treatment was neutralized, dried, and distilled to yield 23.5 g. (36%) of benzyl alcohol, 30.3 g. (77%) of dibenzyl ether, b.p. 108–112° (0.5 mm.), and 6.0 g. of b.p. 150–166° (0.5 mm.). The lower boiling fraction on redistillation boiled at 108–109° (0.8 mm.), n_D^{25} 1.5606, and was identified as dibenzyl ether by the analysis and by the failure to evolve carbon dioxide on heating a methanolic solution with concd. hydrochloric acid.

Anal. Calcd. for $C_{14}H_{14}O$: C, 84.83; H, 7.07. Found: C, 84.52; H, 7.08.

The higher boiling fraction solidified on standing, was combined with the solidified distillation residue, 1.6 g., and on recrystallization twice from petroleum ether (b.p. 120–135°) and once from benzene gave 3.0 g. (5%) of benzyl *N,N*-diphenylcarbamate, m.p. 112–113.5°.

Anal. Calcd. for $C_{20}H_{17}NO_2$: C, 79.21; H, 5.61; N, 4.62. Found: C, 79.34; H, 5.80; N, 4.64.

N,N'-Dicarbethoxypiperazine. A solution of 38.8 g. (0.2 mole) of piperazine hexahydrate in 50 ml. of water was stirred in a three necked flask at 3°. A solution of 19.2 g. (0.48 mole) of sodium hydroxide in 90 ml. of water was placed in one dropping funnel and a solution of 52.1 g. (0.48 mole) of ethyl chloroformate in 50 ml. of ether was placed in a second dropping funnel. The two solutions were added dropwise, simultaneously, over a period of 2.5 hr. while maintaining the temperature below 8°. Upon the completion of the addition the reaction mixture was transferred to a separatory funnel, 50 ml. of ether was added, and the aqueous layer was saturated with sodium chloride. The ether layer was dried and evaporated to yield 48.5 g. of crude product. Upon distillation, 40.8 g. (89%) of pure product was collected at 128–129° (1 mm.), m.p. 44–45° (reported m.p. 45°[8] and 49°[9]).

Reaction of N,N'-dicarbethoxypiperazine and benzyl alcohol. The reaction of 5.75 g. (0.025 mole) of the carbamate with the alkoxide from 0.115 g. (0.005 mole) of sodium and 16.21 g. (0.15 mole) of benzyl alcohol gave the theoretical amount of ethanol in 3 hr. The reaction mixture was diluted with ether, washed with water until neutral and dried over magnesium sulfate. On distillation 7.0 g. of benzyl alcohol was collected at 55° (1 mm.). Addition of ether to the distillation residue resulted in crystallization to yield 2.9 g. (33%) of the benzyl carbamate, m.p. 97–103°. Recrystallization from petroleum ether (b.p. 120–135°) gave 2.15 g., m.p. 107–109°.

Anal. Calcd. for $C_{20}H_{22}N_2O_4$: N, 7.91. Found: N, 7.85.

NEWARK, N. J.

(7) R. L. Shriner and R. C. Fuson, *The Systematic Identification of Organic Compounds*, John Wiley and Sons, New York, 3rd ed., p. 237.

(8) W. A. van Dorp, *Rec. trav. chim.*, **28**, 75 (1909).

(9) R. Baltzly, J. S. Buck, E. Lorz, and W. Schön, *J. Am. Chem. Soc.*, **66**, 263 (1944).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STATE UNIVERSITY OF IOWA]

Nitroolefins. II. Derivatives of α-Nitroacetophenone

RICHARD D. CAMPBELL AND FREDERICK J. SCHULTZ[1]

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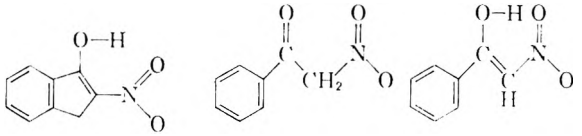
A number of reactions for the preparation of derivatives of α-nitroacetophenone was studied. A series of sixteen related compounds was prepared. The ultraviolet and infrared spectra of these compounds are reported and discussed.

In the previous paper[2] the 2-nitro-3-hydroxyindene (I) system was discussed. A comparison of the spectra of I and of α-nitroacetophenone (II) showed that tautomerism occurs and that chelate



I II IIE

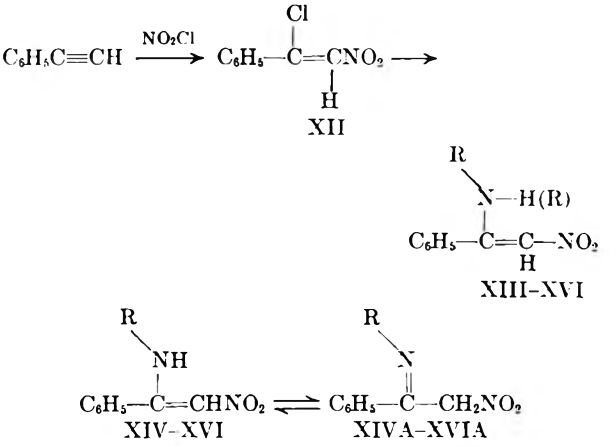
hydrogen bonding occurs in IIE but not in I. It was of interest to study the spectra of analogs of II to look for substituent effects on hydrogen bonding, splitting of the infrared absorption band assigned to symmetrical stretching of the nitro group, tautomerism, and electronic effects causing band displacements.

The reactions of α-nitroacetophenone with ammonia and amines were studied. It was expected that the amine would react with II to give the α-amino-β-nitrostyrene. The analogous reaction in the 1,3-diketone series has been reported.[3] Although II formed a salt readily with ammonia, morpholine, and other bases, the subsequent displacement reaction was not successful. Red oils were formed, suggesting that phenylnitroacetylene[4] might have been produced.

The preparation of the α-amino-β-nitrostyrenes was accomplished by the action of the amines on α-chloro-β-nitrostyrene (XII). This method was reported by Perrot and Berger,[5] but no experimental details were given and no data other than melting points were reported. The preparation of XII by the action of nitrosyl chloride on phenylacetylene gave a 17% yield. A better method employed nitryl chloride and phenyl acetylene to give III in 36% yield. This reaction had variously been reported not to occur[5] and to give α-nitro-β-chlorostyrene.[6] The product obtained by the two methods was identical.

An alternative preparation of XII was attempted. α-Nitroacetophenone was treated with phosphorus pentachloride in methylene chloride. The product which formed is tentatively assigned the structure α-chloro-β-benzoyl-β-nitrostyrene (XIX) on the basis of analytical and spectral data. Under these and other conditions none of the expected product XII was obtained.

The chloro compound XII reacted readily when treated with primary and secondary amines, *viz.*, morpholine, aniline, benzylamine, and cyclohexylamine. When the amine was used as solvent, decomposition occurred and red oily products formed. The reactions in either solution were rapid and exothermic except in the case of aniline.



The structures of these amine reaction products were established as α-amino-β-nitrostyrenes by acid hydrolysis to α-nitroacetophenone. It has been demonstrated[7] in the amino chalcone analogs that hydrolysis gives the α-, or β-dicarbonyl compound from the respective α- or β-aminochalcone.

The reaction product from morpholine, *viz.*, α-morpholino-β-nitrostyrene (XIII) can exist only in one form. However, tautomerism is possible with the benzylamino (XIV), cyclohexylamino(XV), and anilino (XVI) compounds. More extensive conjugation is present than in the imine forms XIVA and XVA. The imine XVIA is a Schiff base structure with conjugation of both phenyl rings through the azomethine linkage.

In the homologous series, β-methyl-β-nitrostyrene (IX) was treated with excess morpholine to give the addition product 1-morpholino-1-phenyl-

(1) Ph.D. Thesis, State University of Iowa, 1960.

(2) R. D. Campbell and C. L. Pitzer, *J. Org. Chem.*, **24**, 1531 (1959).

(3) N. H. Cromwell, *Chem. Revs.*, **38**, 83 (1946).

(4) J. Lovenich and H. Gerber, *Ber.*, **63**, 1707 (1930).

(5) R. Perrot and R. Berger, *Compt. rend.*, **235**, 185 (1958).

(6) W. Steinkopf and M. Kuhmel, *Ber.*, **75**, 1323 (1942).

(7) (a) N. H. Cromwell, D. B. Capps, and S. E. Palmer, *J. Am. Chem. Soc.*, **73**, 1226 (1951); (b) N. H. Cromwell, H. H. Eby, and D. B. Capps, *J. Am. Chem. Soc.*, **73**, p. 1230.

2-nitropropane (XVIII). Numerous attempts to carry out the same reaction with β-nitrostyrene have been unsuccessful. The bromine addition product of IX was prepared.[8] This dibromide (XI) reacted in morpholine to yield α-morpholino-β-methyl-β-nitrostyrene (XVII). This product presumably results from successive dehydrobromination, addition of morpholine, and dehydrobromination. Under the same conditions, the bromine adduct of β-nitrostyrene (III) yields β-bromo-β-nitrostyrene (VIII), and proceeds no further.

Several attempts were made to prepare α-acyloxy-β-nitrostyrenes by acylation of II. Treatment of II with the aroyl chlorides and pyridine in dry benzene yielded 1-phenyl-2-nitroethane-1,1-diol bis-4-nitrobenzoate (XXI) and the corresponding bis-3,5-dinitrobenzoate (XX). The structures of XX and XXI were confirmed by hydrolysis to give nitromethane. Treatment of II with acetyl chloride and pyridine in toluene did not give the expected α-acetoxy-β-nitrostyrene. Instead, a product formed which seems to be α-chloro-β-acetyl-β-nitrostyrene. This product and the corresponding benzoyl compound (XIX) described above are to be studied further.

The ultraviolet spectra of the series with β-nitrostyrene (III) as the reference compound reveal the effect of the substituents on the principal chromophore of β-nitrostyrene at 3110 Å. When the double bond is saturated and conjugation is not possible, the band in the 3000–4000 Å region is absent, as in X, XI, XVIII, XX, and XXI.

The α-hydroxyl and β-bromo substituents cause a bathochromic shift of 410 Å and 130 Å in compounds II and VIII respectively. In compound VII in which both substituents are present the shift is 530 Å demonstrating an additivity of the effect of the two substituents.

The intensity of absorption in compounds II, VII, and the salts of II vary widely in both directions from the reference compound III. This intensity variation indicates concentration variance due to keto-enol equilibrium. The keto form of II is expected to show only the benzoyl chromophore, which absorbs quite weakly in the 3000–4000 Å region. Hence absorption in this range is due to the enol form. The low absorbance in II and VII indicates low enol content. The varying absorption intensity of IV, V, and VII is interesting in that some cations seem to cause higher enol content than would have been expected.

The amino derivatives all seem to be in the enamine form. No other form is possible with the morpholino compound VIII. The other amines show the same direction and almost uniform amounts of shift seen in XVIII. Hydrogen chelation is expected, but does not appear to effect the band locations in these compounds. The aniline compound XVI contains a more extensive conjugation system than is found in the others, hence the more bathochromic band (3780 Å) is to be expected.

The α-halogen and β-methyl groups do not seem to follow a general pattern. The α-chloro group in XII causes a shift (hyposochromic) of −140 Å. In IX the methyl group causes a −40 Å shift. In XVII the methyl group apparently has no effect, as both XVII and XIII absorb at 3560 Å.

The spectrum of α-chloro-β-benzoyl-β-nitrostyrene (XIX) is not what might be predicted.[9,10] The intense band at 2480Å and absence of a band at longer wave length might be explained in terms of extreme steric inhibition of resonance. Further study of this compound is planned.

The infrared spectra provide evidence for the tautomeric forms which are present in the keto-enol alternatives in II and VII. Both have a carbonyl band at 1695 cm.$^{-1}$ (potassium bromide pellet) as expected.[11] A C—C band appears at 1605 cm.$^{-1}$ for II, and as a shoulder at 1600 cm.$^{-1}$ in VII. No C=N absorption was found. The C=C band appears at 1580–1595 cm.$^{-1}$ for these derivatives, and up to 1605 cm.$^{-1}$ for other β-nitrostyrene compounds. These two characteristics establish the structures of XIII–XVII as enamines. No N—H band is observed, again because of hydrogen chelation.[2,11]

The absorption bands for the nitro group appear in the 1550 cm.$^{-1}$ and 1350 cm.$^{-1}$ region for the asymmetric and symmetric modes respectively.[11,12] General patterns for shifts of bands and splitting[13] of bands are difficult to discern. These bands for members of the series may be compared with the values of 1538 cm.$^{-1}$ and 1345 cm.$^{-1}$ for the parent β-nitrostyrene (III). It can be seen that the saturated compounds X, XI, and XVIII have an asymmetric nitro band at a shorter wave length (higher wave number) than does III. (The bands at 1540 and 1525 cm.$^{-1}$ for XX and XII respectively, are due to the aromatic nitro group.) The higher wave number for the unconjugated nitro group and lower wave number for conjugated nitro group is the pattern recognized by Brown.[12]

The asymmetric band for II is high, indicating a saturated nitro group as is found in the keto form. The bromo analog VII fits the same pattern. The amino derivatives XIII–XVII also absorb in the 1545–1572 cm.$^{-1}$ range. For XIII and XVII this band cannot be explained as above since tau-

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(10) W. B. Black and R. E. Lutz, *J. Am. Chem. Soc.*, 77, 5134 (1955).

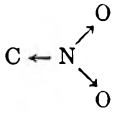
(11) L. J. Bellamy, *Infrared Spectra of Complex Molecules*, John Wiley and Sons, New York, N.Y. (1958).

(12) J. F. Brown, Jr., *J. Am. Chem. Soc.*, 77, 6341 (1955).

(13) P. H. Lindenmeyer and P. M. Harris, *J. Chem. Phys.*, 21, 408 (1953).

tomerism is not possible. It seems that in the electronic ground state the inductive effect of the amino and hydroxyl groups more than balance the conjugative effect.

The symmetric mode band of the nitro group is split in some of the enolic and amino derivatives. This splitting might be explained as evidence of tautomeric equilibrium. The low wave-number bands appear at 1330–1300 cm.$^{-1}$ for II, IV–IX, XII, XV–XVI. However, amines XIII, XIV, and XVII absorb at 1373–1348 cm^{-1}. This shift to higher wave length is anomalous in the above rationale. The higher wave-length components of the split bands in IV, VII, XII, XV, and XVII fall in the same anomalous region. These absorptions may be due to increased bond order of the C—N bond,[12] increasing the force constant of the vibrating system.



The effect of hydrogen chelation and dipole interaction upon the —NO_2 stretching modes is expected to be moderately strong and to be dependent upon configuration of structures, particularly of *cis-trans* isomers, and in structures of fixed configurations.[2] In these cases the dipole effect is expected to cause splitting and anomalous shifts. Further studies are under way to prepare model compounds in an attempt to recognize spectral patterns resulting from these effects.

EXPERIMENTAL

α-Nitroacetophenone (II). This compound was prepared by the method of Long and Troutman[14] with the exception that recrystallization of the product was carried out using petroleum ether (b.p. 60–70°) as the solvent.

Potassium salt of II.[15] A solution of 28 g. of potassium hydroxide in 40 ml. of absolute methanol was added dropwise with stirring to a solution of 8.25 g. of II in 60 ml. of anhydrous benzene. The product, a pale yellow powder, was removed by filtration, washed twice with 25-ml. portions of 50% methanol in benzene, and dried in vacuum. The yield was 8.8 g. (76%).

Ammonium salt of II.[15] A solution of 2.0 g. of II in 200 ml. of anhydrous ether was saturated with anhydrous ammonia by bubbling the dry gas through the solution for 15 min. The white precipitate was removed by filtration and washed with 50 ml. of anhydrous ether. The product was recrystallized from a mixture of 95% ethanol and ether giving 2.1 g. (96%) of yellow platelets which melted at 119°.

Anal. Calcd. for $C_8H_9N_2O_3$: C, 52.8; H, 5.49; N, 15.38. Found: C, 52.52; H, 5.42; N, 15.02.

Morpholinium salt of II.[15] Freshly distilled morpholine (6.13 g.) was added to a solution of 10 g. of II in 30 ml. of warm benzene and the mixture refluxed for 1 hr. The product was removed by filtration after the reaction mixture had cooled to room temperature. After washing with benzene and air drying, the pale yellow crystalline product melted at 138–142° with decomposition to a red oil. The yield was 14.5 g. (94%).

Anal. Calcd. for $C_{12}H_{16}N_2O_4$: C, 57.2; H, 6.35; N, 11.1. Found: C, 56.68; H, 6.25; N, 11.07.

α-Bromo-α-nitroacetophenone (VIII). This compound was prepared as previously described.[16]

1-Phenyl-2-nitroethane-1,1-diol bis-3,5-dinitrobenzoate (XX). 3,5-Dinitrobenzoyl chloride (from 8 g. of 3,5-dinitrobenzoic acid) was dissolved in dry benzene. To this 4.1 g. (0.025 mole) of II was added followed by 2 ml. of dry pyridine. The mixture was refluxed for 2 hr., and the warm solution was filtered. The clear filtrate was then cooled to room temperature. The resulting white needle-like crystals were collected by filtration with suction and recrystallized from acetone. The yield was 11.0 g. (77.4%) of a compound which melted at 187–188°.

Anal. Calcd. for $C_{22}H_{12}N_6O_{14}$: C, 46.3; H, 2.27; N, 12.2. Found: C, 47.65; H, 2.30; N, 11.58.

Hydrolysis of XX. A mixture of 2.0 g. (0.0035 mole) of 1-phenyl-2-nitroethane-1,1-diol bis-3,5-dinitrobenzoate and 25 ml. of 10% sodium hydroxide was warmed on a steam bath for 2 hr. The resulting dark brown solution was cooled to 0° and acidified with 6*M* hydrochloric acid. The acidic solution was extracted with two 30-ml. portions of ether and the combined ether extracts were dried over calcium sulfate.

A small portion of this solution was introduced into the system of a Perkin-Elmer Vapor Fractometer and the resulting chromatograph compared with that of a known solution of nitromethane in ether. On the basis of their similarity it was concluded that the unknown solution contained nitromethane.

1-Phenyl-2-nitroethane-1,1-diol bis-4-nitrobenzoate (XXI). To a solution of 4.1 g. (0.025 mole) of II in 100 ml. of dry benzene, a solution of 5 g. (0.027 mole) of *p*-nitrobenzoyl chloride in 50 ml. of dry benzene was added. Then 2 ml. of dry pyridine was added and the mixture was refluxed for 2 hr. The mixture was filtered while still hot to remove the pyridine hydrochloride which had formed. The filtrate was evaporated to dryness under reduced pressure leaving a yellow crystalline residue which was recrystallized twice from acetone and once from a solution of chloroform in petroleum ether (b.p. 35–60°). The product was pale yellow in color and melted at 168–170°. The yield was 4.8 g. (80%).

Anal. Calcd. for $C_{22}H_{14}N_4O_{10}$: C, 54.88; H, 3.11; N, 8.74. Found: C, 53.91; H, 2.79; N, 8.72.

α-Chloro-β-nitrostyrene (XII), *nitrosyl chloride method.* Ten grams (0.1 mole) of phenylacetylene was dissolved in 75 ml. of anhydrous ether and the solution was cooled thoroughly in an ice-salt mixture. Then 15 g. (0.23 mole) of liquid nitrosyl chloride was added and the reaction vessel was loosely stoppered with a rubber stopper. The mixture was allowed to stand undisturbed, without the addition of ice to the bath, until all evolution of gas had ceased (10 days). During this time the color had faded from deep red to a pale orange. The solvent was removed under vacuum at room temperature leaving a yellow oil which was vacuum distilled. The fraction boiling between 82° and 120° at 1 mm. was collected and redistilled. Three fractions were collected. The first boiled at 82–102° (2 mm.), the second at 102–110° (2 mm.), and the third at 110–120° (2 mm.). After standing for several days, the second fraction crystallized. It was recrystallized from petroleum ether (b.p. 35–60°) giving yellow crystals that melted at 50–52°. This compound was noted to be a strong lachrymator. The yield was 2.1 g. (16.9%).

Anal. Calcd. for $C_8H_6ClNO_2$: C, 52.4; H, 3.28; N, 7.66. Found: C, 52.08; H, 3.28; N, 7.87.

α-Chloro-β-nitrostyrene, nitryl chloride method. Seventy-five milliliters of anhydrous ether contained in a heavy walled tube was thoroughly cooled in a mixture of Dry Ice and acetone. Gaseous nitryl chloride was bubbled into the cold ether until approximately 35 g. (0.43 mole) had been dissolved.

(14) L. M. Long and H. D. Troutman, *J. Am. Chem. Soc.*, **71**, 2471 (1949).

(15) A. Lucas, *Ber.*, **32**, 602 (1899).

(16) J. Thiele and S. Haeckel, *Ann.* **325**, 11 (1902).

TABLE I

INFRARED AND ULTRAVIOLET ABSORPTION BANDS

$$C_6H_5\overset{\alpha}{C}=\overset{\beta}{C}-NO_2$$

Compound	Substituents α	Substituents β	Ultraviolet Å	Ultraviolet ε × 10⁻³	Infrared[a] C=O	Infrared[a] C=C	Infrared[a] NO_2[b]	Infrared[a] NO_2[c]
II	OH	H	2470	11.9	1695	1605	1560	1330
			3520	4.6				
III	H	H	2280	7.8				
			3110	16.6		1642	1538	1348[d]
IV	$O^-NH_4^+$	H	2470	8.4			1563	1350
			3520	18.0				1300
V	O^-K^+	H	2470	4.4				
			3520	10.9			1577	1312[d]
VI	$O^-C_4H_8ON^+$	H	2470	7.3				
			3570	8.6			1570	1325[e]
VII	OH	Br	2570	11.4	1695		1575	1358
			3640	1.4				1325
VIII	H	Br	2290	7.4		1602	1575	
			3240	11.4			1522	1300
IX	H	CH_3	2730	8.5			1518	1323
			3070	10.1				
XII	Cl	H	2290	7.3			1528	1343
			2970	8.9				1313
XIII	$-N(CH_2CH_2)_2O$	H	2440	5.3			1580	1348
			3590	17.8			1558	
XIV	$-NHCH_2C_6H_5$	H	2430	5.9			1572	1373
			3560	23.3			1565	
							1545	
XV	$-NHC_6H_{11}$	H	2300	6.8			1570	1376
			2440	5.7				1355
			3560	17.5				1315
XVI	$-NHC_6H_5$	H	2330	13.7		1595	1565	1362[f]
			2990	6.7				1313
			3780	29.0				
XVII	$-N(CH_2CH_2)_2O$	CH_3	2440	4.9			1554	1353
		O	3560	24.4				
XIX	Cl	$\overset{\alpha}{C_5H_5}-\overset{\beta}{C}=CC_6H_5$	2480	21.7	1690	1601	1582	1312
X	Br	Br	3230	1.6			1565	1350
								1313
XI	Br	Br,CH_3					1558	1329
XVIII	$-N(CH_2CH_2)_2O$	CH_3	2120	8.5			1550	1360
XX	$[-O_2CC_6H_3(NO_2)_2]_2$	H	2200	45.6				
			2300	42.5	1685		1540	1343
			2500	35.0				
XXI	$[-O_2CC_6H_4NO_2]_2$	H			1682		1588	1345
							1525	1320

[a] Data in cm^{-1}. Medium: Potassium bromide pellet. [b] Asymmetric mode. [c] Symmetric mode. [d] Nujol. [e] Chloroform.

Then 27 g. (0.265 mole) of phenylacetylene was added in a thin stream with stirring. The orange solution was allowed to stand in the cooling mixture for 2 days, then removed and allowed to stand at room temperature for 7 days with the tube loosely stoppered. At the end of this time, the color had faded to yellow. No evolution of gas was noted during the reaction period. The solvent was removed under vacuum at room temperature and the resulting orange oil was distilled under a pressure of 1–2 mm. The portion boiling from 85° to 115° was collected as a yellow oil. The yellow oil was redistilled and the portion boiling from 103–109° (2 mm.) was collected and set aside overnight to crystallize. It was necessary to warm the distillation apparatus gently to prevent crystallization of the product in the condenser and adapter tube. The product was recrystallized from petroleum ether (b.p. 35–60°) and melted at 51–53°. The mixed melting point of this product with that obtained from the reaction of phenylacetylene with nitrosyl chloride was not depressed. The yield was 5.2 g. (35.8%).

α-Morpholino-β-nitrostyrene (XIII). Freshly distilled morpholine (0.19 g., 0.022 mole) was added to XII (1 g., 0.0055 mole) in 25 ml. of anhydrous ether. The reaction was exothermic. The ether-soluble, water-insoluble portion was crystallized from petroleum ether (b.p. 60–70°) to give 0.6 g. (47.5%) of yellow crystals of XIII (m.p. 167–169°).[5]

Anal. Calcd. for $C_{12}H_{14}N_2O_3$: C, 61.5; H, 5.93; N, 11.96. Found: C, 62.3; H, 5.92; N, 11.48.

α-Anilino-β-nitrostyrene (XVI). Under the above condi-

tions, with a 2-hr. reflux of the reaction mixture, aniline and XII reacted to give XVI (1.2 g., 91.7%) as yellow crystals, m.p. 123–124°.[5]

Anal. Calcd. for $C_{14}H_{12}N_2O_2$: C, 70.0; H, 5.0; N, 11.67. Found: C, 69.74; H, 4.89; N, 11.42.

α-Benzylamino-β-nitrostyrene (XIV). As above, with 2 hr. at room temperature, the reaction of benzylamine and XII gave XIV (1.3 g., 93.8%). The product was recrystallized from carbon tetrachloride–chloroform, m.p. 91°.[5]

Anal. Calcd. for $C_{15}H_{14}N_2O_2$: N, 11.04; Found: N, 10.93.

α-Cyclohexylamino-β-nitrostyrene (XV). As above, XII and cyclohexylamine reacted on standing overnight to give XV (0.8 g., 65%) from ether, melting at 113–114°.[5]

Anal. Calcd. for $C_{14}H_{18}N_2O_2$: C, 68.3; H, 7.32; N, 11.40. Found: C, 68.31; H, 7.32; N, 11.24.

Hydrolysis of α-amino-β-nitrostyrenes. A mixture of 0.8 g. (0.0033 mole) of α-anilino-β-nitrostyrene (XVI) with 25 ml. of 20% sulfuric acid was refluxed for 45 min. At the end of this time, the reaction mixture was a clear solution containing a small amount of a brown oil. The oil was removed by filtration of the hot solution. The filtrate on cooling to room temperature yielded 0.2 g. (36.5%) of white plates, which, after recrystallization from water, melted at 105°. The mixed melting point with an authentic sample of α-nitroacetophenone was 105–107°. The compound formed a 2,4-dinitrophenylhydrazone which melted at 205° with decomposition. Its mixed melting point with the 2,4-dinitrophenylhydrazone of II was not depressed.

The above procedure was repeated with α-morpholino-β-nitrostyrene (XIII) and α-cyclohexylamino-β-nitrostyrene (XV) with like results.

1-Phenyl-1,2-dibromo-2-nitropropane (XI). This compound was prepared by the method described by an earlier worker.[8]

1-Phenyl-1-morpholino-2-nitropropane (XVIII). One gram (0.0061 mole) of β-methyl-β-nitrostyrene was dissolved in 15 ml. of freshly distilled morpholine and the solution was allowed to stand on the steam bath overnight. After cooling to room temperature, the reaction mixture was diluted with 30 ml. of anhydrous ether, and the solution was washed three times with 50-ml. portions of water to free it of morpholine. The ether solution was freed of solvent by evaporation at room temperature under reduced pressure leaving a light yellow crystalline residue. This was dissolved in hot petroleum ether (b.p. 60–70°), treated with decolorizing carbon, filtered, and cooled. On cooling, a white crystalline product separated which was removed by filtration and recrystallized again from the petroleum ether to give 0.6 g. (39.2%) of a compound which melted at 142–144°.

Anal. Calcd. for $C_{13}H_{18}N_2O_3$: C, 62.2; H, 7.21; N, 11.20. Found: C, 62.36; H, 7.26; N, 10.83.

α-Morpholino-3-methyl-β-nitrostyrene (XVII). A solution of 2 g. (0.0062 mole) of 1-phenyl-1,2-dibromo-2-nitropropane in 20 ml. of freshly distilled morpholine was allowed to stand overnight on a steam bath. The resulting white precipitate was removed by filtration and identified as morpholine hydrobromide by its melting point and by the fact that it was readily soluble in water. The filtrate was poured over 100 g. of ice and the resulting fine suspension was extracted with two 50-ml. portions of ether. The ether solution was evaporated to dryness under reduced pressure at room temperature and the resulting yellow crystalline solid was recrystallized from petroleum ether (b.p. 60–70°) giving a white product. After one additional recrystallization from the petroleum ether the compound melted at 139–141°. The yield was 1.9 g. (91.6%).

Anal. Calcd. for $C_{13}H_{16}N_2O_3$: C, 62.9; H, 6.45; N, 11.30. Found: C, 62.30; H, 7.29; N, 10.83.

α-Chloro-β-benzoyl-β-nitrostyrene (XIX). To a solution of 16.5 g. (0.1 mole) of II in 175 ml. of dry methylene chloride, 20.8 g. (0.1 mole) of phosphorus pentachloride was added. The mixture was refluxed until no more hydrogen chloride was evolved (2 days). The residue was freed of phosphorus oxychloride by vacuum distillation at 70° (12 mm.). The residue from this distillation was extracted twice with 50 ml. portions of petroleum ether (b.p. 60–70°) which were combined and cooled. On cooling, white crystals separated which were removed by filtration and recrystallized from the petroleum ether. The product weighed 3.2 g. (22.3%) and melted at 90°.

Anal. Calcd. for $C_{15}H_{10}ClNO_3$: C, 62.7; H, 3.49; N, 4.88. Found: C, 62.65; H, 3.59; N, 4.89.

1-Phenyl-1,2-dibromo-2-nitroethane (X). This compound was prepared by the method described by an earlier worker.[8]

β-Bromo-β-nitrostyrene (VIII). This compound was prepared by a previously described method.[8]

Spectral determinations. All of the ultraviolet spectra were obtained using a Cary, Model 11, double beam recording spectrophotometer. All samples were run as solutions in 95% ethanol using 1 cm. silica cells.

The infrared spectra discussed were obtained by the use of a Perkin-Elmer, Model 21, double beam recording infrared spectrophotometer. The samples were run as mulls with Nujol or in potassium bromide pellets, as indicated in Table I.

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IOWA CITY, IOWA

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The Hydrogenation of Nitrophthalic Acids

STEWART H. MERRILL

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Aminophthalic acids can be prepared by catalytic hydrogenation of the disodium salts of 3- and 4-nitrophthalic acids in water. Certain amino and nitro aromatic carboxylic acids function as accelerators in the hydrogenation of otherwise unreceptive nitro acids. The corresponding isomeric azidophthalic acids are described.

Chemical reduction of 3- and 4-nitrophthalic acids to aminophthalic acid using stannous chloride,[1] tin-acid,[2] or zinc-acid[3] gives as products metal double salts or materials which are difficult to separate from metal residues. The 4-isomer gives particularly poor yields because of its high solubility and the ensuing problems of isolating either the amine or its hydrochloride. Hydrogenation of nitrophthalic anhydride[4] in acetone or ester[5] in alcohol has given good yields, but hydrogenation of the free acids in alcohol gives a large quantity of unidentified by-products.[5b,6]

In the present investigation, both 3- and 4-nitrophthalic acids have been converted to the corresponding amines in essentially quantitative yields by hydrogenation of the disodium salts in water solution. With Raney nickel catalyst, hydrogenation at moderate pressure was complete in about fifteen minutes at 70°. Low-pressure reduction on the Parr apparatus required several hours. After removal of the catalyst and acidification, the colorless, amino acid solution was used directly for a subsequent diazotization reaction. The amine could be isolated as the hydrochloride if desired.

The yields were estimated by diazotization and conversion to the azide which precipitated as crystalline material. Inasmuch as the diazotization always consumed the calculated amount of sodium nitrite, the small loss in yield probably occurred in the formation and recovery of the azide.

In the low-pressure hydrogenation of the nitrophthalic acids over platinum, the hydrogen pressure (range, 3–1.5 atmospheres) fell at a constant rate during the course of the reduction. When the theoretical amount of hydrogen had been consumed, the pressure remained constant. This signifies a zero-order reaction with respect to both hydrogen and nitro compound. This conclusion is valid only if equilibrium conditions exist at the catalyst.[7] No experiments were made to verify this. Furthermore, there may have been an autocatalytic or accelerator effect of the product, as was noted for the moderate-pressure hydrogenation of 4-nitrophthalic acid using Raney nickel. The moderate-pressure hydrogenations over nickel proceeded so rapidly that rate observations were not feasible. Raney nickel would not catalyze the reduction at low pressure.

Though both 3- and 4-nitrophthalic acids could be reduced with platinum at low pressure, only the 3-isomer would reduce with Raney nickel at moderate pressure. The 4-nitrophthalic acid was recovered unchanged in repeated attempts. However, if a small amount of the 3-isomer was added to the nitrophthalate salt solution, hydrogenation occurred at a rate comparable to that of the pure 3-isomer. Further examination revealed that a number of nitro and amino aromatic carboxylic acids would promote the hydrogenation of 4-nitrophthalic acid with Raney nickel. The results of hydrogenation at 1500 p.s.i. at 70° of 0.1 mole of 4-nitrophthalic acid with 5 mole % of the indicated accelerator and the time (in minutes) required for complete reduction are: 3-nitrophthalic acid, 15; 3-aminophthalic acid, 15; 4-aminophthalic acid, 60; *o*-nitrobenzoic acid, no reduction; anthranilic acid, 75; *m*-nitrobenzoic acid, no reduction; *m*-aminobenzoic acid, 35; *p*-nitrobenzoic acid, 45; *p*-aminobenzoic acid, 45; and aniline, no reduction. About 2 g. of commercially prepared Raney nickel was used. No perceptible pressure drop after three hours was considered as no reduction. The times given here for complete reduction should be considered as only gross approximations because of the difficulty of controlling the temperature and the amount of effective catalyst present.

The conclusion is drawn from these results that the amino compounds are actually the accelerators. Nitro compounds are first reduced; the amines then serve as accelerators. If this is true, *o*- and *m*-nitrobenzoic acids by themselves should not be reduced under these conditions, for they do not

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serve as accelerators, while the corresponding amino acids do. Actually, both of these nitro acids do reduce slowly, requiring three hours for complete reduction. But the addition of 5% *p*-isomer to each of them diminished the time required for reduction of *o*-nitrobenzoic acid to 45 min., and to 90 min. for *m*-nitrobenzoic acid. Thus, the *p*-isomer is capable of promoting the reduction of *o*- and *m*-nitrobenzoic acids, and as an impurity, it may account for the three-hour reduction of these two acids. When these two nitrobenzoic acids were tried as accelerators for the 4-nitrophthalic acid in the amount of 5 mole %, no reduction occurred because the amount, if any, of the *p*-nitrobenzoic acid present as impurity was too small to have a detectable effect.

Infrared spectroscopy of the original *o*-nitrobenzoic acid sample revealed a shoulder at 13.9 μ, probably indicative of *p*-isomer present to the extent of 1.5% maximum. From the spectrum of the *m*-nitrobenzoic acid, no conclusion could be drawn as to the presence of *p*-isomer. More exact interpretation of these spectra was difficult, owing to the lack of isomer samples of known purity.

EXPERIMENTAL

The organic acids were Eastman White Label grade. Melting points are corrected.

3-Aminophthalic acid hydrochloride. a. *By hydrogenation over platinum oxide.* In a solution of 8.2 g. (0.205 mole) of sodium hydroxide in 75 ml. of water was dissolved 21.0 g. (0.100 mole) of 3-nitrophthalic acid. The *p*H of the mixture was adjusted to 8–9 with dilute acetic acid. Reduction on the Parr low-pressure hydrogenation apparatus with 0.1 g. of platinum oxide at 3 atm. initial pressure required 4 hr. at 45°. The pressure fell at a constant rate during that period. The clear, colorless solution which remained after filtration to remove the catalyst was treated with 50 ml. of concd. hydrochloric acid, with cooling to avoid decarboxylation. This precipitated the amine hydrochloride in high purity. However, it was not isolated; the suspension was used for the diazotization which followed.

b. *By hydrogenation over Raney nickel.* A solution of 0.1 mole of disodium 3-nitrophthalate at *p*H 8–9 was prepared as just described. It was hydrogenated in a 300-ml. bomb at about 100 atm. with 2 g. of commercially prepared Raney nickel.[8] The reduction required about 15 min. at 70°. The product was handled as before.

3-Azidophthalic acid. The amine hydrochloride from either of these preparations was diazotized with a 25% solution of the calculated amount of sodium nitrite (6.9 g.) and converted to the azide by the addition in portions of an excess of 20% sodium azide solution, the temperature being kept below 15°. Cooling for several hours completed the crystallization of 19 g. (95%) of the product which melted, with decomposition, at 167–169°. A sample recrystallized from ethanol-water melted, with decomposition, at 171°.

Anal. Calcd. for $C_8H_5O_4N_3$: C, 46.3; H, 2.4; N, 20.3. Found: C, 46.2: H, 2.6; N, 20.6.

4-Aminophthalic acid hydrochloride. The sodium salt of 4-nitrophthalic acid was hydrogenated with platinum oxide at 3 atm., as described for the 3-isomer.

4-Azidophthalic acid. Conversion of the amine to the azide was accomplished as before in an over-all yield of 88%. The lower yield was probably due to the greater solubility in water of this azide isomer. Recrystallization from water gave a product which melted, with decomposition, at 170–171°.

Anal. Found: C, 46.8; H, 3.0; N, 20.6.

Hydrogenation of 4-nitrophthalic acid at 100 atmospheres with Raney nickel to evaluate accelerators. The acids which were tested for their ability to promote hydrogenation were added with the 4-nitrophthalic acid in the amount equal to 5 mole % of the latter to the sodium hydroxide solution, and the *p*H was adjusted to 8–9. When aniline was used, it was charged directly into the bomb with the nitrophthalate solution. The proper drop in hydrogen pressure was taken as an indication of reduction to amine.

Acknowledgment. The author wishes to express his debt to Mr. J. F. Stenberg, for performing many of the hydrogenations; and to Miss T. J. Davis, for interpretation of spectrograms.

ROCHESTER 4, N. Y.

(8) No. 28 Active Raney Catalyst in water. Raney Catalyst Co., Chattanooga, Tenn.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NOTRE DAME]

Condensation of Aromatic Nitro Compounds with Acrylacetonitriles.[1,2] II. Some *p*-Substituted Nitrobenzenes

R. B. DAVIS AND L. C. PIZZINI

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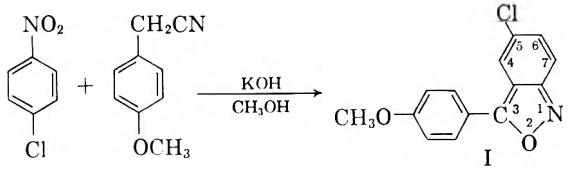
p-Nitrochlorobenzene and *p*-nitrobromobenzene react with some arylacetonitriles and potassium hydroxide in methanol to produce 3-aryl-5-haloanthranils and in pyridine to produce aryl(*p*-nitrophenyl)acetonitriles. *p*-Nitroanisole reacts with the arylacetonitriles and potassium hydroxide both in methanol and in pyridine to yield aryl(*p*-nitrophenyl)acetonitriles. *p*-Nitrotoluene under similar conditions in methanol undergoes self-condensation. Proof of structures is offered. The 3-aryl-5-haloanthranils may be transformed by known methods to 9-acridanones and acridines or to benzophenones. The aryl(*p*-nitrophenyl)acetonitriles may be oxidized to known benzophenones. A mechanism for the formation of the 3-aryl-5-haloanthranils is proposed.

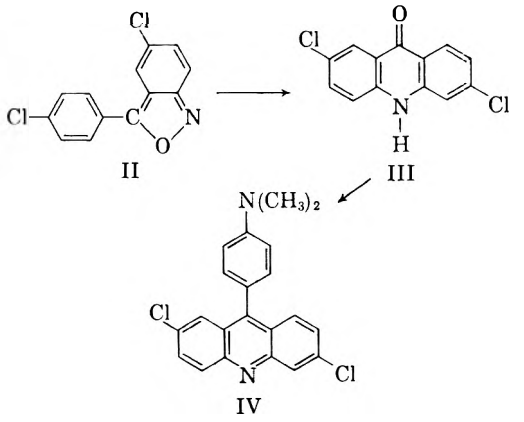
It has been reported[2] that nitrobenzene condenses with arylacetonitriles to produce arylcyanomethylene *p*-quinone oximes (4-arylcyanomethylene-2,5-cyclohexadiene-1-one oximes). We undertook the present investigation in order to determine whether *p*-substituted nitrobenzenes condense with arylacetonitriles to produce arylcyanomethylene *o*-quinone oximes (6-arylcyanomethylene-2,4-cyclohexadiene-1-one oximes).

When *p*-nitrochlorobenzene and *p*-methoxyphenylacetonitrile were allowed to react in methanolic potassium hydroxide solution, 3-(*p*-methoxyphenyl)-5-chloroanthranil (I) was obtained. This anthranil was previously prepared in a different manner by Guyot and Haller[3] and also by Simpson and Stephenson,[4] who likewise reported its reduction to 2-amino-5-chloro-4′-methoxybenzophenone. When our product was so reduced, the reported benzophenone was obtained.



I

The reaction of *p*-nitrochlorobenzene with *p*-chlorophenylacetonitrile in methanolic potassium hydroxide solution produced the known 3-*p*-chlorophenyl-5-chloroanthranil (II), which was rearranged according to the procedure of Tanasescu and Suciu[5] to 2,6-dichloro-9-acridanone (III). The reaction of this acridanone with dimethylaniline according to the method of the same authors produced 2,6-dichloro-9-(*p*-dimethylaminophenyl)-acridine (IV). In similar manner there was obtained



from *p*-nitrochlorobenzene and phenylacetonitrile the new 3-phenyl-5-chloroanthranil, the known 2-chloro-9-acridanone[6] and the known 2-chloro-9-(*p*-dimethylaminophenyl)acridine.[7]

Neresheimer and Ruppel[8] had previously reported the reaction of *p*-nitrochlorobenzene and phenylacetonitrile in the presence of potassium hydroxide and pyridine produces (*p*-nitrophenyl)-phenylacetonitrile. We repeated the reaction according to their directions and indeed obtained (*p*-nitrophenyl)phenylacetonitrile which we oxidized to the known *p*-nitrobenzophenone.[9] When *p*-chlorophenylacetonitrile and also *p*-methoxyphenylacetonitrile were used in place of phenylacetonitrile in the above reaction, we obtained the new (*p*-chlorophenyl)(*p*-nitrophenyl)acetonitrile and (*p*-methoxyphenyl)(*p*-nitrophenyl)acetonitrile, which were oxidized to the known 4-chloro-4′-nitrobenzophenone[10] and 4-methoxy-4′-nitrobenzophenone[11] respectively.

(1) Research project supported in part by National Science Foundation grant, NSF-G10030.

(2) Previous paper, *J. Am. Chem. Soc.*, **82**, 2913 (1960).

(3) A. Guyot and A. Haller, *Bull. soc. chim. France*, [3] **31**, 530 (1904).

(4) J. Simpson and O. Stephenson, *J. Chem. Soc.*, 353 (1942).

(5) I. Tanasescu and M. Suciu, *Bull. soc. chim. France*, [5] **4**, 245 (1937).

(6) R. Goodall and W. Kermack, *J. Chem. Soc.*, 1164 (1936).

(7) I. Tanasescu and M. Macarovici, *Bull. soc. chim. France*, [4] **49**, 1295 (1931).

(8) H. Neresheimer and W. Ruppel, U. S. Patent 2,080,-057 (1937).

(9) G. Schroeter, *Ber.*, **42**, 3356 (1909).

(10) J. Boeseken, *Rec. trav. chim.*, **23**, 107 (1904).

(11) K. Auwers, *Ber.*, **36**, 3899 (1903).

The reactions of *p*-nitrobromobenzene with phenylacetonitrile, *p*-chlorophenylacetonitrile, and *p*-methoxyphenylacetonitrile were found to be analogous to the reactions of *p*-nitrochlorobenzene with the same arylacetonitriles. When methanol was used as the solvent, the new 3-phenyl-5-bromoanthranil, 3-(*p*-chlorophenyl)-5-bromoanthranil, and 3-(*p*-methoxyphenyl)-5-bromoanthranil were obtained. The 3-phenyl-5-bromoanthranil was isomerized to the known 2-bromo-9-acridanone,[12] from which was prepared the known 2-bromo-9-(*p*-dimethylaminophenyl)acridine.[13] The 3-(*p*-chlorophenyl)-5-bromoanthranil was isomerized to the new 2-bromo-6-chloro-9-acridanone, from which was prepared the new 2-bromo-6-chloro-9-(*p*-dimethylaminophenyl)acridine. Attempts to rearrange the 3-(*p*-methoxyphenyl)-5-bromoanthranil and also the 3-(*p*-methoxyphenyl)-5-chloroanthranil (I) to the corresponding acridanones were unsuccessful. On the other hand, when pyridine was used in place of methanol in the above reactions, the same aryl-*p*-nitrophenylacetonitriles were obtained as were produced from *p*-nitrochlorobenzene.

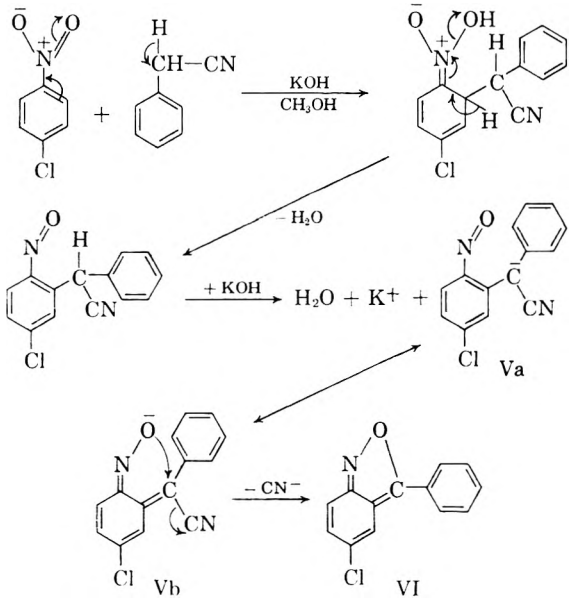
When *p*-nitroanisole was allowed to react with phenylacetonitrile, *p*-chlorophenylacetonitrile and *p*-methoxyphenylacetonitrile in both methanolic potassium hydroxide and in pyridine–potassium hydroxide, there was produced (*p*-nitrophenyl)-phenylacetonitrile, *p*-chlorophenyl-*p*-nitrophenylacetonitrile; and *p*-methoxyphenyl-*p*-nitrophenylacetonitrile respectively. We were unsuccessful in our attempts to isolate anthranils from the reactions conducted in methanol solution. It should also be pointed out that the reactions conducted in methanol solution gave poor yields of the diarylacetonitriles.

We were unsuccessful in our attempts to condense *p*-nitrotoluene with phenylacetonitrile. The material isolated from these attempts was apparently self-condensation products of *p*-nitrotoluene. Since other authors[14,15] have reported the self-condensation of *p*-nitrotoluene in alcoholic alkali solutions, we did not investigate this material further.

The yields of different products obtained from the reactions of the *p*-halonitrobenzenes with the arylacetonitriles and potassium hydroxide in methanol and pyridine demonstrate the fact that these reactions proceed by distinct paths in the two media. For example the reaction of *p*-nitrobromobenzene with phenylacetonitrile and potassium hydroxide produced 3-phenyl-5-bromoanthranil in 79% yield using methanol, and phenyl-*p*-nitrophenylacetonitrile in 76% yield using pyridine. While no completely satisfactory explanation is available for these distinct reaction paths, nevertheless, it may be said that pyridine is apparently more effective than methanol in aiding the removal of a halogen *para* to the nitro group in *p*-halonitrobenzenes. Likewise pyridine is apparently more effective than methanol in aiding the removal of the methoxy group from *p*-nitroanisole. No completely satisfactory explanation is available for the failure to obtain anthranils from the reactions of *p*-nitroanisole with the arylacetonitriles and potassium hydroxide in methanol. One might speculate that the resonance effect of the methoxy group is at least partially responsible.

It is pointed out that a large excess of potassium hydroxide was used in all the reactions of the *para*-substituted nitrobenzenes with the arylacetonitriles, both in pyridine and in methanol. A large excess was used with pyridine because the potassium hydroxide was present as a finely dispersed solid in that medium, apparently offering only its surface area for reaction. Previous investigators[3] likewise used large amounts of this reagent. A large excess was used with methanol because we found during the course of our former investigations[2] that such a practice gave better yields of condensation products.

The following mechanism is offered for the formation of the 3-aryl-5-haloanthranils. The initial steps follow the familiar lines proposed for the condensation of nitrobenzene with phenylacetonitrile,[2] differing only in that the phenylacetonitrile anion here attacks at a position *ortho* to the nitro group. Intermediate V may be considered as the potassium salt of a phenylcyanomethylene *o*-quinone oxime. However, a phenylcyanomethylene *o*-quinone oxime is not isolated because its potassium salt readily undergoes further reaction involving ring closure to a phenylanthranil.



(12) F. Ullmann, *Ann.*, **355**, 341 (1907).

(13) M. Polaczek, *Roczniki Chem.*, **16**, 76 (1936); *Chem. Abstr.*, 487 (1955).

(14) O. Fisher and E. Hepp, *Ber.*, **26**, 2231 (1893).

(15) A. G. Green, A. H. Davies, and R. S. Horsfall, *J. Chem. Soc.*, **91**, 2078 (1907).

It is suggested from this present investigation that phenylanthranils may also be formed in the condensations of nitrobenzene with arylacetonitriles. However, we were unsuccessful in our attempts to isolate anthranils in our former investigations.[2] Furthermore, we have subsequently obtained phenylcyanomethylene *p*-quinone oxime in as high as 92% yield from the reaction of nitrobenzene with phenylacetonitrile. It cannot be validly argued that the material isolated is actually a mixture of phenylcyanomethylene *p*-quinone oxime and 3-phenylanthranil because our method of isolation, particularly the treatment with boiling benzene,[2] is very conducive to removing large amounts of the anthranil. It may, therefore, be concluded that the *para* position in nitrobenzene is definitely the preferred position of attack.

It is pointed out that the formation of the 3-aryl-5-haloanthranils is reminiscent of the reaction of *o*-nitrotoluene in methanolic potassium hydroxide to produce anthranilic acid,[16] and the reaction of *o*-nitrophenylacetic acid with acetic anhydride to produce acetylanthranil,[17] wherein anthranils may be proposed as reaction intermediates.

EXPERIMENTAL[18,19]

Procedure A. (*a*) *3-Phenyl-5-chloroanthranil.* To a solution of 74 g. (1.1 moles) of potassium hydroxide (assay 85%) in 150 ml. of methanol were added with stirring and cooling in an ice bath 8.1 g. (0.069 mole) of phenylacetonitrile and a solution of 9.9 g. (0.063 mole) of *p*-nitrochlorobenzene in 100 ml. of methanol. The mixture was stirred for 4 hr. at 0–5°, and then 400 ml. of water was added with stirring. The precipitate was isolated by filtration, washed with water, and dried. There was obtained upon recrystallization from petroleum ether (b.p. 60–71°) pale yellow needles of 3-phenyl-5-chloroanthranil, m.p. 114–116°, 6.7 g. (46% yield), recrystallized a second time from petroleum ether, m.p. 115–117°.

Anal. Calcd. for $C_{13}H_8ClNO$: C, 67.98; H, 3.51; Cl, 15.44; N, 6.10. Found: C, 68.21; H, 3.73; Cl, 15.78; N, 6.55.

(*b*) *3-(p-Chlorophenyl)-5-chloroanthranil.* Following the procedure described above, 10.5 g. (0.069 mole) of *p*-chlorophenylacetonitrile and 9.9 g. (0.063 mole) of *p*-nitrochlorobenzene produced 7.6 g. (46% yield) of 3-(*p*-chlorophenyl)-5-chloroanthranil, m.p. 201–210°, recrystallized from chloroform, m.p. 214–215° (lit.[5] m.p. 202°).

Anal. Calcd. for $C_{13}H_7Cl_2NO$: C, 59.11; H, 2.67; N, 5.30. Found: C, 59.14; H, 2.74; N, 5.13.

(*c*) *3-(p-Methoxyphenyl)-5-chloroanthranil.* In similar manner, 10.3 g. (0.069 mole) of *p*-methoxyphenylacetonitrile and 9.9 g. of *p*-nitrochlorobenzene gave 8.1 g. (49% yield) of 3-(*p*-methoxyphenyl)-5-chloroanthranil, m.p. 138–143°, recrystallized from benzene, m.p. 143–145° (lit.[4] m.p. 143–145°).

(*d*) *3-Phenyl-5-bromoanthranil.* Likewise, 8.1 g. (0.069 mole) of phenylacetonitrile and 12.7 g. (0.063 mole) of *p*-nitrobromobenzene produced 13.7 g. (79% yield) of 3-phenyl-5-bromoanthranil, m.p. 105–110°, recrystallized from methanol, m.p. 116–118°.

Anal. Calcd. for $C_{13}H_8BrNO$: C, 56.96; H, 2.94; N, 5.11. Found: , C57.21; H, 3.25; N, 5.11.

(*e*) *3-(p-Chlorophenyl)-5-bromoanthranil.* Similarly, 10.5 g. (0.069 mole) of *p*-chlorophenylacetonitrile and 12.7 g. (0.063 mole) of *p*-nitrobromobenzene gave 9.28 g. (48% yield) of 3-(*p*-chlorophenyl)-5-bromoanthranil, m.p. 204–210°, recrystallized from ethyl acetate, m.p. 213–215°.

Anal. Calcd. for $C_{13}H_7BrClNO$: C, 50.60; H, 2.29; N, 4.54. Found: C, 50.72; H, 2.63; N, 4.68.

(*f*) *3-(p-Methoxyphenyl)-5-bromoanthranil.* In the usual way, 10.3 g. (0.069 mole) of *p*-methoxyphenylacetonitrile and 12.7 g. (0.063 mole) of *p*-nitrobromobenzene produced 13.3 g. (69% yield) of 3-*p*-methoxyphenyl-5-bromoanthranil, m.p. 126–130°, recrystallized from methanol, m.p. 134–135°.

Anal. Calcd. for $C_{14}H_{10}BrNO_2$: C, 55.28; H, 3.31; N, 4.61. Found: C, 55.03; H, 3.48; N, 4.67.

Procedure B. (*a*) *2-Chloro-9-acridanone (from 3-phenyl-5-chloroanthranil).* Using a modification of the procedure described by Tanasescu and Suciu,[5] 10 g. (0.15 mole) of sodium nitrite was added with stirring over a half-hour period to a solution of 2.0 g. (0.0087 mole) of 3-phenyl-5-chloroanthranil in 200 ml. of concd. sulfuric acid maintained at −10°. After the addition was completed, the mixture was allowed to warm to room temperature and to stand at room temperature for 17 hr. After pouring this mixture into 1 l. of water and crushed ice, the solid which precipitated was removed by filtration, was washed with water, and dried. There was obtained 1.8 g. (90% yield) of 2-chloro-9-acridanone, m.p. 390°, recrystallized from acetic acid, m.p. 394–395° (lit.[6] m.p. 398°).

(*b*) *2,6-Dichloro-9-acridanone [from 3-(p-chlorophenyl)-5-chloroanthranil].* In a similar manner, 2.0 g. (0.0076 mole) of the indicated anthranil produced 1.9 g. (96% yield) of 2,6-dichloro-9-acridanone, m.p. about 420°, recrystallized from acetic acid, m.p. 422–424° (lit.[5] m.p. 416°).

Anal. Calcd. for $C_{13}H_7Cl_2NO$: C, 59.11; H, 2.67; N, 5.30. Found: C, 59.04; H, 2.95; N, 5.28.

(*c*) *2-Bromo-9-acridanone (from 3-phenyl-5-bromoanthranil)* Similarly, 2.0 g. (0.0073 mole) of the indicated anthranil gave 1.5 g. (72% yield) of 2-bromo-9-acridanone, m.p. about 375° dec., recrystallized from acetic acid, m.p. 382–385° (lit.[12] m.p. above 360°).

(*d*) *2-Bromo-6-chloro-9-acridanone [from 3-(p-chlorophenyl)-5-bromoanthranil].* Isomerization of 1.8 g. (0.0058 mole) of the indicated anthranil in the usual way produced 1.6 g. (87% yield) of 2-bromo-6-chloro-9-acridanone, m.p. 414–416°, recrystallized from acetic acid, m.p. 416–418°.

Anal. Calcd. for $C_{13}H_7BrClNO$: C, 50.60; H, 2.20; N, 4.54. Found: C, 50.72; H, 2.63; N, 4.68.

Procedure C. (*a*) *2-Chloro-9-(p-dimethylaminophenyl)acridine.* Following the method of Tanasescu and Macarovici,[7] 0.67 g. (0.003 mole) of 2-chloro-9-acridanone and 1.0 g. of phosphorus oxychloride were added to 5.0 g. (0.04 mole) of dimethylaniline. The mixture was heated for 2 hr. on a hot water bath, cooled, diluted with 25 ml. of water and made basic to litmus with dilute sodium hydroxide. Unchanged dimethylaniline was removed by steam distillation, and the solid from the residue was isolated and dried. The yield of 2-chloro-9-(*p*-dimethylaminophenyl)acridine was 0.74 g. (74%), m.p. 236–238°, recrystallized from ethanol, m.p. 236–238° (lit.[7] m.p. 230–232°).

(*b*) *2,6-Dichloro-9-(p-dimethylaminophenyl)acridine.* In similar manner, 0.50 g. (0.003 mole) of 2,6-dichloro-9-acridanone and 5.0 g. (0.04 mole) of dimethylaniline gave 0.50 g. (72% yield) of 2,6-dichloro-9-(*p*-dimethylaminophenyl)acridine, m.p. 245–247° (lit.[20] m.p. 240–241°).

(*c*) *2-Bromo-9-(p-dimethylaminophenyl)acridine.* In like

(16) R. Scholl, *Monatsch.*, **34**, 1011 (1913); *Chem. Abstr.*, **7**, 3484 (1913).

(17) G. N. Walker, *J. Am. Chem. Soc.*, **77**, 6698 (1955).

(18) Analyses by Midwest Microlab, Incorporated, Indianapolis, Ind.

(19) All melting points are uncorrected.

(20) I. Tanasescu and M. Macarovici, *Bull. soc. chim France*, [5] **4**, 240 (1937).

manner, 0.82 g. (0.003 mole) of 2-bromo-9-acridanone and 5.0 g. (0.04 mole) of dimethylaniline produced 1.0 g. (88% yield) of 2-bromo-9-(*p*-dimethylaminophenyl)acridine, m.p. 243–245° dec. (lit.[13] m.p. 239–240° dec.).

(*d*) *2-Bromo-6-chloro-9-(p-dimethylaminophenyl)acridine.* Similarly, 1.2 g. (0.0038 mole) of 2-bromo-6-chloro-9-acridanone and 5.0 g. (0.04 mole) of dimethylaniline gave 1.5 g. (95% yield) of 2-bromo-6-chloro-9-(*p*-dimethylaminophenyl)acridine, m.p. 227–235°, recrystallized from benzene–petroleum ether (b.p. 60–71°), m.p. 236–237°.

Anal. Calcd. for $C_{21}H_{16}BrClN_2$: C, 61.26; H, 3.92. Found: C, 61.69; H, 4.20.

Procedure D. 1. *(p-Nitrophenyl)phenylacetonitrile.* (*a*) *From p-nitrochlorobenzene and phenylacetonitrile in potassium hydroxide–pyridine.* Following the procedure described by Neresheimer and Ruppel,[8] a mixture of 20 g. (0.126 mole) of *p*-nitrochlorobenzene, 200 g. of pyridine and 84 g. of a paste, obtained by grinding equal weights of pyridine and potassium hydroxide in a ball-mill, was cooled to −5°. Phenylacetonitrile, 15 g. (0.13 mole) was added with stirring over 10 min. The mixture was stirred at about 0° for 10 hr., then 100 ml. of benzene was added with stirring and the mixture was filtered under suction. The solid material was washed with benzene and with ether. The solid was then placed in 1 l. of water with stirring, and upon the portionwise addition of 50 g. of acetic acid a new solid precipitated, which was isolated, washed with water, and dried. This product was (*p*-nitrophenyl)phenylacetonitrile, 21 g. (68% yield), m.p. 68–72°, recrystallized from ethanol, m.p. 70–72°.

Anal. Calcd. for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.50; H, 4.32; N, 11.79.

(*b*) *From p-nitrobromobenzene and phenylacetonitrile in potassium hydroxide–pyridine.* In a similar manner, 13 g. (0.064 mole) of *p*-nitrobromobenzene and 7.5 g. (0.065 mole) of phenylacetonitrile produced 12 g. (76% yield) of (*p*-nitrophenyl)phenylacetonitrile, m.p. 68–70°, recrystallized from methanol, m.p. 70–72°, which was not depressed on mixing with the sample previously described.

(*c*) *From p-nitroanisole and phenylacetonitrile in potassium hydroxide–pyridine.* In like manner, 10 g. (0.66 mole) of *p*-nitroanisole and 15 g. (0.13 mole) of phenylacetonitrile gave 7.0 g. (45% yield) of (*p*-nitrophenyl)phenylacetonitrile, m.p. 66–70°, recrystallized from methanol, m.p. 70–72°, not depressed on mixing with above sample.

(*d*) *From p-nitroanisole and phenylacetonitrile in methanolic–potassium hydroxide (according to Procedure A).* Following the method previously described, 9.6 g. (0.063 mole) of *p*-nitroanisole and 8.1 g. (0.069 mole) of phenylacetonitrile produced 2.3 g. (15% yield) of (*p*-nitrophenyl-phenylacetonitrile, m.p. 69–72°, recrystallized from methanol, m.p. 71–72°, not depressed on mixing with a sample described above.

2. *(p-Chlorophenyl)-(p-nitrophenyl)-acetonitrile.* (*a*) *From p-nitrochlorobenzene and p-chlorophenylacetonitrile in potassium hydroxide–pyridine.* Following the method formerly described, 10 g. (0.63 mole) of *p*-nitrochlorobenzene and 9.7 g. (0.064 mole) of *p*-chlorophenylacetonitrile produced 15 g. (86% yield) of *p*-chlorophenyl-*p*-nitrophenylacetonitrile, m.p. 108–112°, recrystallized from ethanol, m.p. 110–112°.

Anal. Calcd. for $C_{14}H_9ClN_2O_2$: C, 61.66; H, 3.33. Found: C, 61.57; H, 3.47.

(*b*) *From p-nitrobromobenzene and p-chlorophenylacetonitrile in potassium hydroxide–pyridine.* Likewise, 13 g. (0.064 mole) of *p*-nitrobromobenzene and 9.7 g. (0.064 mole) of *p*-chlorophenylacetonitrile gave 15 g. (87% yield) of *p*-bromophenyl-*p*-nitrophenylacetonitrile, m.p. 105–109°, recrystallized from methanol, m.p. 109–111°, not depressed on mixing with above sample.

(*c*) *From p-nitroanisole and p-chlorophenylacetonitrile in potassium hydroxide–pyridine.* In similar manner, 9.6 g (0.063 mole) of *p*-nitroanisole and 10.5 g. (0.069 mole) of *p*-chlorophenylacetonitrile produced 9.8 g. (55% yield) of *p*-chlorophenyl-*p*-nitrophenylacetonitrile, m.p. 105–109°, recrystallized from ethanol, m.p. 109–111°, not depressed on mixing with a sample described above.

(*d*) *From p-nitroanisole and p-chlorophenylacetonitrile in methanolic–potassium hydroxide (according to Procedure A).* Following the method formerly described, 9.6 g. (0.063 mole) of *p*-nitroanisole and 10.5 g. (0.069 mole) of *p*-chlorophenylacetonitrile gave 3.2 g. (18% yield), m.p. 106–111°, recrystallized from ethanol, m.p. 110–112°, not depressed on mixing with a sample described above.

3.(*p-Methoxyphenyl)-(p-nitrophenyl)-acetonitrile.* (*a*) *From p-nitrochlorobenzene and p-methoxyphenylacetonitrile in potassium hydroxide–pyridine.* In the usual manner, 10 g. (0.063 mole) of *p*-nitrochlorobenzene and 9.4 g. (0.064 mole) of *p*-methoxyphenylacetonitrile produced 11 g. (65% yield) of *p*-methoxyphenyl-*p*-nitrophenylacetonitrile, m.p. 60–65°, recrystallized from methanol, m.p. 69–71°.

Anal. Calcd. for $C_{15}H_{12}N_2O_3$: C, 67.15; H, 4.51; N, 10.44. Found: C, 66.83; H, 4.64; N, 10.02.

(*b*) *From p-nitrobromobenzene and p-methoxyphenylacetonitrile in potassium hydroxide–pyridine.* In similar manner, 13 g. (0.064 mole) of *p*-nitrobromobenzene and 9.4 g. (0.064 mole) of *p*-methoxyphenylacetonitrile produced 11 g. (65% yield) of *p*-methoxyphenyl-*p*-nitrophenylacetonitrile, m.p. 61-65°, recrystallized from methanol, m.p. 71–72°, not depressed on mixing with a previously described sample.

(*c*) *From p-nitroanisole and p-methoxyphenylacetonitrile in potassium hydroxide–pyridine.* Likewise, 10 g. (0.066 mole) of *p*-nitroanisole and 19 g. (0.13 mole) of *p*-methoxyphenylacetonitrile yielded 6.1 g. (34%) of *p*-methoxyphenyl-*p*-nitrophenylacetonitrile, m.p. 63–67°, recrystallized from methanol, m.p. 71–72°, not depressed on mixing with a previously described sample.

(*d*) *From p-nitroanisole and p-methoxyphenylacetonitrile in methanolic–potassium hydroxide (according to Procedure A).* Following the method formerly described, 10 g. (0.066 mole) of *p*-nitroanisole and 9.6 g. (0.066 mole) of *p*-methoxyphenylacetonitrile gave 1.6 g. (9% yield) of *p*-methoxyphenyl-*p*-nitrophenylacetonitrile, m.p. 64–67°, recrystallized from methanol, m.p. 70–71°, not depressed on mixing with a sample previously described.

Procedure E. (*a*) *2-Amino-5-chloro-4′-methoxybenzophenone [from 3-(p-methoxyphenyl)-5-chloroanthranil].* Following the procedure of Simpson and Stephenson,[4] a solution of 2.0 g. (0.0077 mole) of 3-(*p*-methoxyphenyl)-5-chloroanthranil in 20 ml. of acetic acid was heated on a hot water bath, and 3.0 g. (0.064 mole) of iron filings was added over 2.5 hr., during which 6.5 ml. of water was also added. The mixture was then cooled, diluted with 100 ml. of water and was extracted with three 50-ml. portions of ether. The filtered extract was washed with dilute sodium carbonate solution, with water, and was dried over magnesium sulfate. Upon removal of the ether by distillation, there was obtained 1.7 g. (82% yield) of 2-amino-5-chloro-4′-methoxybenzophenone, recrystallized from methanol, m.p. 101–102° (lit.[4] m.p. 100–101°).

(*b*) *p-Nitrobenzophenone[from (p-nitrophenyl)phenylacetonitrile].* Following the directions of Neresheimer and Ruppel,[8] 0.37 g. (0.0015 mole) of (*p*-nitrophenyl)phenylacetonitrile, 1.0 g. (0.01 mole) of chromium trioxide and 50 ml. acetic acid were refluxed for 1 hr. The solution was cooled and then poured into 300 ml. of cold water. The resulting precipitate was isolated, washed with water, and dried. The yield of *p*-nitrobenzophenone thus obtained was 0.26 g. (76%), m.p. 137–139° (lit.[9] m.p. 138°), not depressed on mixing with a sample previously reported.[2]

(*c*) *4-Chloro-4′-nitrobenzophenone [from (p-chlorophenyl)(p-nitrophenyl)acetonitrile].* Following the method just described, 0.41 g. (0.0015 mole) of (*p*-chlorophenyl)(*p*-nitrophenyl)acetonitrile and 1.0 g. (0.01 mole) of chromium trioxide gave 0.21 g. (54% yield) of 4-chloro-4′-nitrobenzophenone, m.p. 98–100° (lit.[10] m.p. 98°), not depressed on mixing with a sample previously reported.[2]

(*d*) *4-Methoxy-4′-nitrobenzophenone* [*from* (*p-methoxyphenyl*)(*p-nitrophenyl*)*acetonitrile*]. In like manner, 0.40 g. (0.0015 mole) of *p*-methoxyphenyl-*p*-nitrophenylacetonitrile and 1.0 g. (0.01 mole) of chromium trioxide produced 0.16 g. (42% yield) of 4-methoxy-4′-nitrobenzophenone, m.p. 122–123° (lit.[11] m.p. 121°).

NOTRE DAME, IND.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE PAINT DIVISION OF THE PITTSBURGH PLATE GLASS CO.]

The Amidomethylation of Aromatic Compounds[1a]

CHESTER L. PARRIS[1b] AND ROGER M. CHRISTENSON

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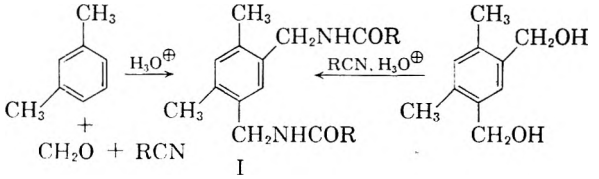
The joint condensation of aromatic compounds with formaldehyde and nitriles constitutes a new general method for the synthesis of *N*-aralkylamides and *N,N′*-bisaralkylamides. The scope and utility of the reaction are discussed.

When *m*-xylene was heated at 70–90° with an excess of paraformaldehyde and acetonitrile in phosphoric acid, or in a mixture of acetic and sulfuric acids, there was obtained *N,N′*-diacetyl-4,6-dimethyl-1,3-di(aminomethyl)benzene (Ia) in yields of 60–70%. The structure of Ia was established by its identity with the diamide obtained by alkylation of acetonitrile with 4,6-dimethyl-1,3-di(hydroxymethyl)-benzene according to the method of Parris and Christenson.[2] When the reaction was carried out with an excess of *m*-xylene the product was *N*-(2,4-dimethylbenzyl)acetamide.[2] Reaction of the monoamide with formaldehyde and acetonitrile gave the diamide Ia. This reaction of aromatic compounds with formaldehyde polymers and nitriles is a general one and has been found useful for the preparation of a large number of *N*-aralkylamides and *N,N′*-bisaralkylamides, frequently in high yields.

Methods for substitution of an aromatic nucleus by an amidomethyl group are known in the literature. German patents issued to Tscherniac[3] in 1901 disclosed the condensation of *N*-hydroxymethylphthalimide with *o*-nitrotoluene and other substituted aromatic compounds to give *N*-aralkylphthalimides. About the same time a large number of methylol derivatives of primary amides were synthesized by Einhorn[4] and condensed with a variety of aromatic compounds, especially substituted phenols, under acidic conditions. Further extensions of the Tscherniac-Einhorn method have been summarized in reviews.[5,6] The reaction of *N*-hydroxymethylamides with aromatic hydrocarbons has been the subject of recent papers by Cinnéide[7] and Nenitzescu and Dinulsecu.[8] However, the simple joint condensation described in this paper has not previously been reported.

The new method of amidomethylation was readily extended to other nitriles. The reaction of *m*-xylene and formaldehyde with acrylonitrile gave a good yield of *N,N′*-diacrylyl-4,6-dimethyl-1,3-di(aminomethyl)benzene[2] (Ib) from which the dipropionamide Ic was obtained by catalytic hydrogenation. The diamides Id, Ie, and If were prepared similarly. The three latter compounds were identical with the diamides prepared by alkylation of chloroacetonitrile, β-chloropropionitrile, and benzonitrile, respectively, with 4,6-dimethyl-1,3-di(hydroxymethyl)benzene, according to the Parris and Christenson method.[2]



Ia. R = CH_3 Id. R = $ClCH_2$
b. R = CH_2=CH e. R = $ClCH_2CH_2$
c. R = C_3H_7 f. R = C_6H_5

In mixtures of acetic acid and sulfuric acid all of the lower aromatic hydrocarbons reacted in similar fashion. *N*-Aralkylacetamides were obtained from the reaction of acetonitrile and formaldehyde with benzene, toluene, ethylbenzene, *o*-xylene, cumene, pseudocumene, and anisole. The product of the amidomethylation of toluene was predominantly *N*-(*p*-methylbenzyl)acetamide together with a lesser amount of difficultly purified *ortho* isomer. Amidomethylation of bromobenzene required the use of concentrated sulfuric acid to give *N*-(*p*-bromobenzyl)acetamide.[9] The properties of these and other related amides are summarized in Table I.

(1) (a) Portion of a paper presented before the Meeting-in-Miniature of the Central Pennsylvania Section, American Chemical Society, March 15, 1958, Pennsylvania State University, State College, Pa. (b) Present address: Pennsalt Chemical Corp., Box 4388, Phila. 18, Pa.

(2) C. L. Parris and R. M. Christenson, *J. Org. Chem.*, 25, 331 (1960).

(3) J. Tscherniac, DRP 134,979 and 134,980.

(4) A. Einhorn, *et al.*, DRP 157,355 and 158,088; *Ann.*, 343, 207 (1905); *Ann.*, 361, 113 (1908).

(5) R. Schröter in Houben-Weyl, *Methoden der Organischen Chemie*, 4th Edition, Vol. II, Georg Thieme Verlag, Stuttgart, 1957 (pp. 795–805).

(6) H. Hellmann, *Angew. Chem.*, 69, 463 (1957).

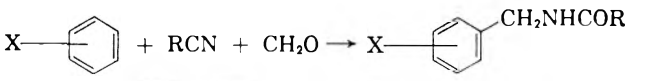
(7) R. O. Cinnéide, *Nature*, 175, 47 (1955).

(8) C. D. Nenitzescu and I. Dinulsecu, *Rev. Chim.* (*Acad. rep. populaire Roumaine*), 2, 47 (1954).

(9) C. W. Shoppee, *J. Chem. Soc.*, 1225 (1931).

TABLE I

N-ARALKYLAMIDES FROM AROMATIC COMPOUNDS, NITRILES, AND FORMALDEHYDE



Ring Substituents, X	R	Formula	Melting Point, Found	Melting Point, Lit.	Yield, %		Analyses, C	Analyses, H	Analyses, N
H	CH_3	$C_9H_{11}NO$	62–63.5	64.5–66.5[a]	50	Calcd.	72.45	7.43	9.39
						Found	72.11	7.30	9.43
							72.03	7.50	
2-Methyl	CH_3	$C_{10}H_{13}NO$	59–75	69[b]	10	Calcd.	73.59	8.03	8.58
				77.5–78[c]		Found	73.50	7.94	8.73
							73.55	8.07	8.63
4-Methyl	CH_3	$C_{10}H_{13}NO$	112–113	111–112[a]	36	Calcd.	73.59	8.03	8.58
						Found	73.56	8.08	8.72
							73.59	7.86	8.53
4-Methyl	CH_2=CH	$C_{11}H_{13}NO$	110–113.5		89	Calcd.	75.40	7.48	8.00
						Found	75.15	7.50	7.88
							75.35	7.34	
2,3(or 3,4-)-Dimethyl	CH_3	$C_{11}H_{15}NO$	94–95		54	Calcd.	74.54	8.53	7.90
						Found	74.86	8.73	7.93
							75.11	8.54	
2,4-Dimethyl	CH_3	$C_{11}H_{15}NO$	113–114	110.5–111.5[a]	52	Calcd.	74.54	8.53	7.90
						Found	74.62	8.31	8.25
							74.45	8.59	
2,4-Dimethyl	H	$C_{10}H_{13}NO$	122–124		25	Calcd.			8.60
						Found			8.54
2,5-Dimethyl	CH_3	$C_{11}H_{15}NO$	91–92			Calcd.	74.54	8.53	7.90
						Found	74.93	8.21	8.07
							74.83	8.13	
4-Ethyl	CH_3	$C_{11}H_{15}NO$	79–81		19	Calcd.	74.89	8.57	7.94
						Found	74.93	8.84	8.13
							75.11	8.71	
4-Isopropyl	CH_3	$C_{12}H_{17}NO$	66–67.5	65[d]	75	Calcd.	75.35	8.96	7.32
						Found	75.47	8.76	7.32
							75.38	8.89	7.16
4-Isopropyl	CH_2=CH	$C_{13}H_{17}NO$	75–76.5		53	Calcd.	76.81	8.43	6.86
						Found	76.91	8.62	6.88
							77.19	8.47	
2,4,5-Trimethyl	CH_3	$C_{12}H_{17}NO$	137–139	143.5[e]	67	Calcd.	75.35	8.96	7.32
						Found	76.07	9.02	7.30
							75.55	9.31	
4-Methoxy	CH_3	$C_{10}H_{13}NO$	94–96	94.5–96[a]	28.5	Calcd.	67.02	7.31	7.82
						Found	67.42	7.13	8.03
							67.50	7.12	
4-Bromo	CH_3	$C_9H_{10}BrNO$	118.5–120	113[f]	37	Calcd.	47.38	4.42	6.14
						Found	47.57	4.47	6.21
							47.83	4.33	

[a] Ref. (2) and references cited therein. [b] H. Strassmann, *Ber.*, 21, 576 (1888). [c] W. H. Carothers and G. A. Jones, *J. Am. Chem. Soc.*, 47, 3051 (1935). [d] H. Goldschmidt and A. Gessner, *Ber.*, 20, 2414 (1887). [e] R. Willstätter and H. Kubli, *Ber.*, 42, 4151 (1909). [f] Ref. (9).

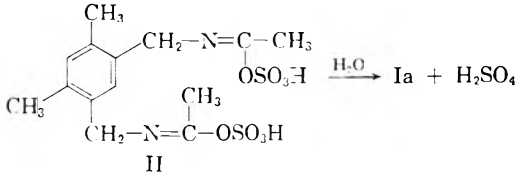
Amidomethylation of *p*-xylene gave mostly *N*,*N*′-diacetyl-2,5-dimethyl-1,4-di(aminomethyl)benzene together with *N*-(2,5-dimethylbenzyl)acetamide. Durene afforded *N*,*N*′-diacetyl-1,3,5,6-tetramethyl-1,4-di(aminomethyl)benzene.[2]

Amidomethylation of naphthalene gave a complex mixture of amides from which three products were isolated after acid hydrolysis. 1-Naphthalenemethylamine was obtained in 12% yield. The structure of this compound was established by the identity of its acetyl derivative[10] with the amide obtained by alkylation of acetonitrile with 1-naphthalenemethanol according to the procedure of Parris and Christenson.[2] The major product was a liquid diamine obtained in 25% yield, characterized by a diacetyl derivative melting at 262–263.5°. The diamide was identical with the product obtained by alkylation of acetonitrile with 1,4-di(hydroxymethyl)naphthalene.[2] The third product was a solid diamine obtained in 6% yield, m.p. 127–129°, characterized by a diacetyl derivative, m.p. 276–279°. This compound was thought to be the 1,5-isomer.

When the reaction of *m*-xylene, paraformaldehyde, and acetonitrile was carried out in mixtures of

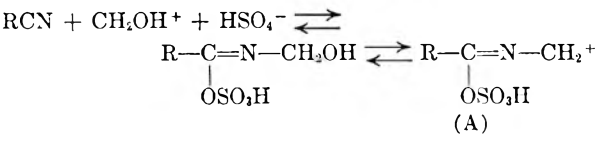
(10) J. von Braun, G. Blessing, and F. Zobel, *Ber.*, 56, 1988 (1923).

acetic and sulfuric acid and the product was allowed to cool for at least one day, a voluminous precipitate was formed. This solid was stable and easily filterable, but had no definite melting point. Qualitative tests for both nitrogen and sulfur were positive. A slurry in water gave a strongly acidic supernatant liquid which gave a positive test for sulfate ions. Prolonged washing with water or neutralization with bases afforded a sulfur-free product which proved to be quite pure diamide Ia. Recrystallization from methanol or acetic acid also gave Ia. The sulfur and nitrogen content agreed well for the *N,N'*-bisaralkylamide sulfate (II).



II

The isolation of stable sulfur-containing intermediates was quite common throughout this work. Frequently the amide sulfates were quite insoluble and crystallized during the course of the reactions, presenting difficulties in agitation of the mixtures. It is interesting to note that Magat[11] isolated a sulfur-containing intermediate in the synthesis of *N,N'*-methylenebisamides by the acid-catalyzed reaction of formaldehyde with nitriles. It is reasonable to suggest that the electrophilic species both in Magat's reaction and in the present case is the amidomethyl sulfate carbonium ion (A).



(A)

The *N*-aralkylamides and *N,N'*-bisaralkylamides were hydrolyzed either by heating with aqueous alkali in an autoclave at 150° or by refluxing with concentrated hydrochloric acid in acetic acid. Thus, hydrolysis of Ia by the former method gave 4,6-dimethyl-1,3-di(aminomethyl)-benzene[12]; acid hydrolysis afforded the diamine as its dihydrochloride. In a few experiments some 2,4-dimethylbenzylamine was also isolated.

4,6-Dimethyldi(aminomethyl)benzene formed crystalline polysalts with adipic and sebacic acids which were converted to high-melting polyamides by melt polymerization. Reaction of 4,6-dimethyldi(aminomethyl)benzene with phosgene in boiling tetralin afforded 4,6-dimethyl-*m*-xylene-α,α'-diisocyanate.

(11) E. E. Magat, B. F. Faris, S. E. Reith, and L. F. Salisbury, *J. Am. Chem. Soc.*, **73**, 1028 (1951).

(12) D. F. DeTar and C. J. De Pomme, U. S. Patent 2,640,080.

EXPERIMENTAL[13]

All aromatic hydrocarbons were obtained from the usual commercial sources and were of highest purity available. Hydrogen cyanide and acrylonitrile were products of the American Cyanamid Company. Acetonitrile was obtained from Union Carbide Chemical Company. All other nitriles were obtained from the Eastman Kodak Company. 1-Naphthalenemethanol, m.p. 58.5–61°, was prepared from 1-(bromomethyl)naphthalene[14] (lit., m.p. 63°,[14] 59.5–60°,[15] 59°[16]). 2-Naphthalenemethanol, m.p. 80.5–82.5°, was obtained by saponification of 2-naphthalenemethanol acetate which was prepared from 2-(bromomethyl)naphthalene by the method of Tarbell, Fukushima, and Dains[17] (lit., m.p. 80°,[18] 80–80.5°[19]). 1,4-Di(hydroxymethyl)naphthalene was prepared from 1-methylnaphthalene by the procedure of Lock and Schneider.[20b]

Preparation of N,N'-diacetyl-1,3-di(aminomethyl)benzene (Ia) *in phosphoric acid.* In a 5-l. three necked flask equipped with a Hershberg stirrer, condenser, and thermometer was placed 1500 ml. of 85% phosphoric acid, 360 g. (11 moles) of 91% paraformaldehyde, 530 g. (5.0 moles) of *m*-xylene, and 535 g. (13 moles) of acetonitrile. The mixture was heated with vigorous agitation to 65° whereupon a spontaneous reaction occurred. The temperature was held at 65–75° until the exothermic reaction was over, and then at 90° for an additional 4 hr. After cooling there remained a layer of 124–135 g. of unchanged xylene. The viscous acid layer was added in a slow stream with vigorous agitation to 8 l. of ice water containing 3 l. of ammonium hydroxide. The resulting suspension was stirred overnight, filtered, washed with dilute ammonium hydroxide, and dried at 75° in a convection oven for 24 hr. The yield of crude diamide, m.p. 225–235°, was 600–611 g. (61–66% based on xylene converted). After recrystallization from methanol the melting point of the analytical sample was raised to 245–246°. By mixture melting point determination and comparison of the infrared spectra the compound was proved to be identical with the diamide obtained by alkylation of acetonitrile with 4,6-dimethyl-1,3-di(hydroxymethyl)benzene.[2]

In similar manner, *N,N'*-diacrylyl-4,6-dimethyl-1,3-di(aminomethyl)benzene was obtained from acrylonitrile, m.p. about 250° with polymerization. The infrared spectrum was identical with the diacrylamide obtained by alkylation of acrylonitrile with 4,6-dimethyl-1,3-di(hydroxymethyl)benzene.[2]

Preparation of Ia *in acetic acid–sulfuric acid mixture.* A suspension of 264 g. (8.0 moles) of powdered 91% paraformaldehyde in 1750 ml. of glacial acetic acid and 450 ml. of concd. sulfuric acid was heated at 50° until the paraformaldehyde was dissolved. The clear solution was cooled to about 35° and then 328 g. (8.0 moles) of acetonitrile was added dropwise at 35–45°. Stirring was continued until the spontaneous reaction was completed, then 424 g. (4.0 mole)

(13) All melting points and boiling points are uncorrected. The carbon and hydrogen analyses were by Galbraith Laboratories, Knoxville, Tenn. The Kjeldahl analyses were by Dr. James B. Lear and staff of these laboratories.

(14) R. H. F. Manske and A. E. Ledingham, *Can. J. Res.*, **17B**, 14 (1939).

(15) E. Bamberger and W. Lodter, *Ber.*, **21**, 256 (1888).

(16) E. Bourquelot and M. Bridel, *Compt. rend.*, **168**, 323 (1919).

(17) D. S. Tarbell, D. K. Fukushima, and H. Dains, *J. Am. Chem. Soc.*, **67**, 197 (1945).

(18) H. Rupe and F. Becherer, *Helv. Chim. Acta*, **6**, 880 (1923).

(19) E. Bamberger and O. Boekmann, *Ber.*, **20**, 1115 (1887).

(20) (a) G. Lock and E. Walter, *Ber.*, **75B**, 1158 (1942); (b) G. Lock and R. Schneider, *Ber.*, **84**, 636 (1951).

of *m*-xylene were added. The two-phase mixture was heated slowly to 65–75° whereupon a self-sustaining reaction occurred with formation of a clear yellow, homogeneous mixture. The temperature was raised to 85–90° for 5 hr. then cooled to about 50°. The slightly viscous product was treated with 250 ml. of water and the apparatus arranged for distillation at reduced pressure. The flask contents were heated on a steam bath with continued stirring while a vacuum of 20–25 mm. was applied to the system. A total of 1200-1700 ml. of aqueous acetic acid was thus distilled. The viscous residue was cooled, treated carefully with 1 l. of cold water, and then neutralized with an ice cold solution of 600 g. of sodium hydroxide in 1500 ml. of water. The resulting fine, sandy precipitate was filtered and washed with water until the washings were neutral. After drying at 75° the yield of crude diamide, m.p. 215–235°, was 757 g. (75%). Recrystallization raised the melting point to 246.5–248°. The infrared spectrum of this product was identical with Ia obtained by the phosphoric acid procedure.

The dichloroacetamide Id, prepared similarly, m.p. 231–232° (lit.,[8] m.p. 205°), did not depress the melting point of the product obtained by alkylation of chloroacetonitrile with 4,6-dimethyl-1,3-di(hydroxymethyl)benzene, m.p. 231–232°.[2]

Anal. Calcd. for $C_{14}H_{18}Cl_2N_2O_2$: C, 53.01; H, 5.72; N, 8.83; Cl, 22.35. Found: C, 53.21, 53.39; H, 5.51, 5.60; N, 8.83, 8.76; Cl, 22.21, 21.94.

The di-β-chloropropionamide Ie, m.p. 206° dec., did not depress the melting point of the diamide obtained by alkylation of β-chloropropionitrile with 4,6-dimethyl-1,3-di(hydroxymethyl)benzene, m.p. 206° dec.[2]

The dibenzamide, If, m.p. 262–263.5°, was identical with the diamide obtained by alkylation of benzonitrile with 4,6-dimethyl-1,3-di(hydroxymethyl)benzene, m.p. 263–264.5°.[2]

Isolation of the disulfate of Ia. To a suspension of 72.0 g. (2.2 moles) of 91% paraformaldehyde in a mixture of 1750 ml. of glacial acetic acid and 150 ml. of sulfuric acid was added 107.0 g. (2.4 moles) of acetonitrile at 30–70°. After the reaction was complete, 106.0 g. (1.0 mole) of *m*-xylene was added and the mixture heated at 90° for 6 hr. Upon cooling overnight there was formed a voluminous white solid which was collected on a sintered glass funnel, washed with fresh acetic acid, and then with ether. After air drying the yield was 384 g. (86.5%).

Anal. Calcd. for $C_{14}H_{20}N_2S_2O_8$: N, 6.85; S, 15.75. Found: 6.70; S, 14.62.

A 50-g. portion of the sulfate complex was stirred with 500 ml. of cold water. The suspension was made alkaline to phenolphthalein with sodium hydroxide, filtered, washed thoroughly with water, and dried at 70° to give 21 g. (75%) of Ia, m.p. 245–248°. Recrystallization from methanol raised the melting point to 247–249°. The product was shown by mixture melting point and its infrared spectrum to be Ia.

Preparation of N-(2,4-dimethylbenzyl)acetamide. A suspension of 75.0 g. (2.28 moles) of paraformaldehyde in 1050 ml. of acetic acid and 225 ml. of sulfuric acid was treated with 112.5 g. (2.8 moles) of acetonitrile at 30–70°, then 1594 g. (15 moles) of *m*-xylene were added. The mixture was heated for 4.5 hr. at 85–90°, then cooled. The clear organic phase was decanted and discarded. The lower orange acidic phase, which solidified upon cooling, was filtered. The residue was washed thoroughly with water until the washings were neutral. After air drying there was obtained 228 g. (52%) of crude amide, m.p. 95–115°, which was distilled. The product was a colorless oil, b.p. 190–195° (1 mm.), which solidified in the receiver, m.p. 110–112°. The distillate was recrystallized from a mixture of benzene and petroleum ether (b.p. 30–60°) to give white crystals, m.p. 113–114°. The melting point was not depressed by admixture with an authentic sample prepared by the method of Parris and Christenson.[2]

Amidomethylation of N-(2,4-dimethylbenzyl)acetamide. A suspension of 18.0 g. (0.6 mole) of paraformaldehyde in 440 ml. of acetic acid and 28 ml. of sulfuric acid was treated with 26.9 g. (0.65 mole) of acetonitrile in the usual way. Forty-four grams (0.25 mole) of *N*-(2,4-dimethylbenzyl)-acetamide was added and the temperature raised to 90° for 5 hr. After cooling and standing at room temperature for 1 week a white solid was deposited which was filtered and washed with water until the washings were neutral. There was obtained 28 g. (45%) of Ia, m.p. 247–248°.

N,N'-Dipropionyl-4,6-dimethyl-1,3-di(aminomethyl)benzene (Ic). A suspension of 27.2 g. (0.1 mole) of the diacrylamide Ib in 200 ml. of methanol was shaken with 0.5 g. of 5% palladized carbon catalyst at 20–60 p.s.i. and room temperature. The theoretical amount of hydrogen was rapidly absorbed. The product was boiled, filtered while hot through a Celite pad, and concentrated. Upon cooling there was obtained 23.3 g. (85%) of Ic, m.p. 216°. After two recrystallizations from methanol the melting point was 217.5–218°.

Anal. Calcd. for $C_{16}H_{24}N_2O_2$: C, 69.53; H, 8.75; N, 10.10. Found: C, 69.41, 69.48; H, 8.32, 8.47; N, 10.02, 10.25.

Preparation of N,N'-diacetyl-2,5-dimethyl-1,4-di(aminomethyl)benzene and N-(2,5-dimethylbenzyl)acetamide. A suspension of 144.0 g. (4.4 moles) of 91% paraformaldehyde in 1750 ml. of acetic acid and 360 ml. of sulfuric acid was treated with 214 g. (5.25 moles) of acetonitrile in the usual way. When the spontaneous reaction was complete 212 g. (2.0 moles) of *p*-xylene were added and the mixture heated at 90°. After about 3 hr. a white precipitate began to form and eventually the mixture could not be stirred. The solid was collected on a sintered glass funnel and washed thoroughly with petroleum ether (b.p. 30–60°). Both the residue and the filtrate were processed.

The solid was dried at 75° to give 600 g. (67.5%) of crude sulfate. This material was slurried with water, filtered, and washed thoroughly on the filter until the washings were neutral. After drying the yield of crude diamide was 282.5 g. (55% overall), m.p. 242–250°. The analytical sample, prepared by recrystallization from methanol, melted at 269°.

Anal. Calcd. for $C_{14}H_{20}N_2O_2$: C, 67.71; H, 8.12; N, 11.28. Found: C, 67.52, 67.53; H, 7.96, 7.73; N, 11.50.

The original filtrate was diluted with water, made basic with ammonium hydroxide, and extracted thoroughly with butanol. The extract was concentrated and the residue was distilled. The product consisted of 75 g. (21%) of colorless oil, b.p. 140–180° (0.1–0.3 mm.) which solidified in the receiver, m.p. 75–85°. The distillate was crystallized from a mixture of benzene and petroleum ether to give an analytical sample melting at 90–91°. The compound had the correct analysis for *N*-(2,5-dimethylbenzyl)acetamide (Table I).

Preparation of N,N'-diacetyl-2,3,5,6-tetramethyl-1,4-di(aminomethyl)benzene. A suspension of 72.0 g. (2.4 moles) of paraformaldehyde in 1750 ml. of acetic acid and 150 ml. of sulfuric acid was treated dropwise with 107.0 g. (2.6 moles) of acetonitrile at 30–70°. When the spontaneous reaction was complete 134 g. (1.0 mole) of durene were added and the temperature was raised to 85°. After 45 min. a voluminous precipitate began to appear. Heating was maintained for 5 hr. and, after cooling, the mixture was filtered on a sintered glass funnel, washed thoroughly with hexane, and dried *in vacuo*.

Anal. Calcd. for $C_{16}H_{24}N_2S_2O_8$: N, 6.42; S, 14.69; H_2SO_4, 45.0%. Found: N, 6.20, 6.22; S, 14.26; H_2SO_4 (by titration) 43.0%.

The product was washed thoroughly with water until the washings were neutral. After drying at 75°, the yield of white solid, not melting below 310°, was 198 g. (72%). An analytical sample was prepared by three recrystallizations from glacial acetic acid.

Anal. Calcd. for $C_{16}H_{24}N_2O_2$: C, 69.53; H, 8.75; N, 10.14. Found: C, 69.53, 69.36; H, 8.50, 8.58; N, 10.25.

N-(o- and p-Methylbenzyl)acetamide. A suspension of 165 g. (5.8 moles) of paraformaldehyde in 1050 ml. of acetic acid and 450 ml. of sulfuric acid was treated with 226 g. (5.5

moles) of acetonitrile at 30–70°. When the exothermic reaction was treated with 226 g. (5.5 moles) of acetonitrile at 30–70°. When the exothermic reaction was over, 460 g. (5.0 moles) of toluene was added and the mixture was heated for 4 hr. at 90°. The cooled mixture was poured into 10 l. of cold water and extracted thoroughly with fresh toluene. The extract was washed, concentrated, and distilled to give 433 g. (53%) of mixed isomers, b.p. 130° (0.05 mm.), m.p. 65–100°. The material was redistilled and a middle fraction was collected for analysis.

Anal. Calcd. for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.67, 73.28; H, 7.84, 8.07; N, 8.84.

A crude undistilled mixture of isomers prepared as above was dissolved in a hot mixture of acetone and petroleum ether (b.p. 30–60°). Upon cooling a yellow oil separated which partially solidified upon standing. The solid was filtered and pressed tightly on the funnel to remove adhering oil droplets. Both the solid residue and oily filtrate were processed.

The solid was recrystallized from a mixture of benzene and petroleum ether (b.p. 30–60°) to give colorless needles of *N*-(*p*-methylbenzyl)acetamide, m.p. 110–112°. The analytical sample, prepared by two additional recrystallizations from benzene, melted at 112–113° (Table I).

The oily filtrate was distilled to give 82.5 g. of colorless oil, b.p. 132–135° (0.05 mm.), which solidified in the receiver, m.p. 44–68°. Three recrystallizations raised the melting range to 59–75° but the *N*-(*o*-methylbenzyl)-acetamide could not be purified further (Table I).

N-Acetyl-1-naphthalenemethylamine. To 100 ml. of acetonitrile at 5° was added dropwise with stirring 7.5 ml. of concd. sulfuric acid. After 0.5 hr., 15.8 g. (0.1 mole) of 1-naphthalenemethanol was added in small portions at 5°, then allowed to warm slowly to room temperature. Polymer which precipitated during the reaction was removed mechanically. After 5 days the product was diluted with water and extracted thoroughly with ethyl acetate. The extract was washed, dried and concentrated. The residue was distilled to give 6.0 g. of yellow oil, b.p. 150–215° (0.1 mm.) which solidified in the receiver. The distillate was recrystallized twice from a mixture of benzene and petroleum ether (b.p. 30–60°) and twice more from a mixture of ethyl acetate and petroleum ether to give white crystals, m.p. 127–128.5° (lit.,[10] m.p. 134°).

Anal. Calcd. for $C_{13}H_{13}NO$: C, 78.37; H, 6.58; N, 7.03. Found: C, 78.47, 78.54; H, 6.52, 6.76; N, 7.09, 7.09.

N-Acetyl-2-naphthalenemethylamine. By the same procedure employed for the 1-isomer above, there was obtained from 2-naphthalenemethanol a colorless oil, b.p. 169–200° (0.1 mm.), m.p. 113–119° after recrystallization from benzene and petroleum ether (b.p. 30–60°). After repeated recrystallization from a mixture of ethyl acetate and petroleum ether the analytical sample melted at 125–125.5° (lit.,[25] m.p. 126°). A mixture with the 1-isomer showed a melting point depression of 35°.

Anal. Calcd. for $C_{13}H_{13}NO$: C, 78.37; H, 6.58; N, 7.03. Found: C, 78.90, 78.73; H, 6.56, 6.38; N, 7.18, 7.20.

N,N'-Diacetyl-1,4-di(aminomethyl)naphthalene. To a solution of 3.8 ml. of sulfuric acid in 25 ml. of acetonitrile was added 4.7 g. (0.025 mole) of 1,4-di(hydroxymethyl)naphthalene with shaking and cooling at 5°. After having stood overnight, the mixture had separated into two phases. It was diluted with water, made basic with ammonium hydroxide and extracted thoroughly with ethyl acetate. The organic phase was filtered to give a 0.5 g. of residue, m.p. 261–262.5°, after recrystallization from methanol. Concentration of the organic phase yielded a gummy residue which, after repeated recrystallization from methanol, gave an additional yield of diamide, m.p. 260–262.5°. The total yield was 2.5 g. (37%).

Anal. Calcd. for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.37. Found: C, 70.42, 70.53; H, 7.18, 7.07; N, 10.26.

Amidomethylation of naphthalene. To a solution of 180.0 g. of paraformaldehyde in 1740 ml. of acetic acid and 450 ml. of sulfuric acid was added 270 g. (6.6 moles) of acetonitrile dropwise at 30–50° in the usual way. After cooling slightly 384 g. (3.0 moles) of naphthalene were added and the temperature was maintained at 70° until the mixture was homogeneous. The temperature was then held at 90° for 5 hr. longer and cooled. The apparatus was arranged for distillation *in vacuo* and about 1200 ml. of acetic acid was distilled at 20 mm. pressure. The viscous residue was treated with 1 l. of water and then neutralized with ammonium hydroxide.

The product was a heavy gummy solid which was isolated by decantation of the liquid. The gum was washed briefly with water then refluxed for 24 hr. with a mixture of 1250 ml. of acetic acid and an equal volume of concd. hydrochloric acid. The mixture was concentrated by distillation at reduced pressure. The residue was neutralized with sodium hydroxide and a small amount of polymer which precipitated was removed mechanically. The *p*H was then adjusted to 11 with additional alkali and the resulting oil was extracted with butanol. After removal of the solvent distillation of the residue gave 285.2 g. of an oil, b.p. 138–190° (0.2 mm.), which partially crystallized upon refrigeration for 24 hr. The product was filtered and pressed on the filter with a rubber dam to remove adhering oil droplets. Both filtrate (A) and residue (B) were processed.

The viscous yellow-green filtrate (A) was distilled through a Vigreux column:

Fraction 1, b.p. 97–109° (0.1 mm.), consisted of 55.5 g. of colorless oil. A center fraction of the material obtained upon redistillation boiled at 92° (0.1 mm.).

Anal. Calcd. for $C_{11}H_{11}N$: C, 84.00; H, 7.06; N, 8.91. Found: C, 83.46, 83.67; H, 7.09, 7.08; N, 8.92.

The hydrochloride was prepared in the usual way and recrystallized from acetic acid, m.p. 253.5–255°.

Anal. Calcd. for $C_{11}H_{12}ClN$: C, 68.21; H, 6.25; N, 7.23. Found: C, 68.20, 68.28; H, 6.26, 5.93; N, 7.26.

The acetyl derivative, prepared by treatment of the amine with acetyl chloride in pyridine solution, melted at 127.5–128.5°. A mixture with the *N*-acetyl-1-naphthalenemethylamine prepared from 1-naphthalenemethanol showed no depression in melting point.

Anal. Calcd. for $C_{13}H_{13}NO$: C, 78.37; H, 6.58; N, 7.03. Found: C, 78.58, 78.21; H, 6.79, 6.72; N, 7.08.

Fraction 2, b.p. 158–165° (0.3 mm.), consisted of 124.5 g. of slightly viscous yellow-green oil. A center fraction of redistilled material boiled at 147° (0.2 mm.). Upon exposure to air a bluish fluorescence was developed.

Anal. Calcd. for $C_{12}H_{14}N_2$: C, 77.38; H, 7.56; N, 15.04. Found: C, 77.09, 76.97; H, 7.81; N, 14.84, 14.78.

The dihydrochloride did not melt below 300° after repeated recrystallization from aqueous acetic acid, then from a mixture of benzene and methanol.

Anal. Calcd. for $C_{12}H_{16}Cl_2N_2$: C, 55.61; H, 6.22; N, 10.81. Found: C, 55.96, 55.87; H, 6.46, 6.24; N, 10.60.

The diacetyl derivative prepared from acetyl chloride in pyridine melted at 261–263°. A mixture melting point with the diacetamide prepared from 1,4-di(hydroxymethyl)-naphthalene (*vide supra*) showed no depression.

Anal. Calcd. for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.37. Found: C, 71.03, 71.31; H, 6.74, 6.60; N, 10.15.

The solid residue (B) (31 g.) melted at 115–125° after washing with a little fresh benzene and petroleum ether. The analytical sample melted at 128–129.5° after two recrystallizations from benzene.

Anal. Calcd. for $C_{12}H_{14}N_2$: C, 77.38; H, 7.56; N, 15.04. Found: C, 77.17, 76.94; H, 7.80, 7.63; N, 14.81.

The dihydrochloride melted above 300° after repeated recrystallization from aqueous acetic acid.

Anal. Calcd. for $C_{12}H_{16}Cl_2N_2$: C, 55.61; H, 6.22; N, 10.81. Found: C, 55.83, 55.57; H, 6.18, 5.95; N, 10.99.

The diacetyl derivative, prepared from acetyl chloride in pyridine, melted at 276–279°.

Anal. Calcd. for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.37 Found: C, 71.57, 71.17; H, 6.67, 6.87; N, 10.31.

Alkaline hydrolysis of N,N'-diacetyl-1,3-di(aminomethyl)-benzene. A one-gallon stainless steel autoclave, charged with 496 g. (2.0 moles) of the diamide Ia and a solution of 240 g. (6.0 moles) of sodium hydroxide in 1800 ml. of water was heated for 16 hr. at 175°. The cooled autoclave contents were extracted with butanol and the extract was concentrated. The residue was heated to about 125° and then vacuum from a rotatory oil pump was applied. The hot diamine was distilled rapidly into the receiver where it crystallized. The product was melted under nitrogen and poured into a Pyrex tray. The cooled solid, m.p. 120–127°, was further purified by recrystallization from methanol, m.p. 126–127°.

Acid hydrolysis of diamide Ia. A mixture of 744.0 g. (3.0 mole) of crude diamide Ia in a mixture of 1 l. of glacial acetic acid and 1 l. of concd. hydrochloric acid was refluxed for 24 hr. The excess acids were distilled at reduced pressure until the residue became a thick gummy mass. The residue was stirred vigorously with 1200 ml. of 25% sodium hydroxide and 1 l. of toluene. The resulting mixture consisted of a solid phase and two liquid layers. The lower aqueous layer was rejected and the organic product was filtered. Both residue and filtrate were processed.

The residue was washed with toluene and hexane, then recrystallized from methanol to give 163 g. of 4,6-dimethyl-1,3-di(aminomethyl)benzene, m.p. 124–126°. Recrystallization from benzene gave an analytical sample melting at 125–126.5° (lit.,[12] m.p. 124–125°).

Anal. Calcd. for $C_{10}H_{16}N_2$: C, 73.12; H, 9.82; N, 17.06. Found: C, 72.92, 73.03; H, 9.69, 9.70; N, 17.17, 17.08.

The monohydrochloride, prepared from a little hydrogen chloride in methanol and benzene, melted at 213–213.5° dec.

Anal. Calcd. for $C_{10}H_{17}ClN_2$: C, 59.84; H, 8.54; N, 13.96. Found: C, 59.88, 59.92; H, 8.13, 8.44; N, 13.83.

The dihydrochloride prepared from excess methanolic hydrogen chloride in benzene melted at 274.5–276.5° dec.

Anal. Calcd. for $C_{10}H_{18}Cl_2N_2$: N, 11.81. Found: N, 11.64.

The polysebacate prepared in methanol melted at 152–153°.

Anal. Calcd. for $C_{20}H_{34}N_2O_4$: C, 65.54; H, 9.35; N, 7.65. Found: C, 65.28, 65.36; H, 9.14, 9.07; N, 7.68.

The toluene phase was dried, concentrated, and distilled. There was obtained 43 g. of 2,4-dimethylbenzylamine, b.p. 86–90° (10 mm.), 105–115° (20 mm.). The hydrochloride prepared in the usual way melted at 231–233°.

Anal. Calcd. for $C_9H_{14}ClN$: N, 8.20; Cl, 20.75. Found: N, 8.07; Cl. 20.30.

N-(2,4-Dimethylbenzyl)formamide. A mixture of 6.8 g. (0.05 mole) of 2,4-dimethylbenzylamine, 20 g. (0.40 mole) of 90% formic acid and 100 ml. of toluene was refluxed while the theoretical amount of water was removed *via* a Dean-Stark trap. On chilling the residue there was obtained 7.5 g. (91%) of product, m.p. 120–121.5°. After two recrystallizations from benzene the analytical sample melted at 122–124°, and did not depress the melting point of the monoamide prepared from *m*-xylene, formaldehyde, and hydrogen cyanide (Table I).

Anal. Calcd. for $C_{10}H_{13}NO$: N, 8.60. Found: N, 8.62.

Melt polymerization of 4,6-dimethyl-1,3-di(aminomethyl)-benzene sebacate. Two grams of the salt were heated in a sealed evacuated Carius tube for 2 hr. at a temperature of 190–200°. The tube was cooled, opened and then heated for 2 hr. at 295–310° and 0.1 mm. The polymer formed a clear, slightly greenish melt. Upon cooling an opaque white solid was obtained, m.p. 258–260°.

4,6-Dimethyl-m-xylene-α,α'-diisocyanate. In a 1-l. three necked flask equipped with a Hershberg stirrer, reflux condenser, and gas inlet tube was placed 59.3 g. (0.25 mole) of 4,6-dimethyl-1,3-di(aminomethyl)benzene dihydrochloride and 1650 ml. of dry tetralin. The mixture was heated at 200–205° and treated with a stream of chlorine-free phosgene. After 7 hr. evolution of hydrogen chloride had ceased and the mixture was purged with a stream of inert gas. The dark solution was cooled, filtered through Celite, and concentrated. The residue was distilled to give 36–38 g. (69–70%) of a colorless oil, b.p. 171–173° (8 mm.), n_D^{24} 1.5407.

Anal. Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.60. Found: C, 66.84, 67.02; H, 5.68, 5.74.

A small portion of the diisocyanate was treated with excess methanol. An exothermic reaction occurred and a crystalline mass was formed. After one recrystallization from methanol the 4,6-dimethyl-1,3-di(carbomethoxyaminomethyl)benzene melted at 173–174°.

Anal. Calcd. for $C_{14}H_{20}N_2O_4$: C, 59.98; H, 7.19; N, 10.00. Found: C, 60.69, 60.65; H, 7.28, 7.45; N, 9.85.

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On the Configuration of *N*-Substituted Benzimide-chlorides from the Beckmann Rearrangement

BERNARD GREENBERG AND JOHN G. ASTON

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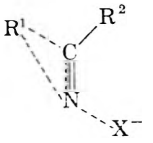
The imide-chloride prepared from 4,4′-dinitrobenzanilide with phosphorus pentachloride which has been prepared for the first time has the *anti* configuration. The Beckmann rearrangement of 4,4′-dinitrobenzophenone oxime with phosphorus pentachloride gives this imide-chloride with the *anti* configuration. As no corresponding *syn*-imide-chloride could be prepared independently, this can throw no further light on the mechanism of the Beckmann rearrangement. Similar results were obtained with the corresponding 4,4′-dibromo compounds which were prepared for the first time.

According to the mechanism proposed by Dewar[1] for the Beckmann rearrangement of oximes and oxime ethers, intermediates of the type $R^1—N{=}C\begin{matrix}X\\ \diagdown\\ \diagup\\ R^2\end{matrix}$ are postulated, where X^- is a negative group. The interpretation given is that there is a π-complex mechanism operating and that the *trans* migration follows from the fact that in the transition state one lobe of the nascent π-bond is used to bind the departing X^- ion.



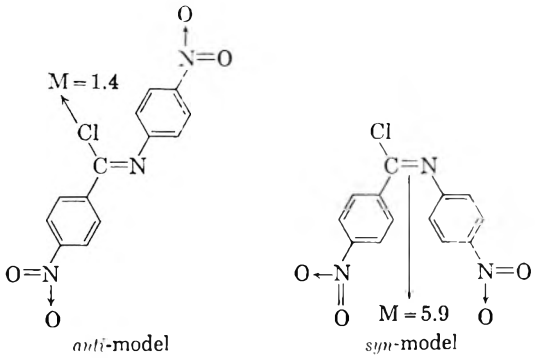
The use of phosphorus pentachloride to effect rearrangement leads to imide-chlorides as intermediates. These are isolable and stable provided moisture is excluded.

Evidently it is of interest to isolate the geometric isomers of the imide-chlorides and examine their stability. If, and only if both isomers are demonstrated to be long lived under the rearrangement conditions could their configuration be used to throw further light on the mechanism of the Beckmann rearrangement.

This present paper records attempts to prepare *syn* and *anti*-imide-chlorides. Unfortunately, the results indicate that such compounds change rapidly to the more stable *anti* configuration invalidating conclusions concerning the stereochemistry of the Beckmann rearrangement.

RESULTS

The rearrangement product of 4,4′-dinitrobenzophenone oxime with phosphorus pentachloride was isolated according to the procedure described below and is a stable material melting at 130.8–131.2°. Its melting point does not change on sublimation in vacuum at 120°, on repeated recrystallizations from benzene or carbon tetrachloride, and on careful elution through an alumina chromatographic column with a 1:1 hexane-benzene mixture, where no band other than the single imide-chloride band appeared. The dipole moment of the material as determined in benzene solution at 25° was 1.20 D± 0.5 D.[2] The value calculated for the *anti*-imide-chloride is 1.4 D and the value calculated for the *syn*-imide-chloride is 5.9 D. In calculating the dipole moments of these above models the group moments and angles for benzene derivatives were used.



anti-model *syn*-model

The product obtained from treating 4,4′-dinitrobenzanilide with phosphorus pentachloride, the only other known procedure for preparing this type of imide-chloride, was isolated in pure form and its melting point and mixed melting point with the material of the Beckmann rearrangement were identical at 130.8–131.2°. This melting point was not altered by repeated recrystallizations, sublimation in vacuum, or chromatic elution.

In the same manner the product of the Beckmann rearrangement of 4,4′-dibromobenzophenone oxime was shown to be identical with the product of the reaction of 4,4′-dibromobenzanilide and phosphorus pentachloride. Both melted at 93–94° with no depression on mixing. All samples of imide-chlorides yielded the respective anilides on hydrolysis in 1:1 acetone–ammonia water.

(1) M. R. S. Dewar, *Electronic Theory of Organic Chemistry*, Oxford, London, 1949, p. 219.

(2) Capacitance measurements with Type 650-A Impedance Bridge, General Radio Co., Cambridge, Mass.; Audio generator at 6000 c.p.s.; Oscilloscope detector.

TABLE I

DIELECTRIC DATA FOR 4-NITROBENZ-4-NITROPHENYL-IMINO-CHLORIDE

Capacitance of cell empty = 42.0 mmf. Temp. = 25° ± 0.1°. Capacitance of cell with benzene = 78.0 mmf

N_2	7.14×10^{-4}	1.83×10^{-3}	5.59×10^{-3}	1.09×10^{-2}	1.66×10^{-2}	2.18×10^{-2}
N_1	0.999	0.998	0.994	0.989	0.983	0.978
$\epsilon_{25}°$	2.28	2.28	2.29	2.31	2.32	2.34
Density	0.875	0.875	0.877	0.879	0.881	0.883
P_{12}	25.2	26.3	26.8	27.7	28.6	29.5
P_2	110	115	125	138	155	179

Nothing about the stereochemistry of the Beckman rearrangement can be deduced from the results of the above experiments as the only other available preparative method for this type of imide-chloride failed to yield a *syn*-isomer. Nowhere in the literature is it reported that a pair of isomeric imide-chlorides have been prepared, all preparations yielding a single compound, presumably the *anti*-isomer. Coleman and Pyle[3] report that the imide-chlorides of benzanilide and *p*-chlorobenzanilide are identical with the imide-chlorides from the Beckmann rearrangement of the proper ketoximes.

EXPERIMENTAL

4,4'-Dinitrobenzanilide and *4,4'-dibromobenzanilide* were prepared by the method of Barnett and Nixon[4]; 4,4'-dinitrobenzophenone was prepared by the method of Staedel,[5] and converted to its oxime by the method of Shriner and Fuson[6]; *4,4'-dibromobenzophenone* by the method of Montagne[7] and converted to its oxime in an identical fashion as above.

4-Nitrobenz-4-nitrophenyl-imide-chloride. Method A. Five grams of 4,4'-dinitrobenzanilide which had been previously dried in an oven at 110° for 3 hr. and 4 g. of finely divided phosphorus pentachloride were placed in a 10-ml. distilling flask and connected to the aspirator by means of a filter flask which also served as a receiver. The distilling flask was heated on an oil bath to 95°, whence the mass melted and the evolution of hydrogen chloride commenced. After 10 min. the reaction subsided and the pressure was gradually reduced with the aspirator. The phosphorus oxychloride distilled and the reaction mixture became solid again. The solid was dissolved in hot, dry benzene and removed from the flask by forcing it through a glass tube containing a cotton plug by means of a pressure of dry air. Large yellow crystals were deposited on cooling and were filtered from the liquor and dried under vacuum; m.p. 129–130°; yield 4.3 g., 81%.

Repeated recrystallization from benzene and/or carbon tetrachloride gave a material which melted at 130.8–131.2°.[8] Slow sublimation under a pressure of 0.5 mm. at 100° did not change this melting point. The material was dissolved in a 1:1 hexane-benzene mixture and the solution passed through a column of activated alumina. Only one band appeared and was eluted. The solid which was crystallized from various cuts of the eluent all melted at 130.8–131.2°. The equivalent weight of the material determined argentometrically[9] was 309.6 which compares with 305.5 for the calculated value.

Method B. Seven grams of 4,4'-dinitrobenzophenone oxime was dissolved in the minimum amount of benzene, 225 ml., at 75° in a 500-ml. distilling flask, fitted with a condenser and a receiving flask. Solid phosphorus pentachloride, 6.4 g., was added at such a rate as to produce a vigorous reaction which did not become violent. After the addition of the phosphorus pentachloride, 10–12 min., the pressure of the system was gradually reduced by connecting an aspirator to the receiving flask and the benzene and phosphorus oxychloride were removed. A solid yellow mass remained which was dissolved in benzene and isolated in the identical manner as above; yield 6.1 g., 82%, m.p. 130.5–131°. Repeated recrystallizations gave a melting point which was constant at 130.8–131.2° which was not depressed on mixing with the imidechloride prepared from the anilide.

Table I gives the values of P_2 of 4-nitrobenz-4-nitrophenylimino-chloride as a function of concentration. N_1 and N_2 are respectively the mole-fractions of solute and solvent while $\epsilon_{25}°$ is the dielective constant at 25° with a frequency of 6000 cycles per second. P_{12} is the molar polarization of the mixtures while P_2 is that of the solute calculated on the basis that

$$P_{12} = N_1P_1 + N_2P_2 \quad (1)$$

The value for P_1 for benzene was of course equal to the value of P_{12} at infinite dilute. The total polarization of the solute P_2, at infinite dilution and obtained by extrapolation, was 108. The contribution of dipole orientation, P, to P_2^0 was calculated from the formula

$$P_2^0 = P_a + P_e + P \quad (2)$$

Atomic polarization was neglected and P_e- was calculated from the molar refraction which was obtained from tables of refractivities given by Partington.[10] It was found to be 78. These give a value of 30 for the orientation polarization which yields a moment of 1.20 D when substituted in the moment equation.

$$\begin{aligned} P &= 108 - 78 = 30 \\ &= 0.0127 \times 10^{-18}(T \times P)^{1/2} \\ &= 1.20 \text{ D} \end{aligned}$$

4-Bromobenz-4-bromophenylimide-chloride. Method A. Eighteen grams of 4,4'-dibromobenzophenone oxime and 10.5 g. of phosphorus pentachloride, using the same pro-

(3) G. H. Coleman and E. R. Pyle, *J. Am. Chem. Soc.*, 68, 2007 (1946).

(4) E. Barnett and I. G. Nixon, *Chem. News*, 129, 90–91 (1924).

(5) W. Staedel, *Ann.*, 283, 168 (1894).

(6) R. L. Shriner and R. C. Fuson, *Identification of Organic Compounds*, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 202, Method A.

(7) P. J. Montagne, *Rec. Trav. Chim.*, 29, 156 (1910).

(8) Melting points of the purified materials were measured on a micro-melting stage with thermocouple and potentiometer previously calibrated.

(9) E. H. Swift, *A System of Chemical Analysis*, Prentice Hall, Inc., New York, N. Y., 1940, p. 347.

(10) *An Advanced Treatise on Physical Chemistry*, Vol. IV, Longmans Green, and Co., Ltd., London, 1953, pp. 56–61.

cedure as above, gave 15 g. (80%) of product melting at 93.0–94.0° upon two recrystallizations from benzene.

Method B. The imide-chloride prepared in an identical manner as above from 2.1 g. of phosphorus pentachloride and 3.5 g. of 4,4′-dibromobenzanilide also melted at 93.0–94.0°, when recrystallized twice from benzene. This was not depressed on mixing with the material from the Beckmann rearrangement of the ketoxime; yield 2.7 g., 72%.

UNIVERSITY PARK, PA.

[CONTRIBUTION FROM THE DIVISION OF ONCOLOGY, THE CHICAGO MEDICAL SCHOOL]

K Region Fission and Addition Products of 7,12-Dimethylbenz[a]anthracene[1]

HERBERT I. HADLER[2] AND ALLEN C. KRYGER

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The K region (5,6-positions) of 7,12-dimethylbenz[a]anthracene was cleaved by treating the appropriate dihydrodiol with sodium periodate. The resultant dialdehyde was converted to several oxygenated products as well as 5,6-dihydro-7,12-dimethylbenz[a]anthracene. This latter compound was also obtained in good yield by the hydrogenation of the parent polynuclear hydrocarbon using palladium on strontium carbonate as catalyst.[3]

The carcinogenic property of the polynuclear hydrocarbon 7,12-dimethylbenz[a]anthracene, I, has been extensively investigated.[4] This hydrocarbon has been found to be extremely potent as a skin carcinogen.[5–9] Nevertheless, very little has been reported on the metabolism of this hydrocarbon. An important factor contributing to this lack of information is the paucity of chemical studies which began with methyl-substituted polynuclear hydrocarbons in general and 7,12-dimethylbenz[a]anthracene in particular.

For some time,[10] as indicated by several reviews[11,12,13] it has been speculated that a biochemical process which occurred at the K region[14] of a polynuclear hydrocarbon was significant to carcinogenesis. Metabolism at the K region of the carcinogen dibenz[a,h]anthracene was established when the dibasic acid resulting from fission at this region was characterized as a metabolite.[15] Consequently, a variety of alteration products which involved either fission or addition to the K region of 7,12-dimethylbenz[a]anthracene have been prepared.

When starting with unsubstituted polynuclear hydrocarbons, the customary route to K region fission products has been the addition of osmium tetroxide followed by hydrolysis to the dihydrodiol.[16] Oxidation with a dichromate salt[15,17] or chromic acid[18] converted the dihydrodiol to an *ortho* quinone. The *ortho* quinone was cleaved to a dibasic acid with peracetic acid.[15,17] This route was unsuccessful when applied to 7,12-dimethylbenz[a]anthracene. Although the dihydrodiol, II, of the substituted hydrocarbon was available through the action of osmium tetroxide on 7,12-dimethylbenz[a]anthracene,[16] the oxidative step to the *ortho* quinone was fruitless.

An alternative route to K region fission products of 7,12-dimethylbenz[a]anthracene was developed. The dihydrodiol, II, when treated with sodium periodate gave the dialdehyde, III, in quantitative yield.[19] An attempt to use alkaline silver oxide for the oxidation of the dialdehyde, II, to the corresponding dibasic acid failed. An acidic product was isolated with difficulty from the reaction mixture. This product, on the basis of elemental analysis, corresponded to an alcohol acid and presumably was IV. The lactonization of IV would be in keep-

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(2) Present address: Department of Biochemistry, University of Wisconsin, Madison, Wis.

(3) An abstract of some of this work appeared in *Proc. Am. Assoc. Cancer Research* **3**, 25 (1959).

(4) P. Shubik and J. L. Hartwell, *Survey of Compounds Which Have Been Tested for Carcinogenic Activity*, Supplement I, United States Government Printing Office, Washington, 1957, p. 153.

(5) W. E. Bachman, E. L. Kennaway, and N. M. Kennaway, *Yale J. Biol. and Med.*, **11**, 97 (1938).

(6) M. Klein, *Cancer Research*, **16**, 123 (1956).

(7) V. Darchun and H. I. Hadler, *Cancer Research*, **16**, 316 (1956).

(8) H. I. Hadler, V. Darchun, and K. Lee, *J. Nat. Cancer Inst.* **23**, 1383 (1959).

(9) G. Della Porta, H. Rappaport, U. Saffiotti, and P. Shubik, *A. M. A. Archiv. Path.*, **61**, 305 (1956).

(10) O. Schmidt, *Naturwissenchaften* **29**, 146 (1941).

(11) C. A. Coulson, *Adv. in Cancer Research*, I, 1 (1953).

(12) G. M. Badger, *Adv. in Cancer Research*, **2**, 73 (1954).

(13) A. Pullman and B. Pullman, *Adv. in Cancer Research*, **3**, 117 (1955).

(14) The possession of a phenanthrene moiety has been accepted as a required structural feature for carcinogenic activity in a polynuclear hydrocarbon. The 9,10-double bond of the phenanthrene moiety has been termed the K region of the polynuclear hydrocarbon. This region is susceptible to 1,2-addition reactions. In 7,12-dimethylbenz[a]anthracene the 5,6-positions are the K region.

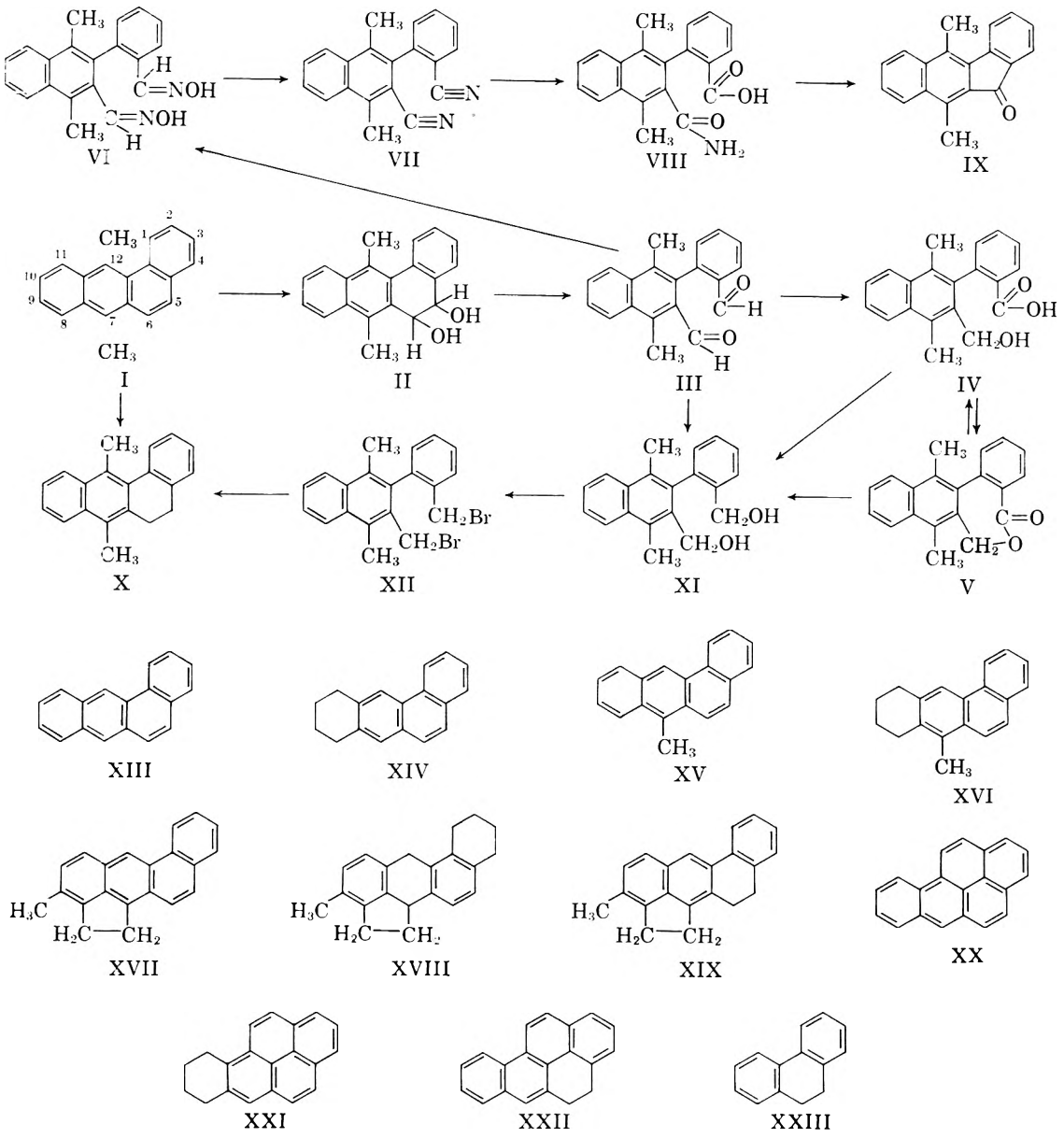
(15) P. M. Bhargava, H. I. Hadler, and C. Heidelberger, *J. Am. Chem. Soc.*, **77**, 2877 (1955).

(16) J. W. Cook and R. Schoental, *J. Chem. Soc.*, 170 (1948).

(17) E. F. M. Stephenson, *J. Chem. Soc.*, 2620 (1949).

(18) C. J. Collins, J. G. Burr, Jr., and D. N. Hess, *J. Am. Chem. Soc.*, **73**, 5176 (1951).

(19) Collins, Burr and Hess[18] reported that the K region dihydrodiol of the unsubstituted polynuclear hydrocarbon, benz[a]anthracene, was not cleaved by lead tetraacetate.



ing with the difficulty encountered in the isolation of IV. Evidently an intramolecular Cannizzaro reaction was brought about by the alkalinity of the silver oxide reagent. The conversion of III to IV by strong alkali alone, confirmed the occurrence of the intramolecular Cannizzaro reaction. The isolation of the alcohol acid IV was feasible when precautions were taken to minimize lactonization. The alcohol acid was easily lactonized to V with catalytic amounts of *p*-toluenesulphonic acid.

The excellent recovery of single isomers (III to IV and III to V in 82% and 93% yield respectively) indicated that the Cannizzaro reaction was under appreciable steric control. In the first step of the postulated mechanism of the Cannizzaro reaction the hydroxyl anion attacks the aldehydo group which eventually ends up as the carboxyl group in the final product.[20] Thus, structure IV has been written with the carboxyl group in the position corresponding to the most exposed aldehydo group in III. The ready saponification of the lactone V to the acid IV supported the structures assigned to IV and V. It was of interest that although the intramolecular spatial relationship between the two aldehydo groups in III was influenced by the serious restricted rotation about the biphenyl bond in III, the intramolecular reaction proceeded with ease. The possibility of steric acceleration was not investigated.

Although one of the aldehydo groups in III was hindered by two *ortho* substituents and a buttressing[21] *meta* group, the dioxime, VI, was readily formed. Dehydration of VI with acetic anhydride

(20) E. R. Alexander, Principles of Ionic Organic Reactions, John Wiley and Sons, Inc., New York, N. Y., 1950, p. 168.

(21) M. Rieger and F. H. Westheimer, *J. Am. Chem. Soc.*, **72**, 19 (1950).

yielded the dinitrile, VII. Vigorous saponification of VII did not proceed past the monoamide stage of the dibasic acid. The residual acid amide group was assigned to the most hindered position in VIII. When the acid amide, VIII, was treated with 100% phosphoric acid, a reagent recommended for the hydrolysis of hindered acid amides,[22] there was obtained a neutral yellow moderately volatile solid. The analysis of this product agreed with that of the fluorenone IX. A possible sequence yielding this product would be hydrolysis, decarboxylation, and intramolecular acylation.

Two routes were considered for the synthesis of the dihydro K region derivative, X. One route was that developed by Hall and Turner[23,24,25] for the synthesis of 9,10-dihydrophenanthrene in order to circumvent the hydrogenation of phenanthrene. The other route was direct hydrogenation of 7,12-dimethylbenz[a]anthracene. Both routes proved to be successful.

Hall and Turner[23,24] cyclized 2,2′-di(bromomethyl)-diphenyl with phenyllithium to obtain 9,10-dihydrophenanthrene. In order to apply this synthetic method, the dialcohol, XI, was obtained by the action of lithium aluminum hydride on any one of the ring fission products III, IV, or V. Treatment of the dialcohol, XI, with 48% hydrobromic acid in acetic acid gave the appropriate bisbromomethyl compound, XII. When XII was cyclized with phenyllithium, the desired dihydro K region product, X, resulted. Both the dihydrodiol, II, and the dihydrocompound X, had the same chromophore as shown by their ultraviolet absorption spectra. There was a bathochromic shift of the spectral bands in II and X relative to XI. This was explained by the higher energy of the ground states of II and X relative to XI because of the strain imposed by the 5,6-bond in II and X on the hindered biphenyl system.

The usual procedure for the partial hydrogenation of polynuclear hydrocarbons at room temperature and pressure has been to use a platinum catalyst in an acidic medium and to interrupt the reaction before hydrogen absorption was complete. Under these conditions, the major product isolated from the reduction mixture characteristically had a saturated terminal ring, irrespective of whether the parent polynuclear hydrocarbon was substituted or unsubstituted. On occasion a small amount of K region hydrogenated product was also isolated.

Fieser and Hershberg[26] isolated 8,9,10,11-tetrahydrobenz[a]anthracene, XIV, in 77% yield after allowing benz[a]anthracene, XIII, to absorb two moles of hydrogen in the presence of Adams catalyst, ferrous chloride, and hydrochloric acid. The substituted polynuclear hydrocarbon 7-methylbenz[a]anthracene, XV, gave after absorbing two moles of hydrogen (in the presence of Adams catalyst and a trace of hydrochloric acid) 8,9,10,11-tetrahydro-7-methylbenz[a]anthracene, XVI, in 59% yield.[26] These same authors also studied the hydrogenation of 3-methylcholanthrene,[27] XVII. They found that after the absorption of four moles of hydrogen (in the presence of acetic acid and Adams catalyst containing some palladium), the hexahydroproduct, XVIII, was obtained in 40% yield and the dihydro K region product XIX, was obtained in 20% yield. More starting material was recovered when lesser amounts of hydrogen were absorbed; however, the ratio of XVIII to XIX remained unchanged. From these data Fieser and Hershberg concluded that two independent concurrent courses for the hydrogenation of 3-methylcholanthrene existed.

Lijinsky and Zechmeister[28] hydrogenated the unsubstituted polynuclear hydrocarbon benzo[a]pyrene, XX, with two moles of hydrogen (in the presence of Adams catalyst and acetic acid) and isolated the tetrahydro product, XXI, in 37% yield and the K region dihydro product XXII,[29] in 11% yield.

The literature cited above suggested that although the interrupted hydrogenation of 7,12-dimethylbenz[a]anthracene, I, in the presence of platinum and acid might yield some K region dihydro product, X, it was advisable to investigate other conditions. Also, it had been known for some time that phenanthrene itself in the presence of copper chromium oxide catalyst was hydrogenated at elevated temperature and pressure to yield the K region dihydro product, XXIII.[30,31] When palladium on strontium carbonate, precipitated under alkaline conditions, was chosen as the hydrogenation catalyst a good yield (73%) of purified material of 5,6-dihydro-7,12-dimethylbenz[a]anthracene, X, was obtained from the parent polynuclear hydrocarbon, I, at room temperature and pressure. The uptake of hydrogen stopped after 1.2 moles were absorbed.

Several considerations pointed to the selection of palladium on strontium carbonate for the exclusive hydrogenation of the K region of 7,12-dimethylbenz[a]anthracene. The double bond in

(22) G. Berger and S. C. J. Olivier, *Rec. Trav. Chim.*, **46**, 600 (1927).

(23) D. M. Hall and E. E. Turner, *Nature* **163**, 537 (1949).

(24) D. M. Hall, M. S. Leslie, and E. E. Turner, *J. Chem. Soc.*, 711 (1950).

(25) G. M. Badger, P. R. Jefferies, and R. W. L. Kimber, *J. Chem. Soc.*, 1837 (1957).

(26) L. F. Fieser and E. B. Hershberg, *J. Am. Chem. Soc.*, 59, 2502 (1937).

(27) L. F. Fieser and E. B. Hershberg, *J. Am. Chem. Soc.*, 60, 941 (1938).

(28) W. Lijinsky and L. Zechmeister, *J. Am. Chem. Soc.*, 75, 5495 (1953).

(29) The structure assignment was tentative.

(30) D. D. Philips, *Org. Syntheses*, 24, 31 (1954).

(31) A. Burger and E. Mosettig, *J. Am. Chem. Soc.*, 58, 1861 (1936).

question was the most olefinic and least aromatic in the parent compound.[32] Acidic conditions brought about either by the method used to prepare the catalyst or by the addition of acid to the hydrogenation medium would be expected to promote hydrogenation of aromatic rings[33] (on an empirical basis), as illustrated above[26,27,28] with XIII, XV, XVII, and XX. In a neutral or alkaline medium the geometry of the olefinic substrate being hydrogenated would exert its maximal steric influence on the incoming *cis* hydrogen.[34] In an acidic medium the probability of the intervention of a different hydrogenation mechanism or of additional polar factors would be increased.[34] The hydrogenation of the K region was slower than that of an aromatic ring (inferred from the results of Fieser and Hershberg[26] discussed above) and hydrogenation by the slower of the possible hydrogenation mechanisms was favored by the absence of acid.[34] Thus, to obtain the results of a single mechanism under the most homogeneous steric influence due to the geometry of the substrate, to limit the hydrogenation of the aromatic rings, and to select the slower of the possible mechanisms of hydrogenation, the chosen catalyst was precipitated under alkaline conditions and no acid was added to the hydrogenation medium. The K region of a polynuclear hydrocarbon also might be considered analogous to a styrene bond. Palladium on strontium carbonate (prepared differently from the catalyst used in these experiments) had been used successfully for the hydrogenation of another hindered styrene type double bond.[35]

EXPERIMENTAL[36]

3,4-Dihydroxy-3,4-dihydro-7,12-dimethylbenz[a]anthracene, II. The generalized procedure of Cook and Schoental[16] was followed. A solution of 2 g. (0.00786 mole) of osmium tetroxide in 40 ml. of dry benzene was added at room temperature, under nitrogen, over a 10-min. period to a stirred solution of 2.0146 g. (0.00786 mole) of 7,12-dimethylbenz[a]anthracene (the commercial product was eluted from Florisil with cyclohexane and crystallized from cyclohexane), m.p. 122.5–123.3° in 60 ml. of dry benzene containing 1 ml. of dry pyridine. The stirring was stopped and 2 days later the benzene was removed *in vacuo*. The dark residue was dissolved *completely* in about 200 ml. of methylene chloride and shaken for 2 hr. with 200 ml. of 5*N* sodium hydroxide and 60 ml. of 1*M* D-mannitol. The two layers were separated and the shaking repeated with a fresh aqueous solution (if necessary) until there was no more pink color in the methylene chloride layer. The organic layer was washed with water, dried with sodium sulfate, and evaporated. The residue was crystallized from benzene-cyclohexane and gave 1.786 g. (78%) of a colorless solid, m.p. 172.5–173.5° (lit.[16] m.p. 171–172°).

Florisil was used for chromatographic purification. The starting hydrocarbon, I, was eluted with cyclohexane and the dihydrodiol, II, was eluted either with 10% acetone-90% benzene or with chloroform.

λ_{max} ($\log_{10}\epsilon$); 219.5 (4.371); 260.5 (4.625); 269 (4.673); 303 (3.886); λ_{min} ($\log_{10}\epsilon$); 234 (4.083); 264.5 (4.585); 284 (3.642).

1,4-Dimethyl-2-phenylnaphthalene-3,2'-dicarboxaldehyde, III. To a solution of 1.408 g. (0.00484 mole) of dihydrodiol, II, m.p. 174–175.7° dissolved in a mixture of 1300 ml. of methanol and 250 ml. of water there was added at room temperature a solution of 4.15 g. (0.0194 mole) of sodium periodate dissolved in 70 ml. of water and 350 ml. of methanol. After 2 days the reaction mixture was concentrated *in vacuo* or atmospheric pressure to one third of its original volume. The organic material was taken up in benzene washed successively with water, 5% sodium bicarbonate, water, brine, and dried with sodium sulfate. After evaporating the solvent, there remained a quantitative yield of a pale yellow solid m.p. 136.3–138°. Repeated crystallization from ethanol-methanol gave a colorless solid, m.p. 137–137.5°.

Anal. Calcd. for $C_{20}H_{16}O_2$ (288.33): C, 83.31; H, 5.59. Found: C, 83.20; H, 5.57.

The dialdehyde, III, was eluted from Florisil with 0.5% acetone-99.5% benzene.

λ_{max} ($\log_{10}\epsilon$); 221 (4.554); 255 (4.588); 260 (4.607); 297 (3.809); 358 (3.482): λ_{min} ($\log_{10}\epsilon$); 235 (4.346); 326 (3.253).

1,4-Dimethyl-3-hydroxymethyl-2-phenylnaphthalene-2'-carboxylic acid IV. A. *Using alkaline silver oxide.* To a fresh suspension prepared from 0.34 g. (0.002 mole) of silver nitrate dissolved in 10 ml. of water and 0.4 g. (0.01 mole) of sodium hydroxide in 4 ml. of water, a solution of 0.144 g. (0.0005 mole) of the dialdehyde, III, m.p. 138–138.5 in 10 ml. of dioxane and 40 ml. ethanol was shaken at room temperature overnight. The black precipitate was filtered and then washed well with water, ethanol, water, and alkali. The green filtrate was reduced *in vacuo* to 25 ml. and 100 ml. of water added. The alkaline solution was washed with benzene and acidified with 0.5*N* nitric acid. The organic material was taken up in chloroform, washed with water, and dried with sodium sulfate. The solvent was evaporated to give 0.127 g. of a semisolid. Repeated crystallization from acetone-cyclohexane gave 0.012 g. of a solid, m.p. 165–165.2 (m.).

Anal. Calcd. for $C_{20}H_{18}O_3$ (306.34): C, 78.41; H, 5.92. Neut. equiv., 306. Found C, 78.73; H, 6.12. Neut. equiv., 301.

The alcohol acid IV required 100% ethyl acetate for elution from silica.

λ_{max} ($\log_{10}\epsilon$); 236.5 (4.912); 286 (3.875); 330 (2.844); λ_{min} ($\log_{10}\epsilon$); 263 (3.651): 227 (2.733).

B. *Using only alkali.* To an ice cold solution of 1.00 g. (0.00437 mole) of dialdehyde, III, m.p. 138.6–138.9°, dissolved in 200 ml. of methanol there was added slowly with cooling an ice cold solution of 235 g. (4.37 moles) of potassium hydroxide dissolved in 200 ml. of water and 200 ml. of methanol. The next day the volume was reduced by two thirds *in vacuo*. Water was added to dissolve the solid and the aqueous solution was washed with benzene. The

(32) G. M. Badger, *The Structures and Reactions of the Aromatic Compounds*, University Press, Cambridge, Great Britain, 1954, p. 160.

(33) H. Adkins and R. L. Shriner, in *Organic Chemistry, an Advanced Treatise*, H. Gilman, editor-in-chief, John Wiley and Sons, New York 2nd ed., 1943, p. 817.

(34) H. I. Hadler, *Experientia*, 11, 175 (1955).

(35) W. S. Johnson, E. R. Rogier, J. Szmuskovicz, H. I. Hadler, J. Ackerman, B. K. Bhattacharyya, B. M. Bloom, L. Stalman, R. A. Clement, B. Bannister, and H. Wynberg, *J. Am. Chem. Soc.* 78, 6289 (1956). See foot-note 39 of this reference.

(36) Melting points were corrected and taken on a hot stage when followed by (m). Ultraviolet absorption spectra were determined on a Beckman spectrophotometer model DK1; 95% alcohol was employed as the solvent. Microanalyses were carried out by Drs. G. Weiler and F. B. Strauss, Oxford, England, and Microtech Laboratory, Skokie, Ill.; U.S.A. evaporations were conducted on a steam bath under a stream of nitrogen. Chromatographic purification procedures have been included because of the interest in the biological testing of some of these compounds and to aid metabolic studies.

alkaline solution was added in portions to an extraction funnel containing hydrochloric acid, ice chips and chloroform. Thus, on shaking acidification and extraction were carried out simultaneously.

The chloroform extract was washed with water and dried with sodium sulfate. After evaporation of the solvent there was obtained a quantitative yield of solid, m.p. 149.5–154.5°. One crystallization from acetone-cyclohexane gave 0.875 g. (82%) of colorless needles, m.p. 163–165°, identical (mixed m.p.) with the acid produced by method A.

C. *From the lactone*, V. To a stainless steel flask containing 5.6 g. (0.1 mole) of potassium hydroxide dissolved in 5 ml. of water and 5 ml. of methanol there was added a solution of 0.058 g. (0.0002 mole) of lactone V, m.p. 174–175° (see below) in 10 ml. of methanol. The mixture was heated in an atmosphere of nitrogen at reflux for 2 hr. The volume was reduced by one third by evaporation and the acidic material isolated by method B described above. There was obtained 0.050 g. (82%) of white needles, m.p. 157.5–159.5°.

Methyl ester. A solution of 0.153 g. (0.0005 mole) of alcohol acid, IV, m.p. 159–160°, in 10 ml. of ethyl acetate was added to a cold ethereal solution of diazomethane. The solvents were evaporated the next day and the residue taken up in benzene, washed successively with saturated sodium bicarbonate water, and dried with sodium sulfate. On evaporation a quantitative yield of solid, m.p. 130–140°, was obtained. One crystallization from benzene-cyclohexane gave 0.140 g. (87%) of solid, m.p. 141.5–142.5°. After repeated crystallization from benzene-cyclohexane the melting point was 142.5–143.5°.

Anal. Calcd. for $C_{21}H_{20}O_3$ (320.37): C, 78.72; H, 6.29. Found: C, 78.75; H, 6.36.

The methyl ester of IV was eluted from Florisil with 2% acetone–98% benzene.

λ_{max} ($\log_{10}\epsilon$); 236 (4.591); 285 (3.597); 330 (2.520); λ_{min} ($\log_{10}\epsilon$); 263 (3.382); 327 (2.415).

1,4-Dimethyl-3-hydroxymethyl-2-phenylnaphthalene-2'-carboxylic acid, ϵ lactone, V. The crude acidic product of IV, was obtained from 0.144 g. (0.005 mole) of dialdehyde, III, m.p. 138–138.5°, using procedure B. The crude product was dissolved in 200 ml. of dry benzene, a crystal of *p*-toluenesulphonic acid was added and the solution heated at reflux with a water separator for several days. The benzene solution was washed successively with water, saturated sodium bicarbonate, and water, and dried with sodium sulfate. After evaporating the solvent there was obtained 0.134 g. (93%) of colorless solid, m.p. 171–173°. After elution from silica with a mixture of 10% ethyl acetate and 90% benzene and repeated crystallization from benzene-cyclohexane, there were obtained colorless crystals, m.p. 178.5–179°.

Anal. Calcd. for $C_{20}H_{16}O_2$ (288.34): C, 83.31; H, 5.59. Found: C, 83.43; H, 5.55.

The lactone V was eluted from Florisil with 1% acetone–99% benzene.

λ_{max} ($\log_{10}\epsilon$) 225.2 (4.579); 252 (4.687); 303 (3.659); λ_{min} ($\log_{10}\epsilon$) 234 (4.509); 285 (3.590).

1,4-Dimethyl-2-phenylnaphthalene-3,2'-dicarboxaldehyde dioxime, VI. A solution of 0.029 g. (0.0001 mole) of dialdehyde, III, 0.027 g. (0.0004 mole) of hydroxylamine hydrochloride, 2 ml. of dry pyridine, and 2 ml. of absolute ethanol were heated at reflux for 2 hr. The solvents were evaporated *in vacuo*. The residue was taken up in benzene, washed with water, dried with sodium sulfate, and the solvent evaporated to give a quantitative yield of solid, m.p. 195.5–198.5° (m). The melting point was 197.5–199° after repeated crystallization from acetone-cyclohexane

Anal. Calcd. for $C_{20}H_{18}N_2O_2$ (318.36): C, 75.45; H, 5.69. Found: C, 75.43; H, 5.64.

1,4-Dimethyl-2-phenylnaphthalene-3,2'-dicarbonitrile, VII. A solution of 0.840 g. (0.00263 mole) of dioxime, VI, m.p. 199–201° (m), and 30 ml. of acetic anhydride was heated at reflux for 1 hr. Two hundred milliliters of water was added and 15 min. later the organic material was taken up in benzene and washed successively with water, saturated sodium bicarbonate and water, and dried with sodium sulfate. The solvent was evaporated and the residue (quantitative yield, m.p. 235–235.5°) was crystallized from ethyl acetate–cyclohexane to give 0.689 g. (92%), m.p. 235–235.5°. After repeated crystallization the melting point was 237–238°.

Anal. Calcd. for $C_{20}H_{14}N_2$ (282.33): C, 85.08; H, 5.00. Found: C, 84.65; H, 5.23.

1,4-Dimethyl-3-carbamyl-2-phenylnaphthalene-2'-carboxylic acid, VIII. A solution of 0.141 g. (0.0005 mole) of dinitrile, VII, m.p. 235–235.5° in 30 ml. of ethylene glycol monomethyl ether containing 5 g. of potassium hydroxide was heated at reflux for 18 hr. in a stainless steel flask fitted with a reflux condenser. After cooling, 90 ml. of water were added and the neutral material extracted with benzene. The alkaline solution was acidified with ice cold hydrochloric acid and the organic material taken up in ethyl acetate. The extract was washed with water, dried with sodium sulfate, and the solvent evaporated. The residue was dissolved in benzene and placed on a column of silica. After washing the column with benzene and ethyl acetate–benzene, a pale yellow solid was eluted with ethyl acetate in quantitative yield, m.p. 220–221°, then 237–240°. Several crystallizations from ethyl acetate–cyclohexane and from acetone-cyclohexane gave a colorless solid with a double m.p. *viz.*, 232.5–233° and 240.5–241°, with a crystal transformation at 220°.

Anal. Calcd. for $C_{20}H_{17}O_3N$ (319.35): C, 74.90, H, 5.46; N, 4.39. Found: C, 74.80, 74.85; H, 5.60, 5.43; N, 4.40, 4.46.

When VIII was heated at reflux for 24 hr. with ethylene glycol containing potassium hydroxide, the starting material was recovered unchanged.

1,4-Dimethyl-2,3-benz-9-fluorenone, IX. The procedure suggested by Berger and Olivier[22] for the hydrolysis of hindered amides was used. A solution of 1.42 g. (0.01 mole) of phosphorus pentoxide in 3.3 g. (0.02 mole) of 85% phosphoric acid was added to 0.064 g. (0.0002 mole) of the amide, VIII. The homogeneous mixture was heated, under nitrogen in an oil bath kept at 180° for 90 min. Some yellow solid appeared on the condenser. After cooling the mixture was diluted with 125 ml. of water containing 0.5 ml. of concd. hydrochloric acid. The organic material was taken up in ethyl acetate, and washed in succession with water, ice cold 0.5*N* sodium hydroxide, and water. After evaporating the solvent there was obtained a quantitative yield of yellow solid, m.p. 118–120°. Crystallization from cyclohexane and acetone-cyclohexane and sublimation at 220° at 15 mm. gave yellow needles, m.p. 122–123.5° (m.).

Anal. Calcd. for $C_{19}H_{14}O$ (258.30): C, 88.34; H, 5.46. Found: C, 88.68; H, 5.45.

The fluorenone was eluted from Florisil with 1% acetone 99% benzene.

1,4-Dimethyl-2',3-dihydroxymethyl-2-phenylnaphthalene, XI. To a solution of 0.085 g. (0.0003 mole) of lactone, V, m.p. 168–171°, in 25 ml. of dry ether there was added 4 ml. (0.0006 mole) of lithium aluminum hydride dissolved in tetrahydrofuran. The mixture was heated gently at reflux for 30 min., cooled, and ethyl acetate cautiously added. After the addition of 25 ml. of saturated sodium potassium tartrate solution, the ether layer was separated, washed successively with saturated sodium bicarbonate, then water, and dried with sodium sulfate. The solvent was evaporated to give 0.082 g. (94%) of a colorless solid m.p. 137–149°. Repeated crystallization from benzene-cyclohexane containing a trace of pyridine gave colorless crystals, m.p. 157–157.5°, with a transition point at 146–147°.

Anal. Calcd. for $C_{20}H_{20}O_2$ (292.36): C, 82.15; H, 6.89 Found: C, 82.22; H, 6.89.

The dialcohol, XI, was eluted from Florisil with 8% acetone–92% benzene. λ_{max} ($\log_{10}\epsilon$); 237 (4.988); 286 (3.865); 293 (3.888) λ_{min} ($\log_{10}\epsilon$); 260 (3.618).

By means of this procedure III and IV were each converted to XI.

1,4-Dimethyl-2',3-dibromomethyl-2-phenylnaphthalene, XII. To a solution of 0.594 g. (0.002 mole) of dialcohol, XII, m.p. 156–157.5°, in 40 ml. of acetic acid there was added 12.5 ml. of 48% hydrobromic acid. After heating at reflux for 15 min., 6.25 ml. of 48% hydrobromic acid was added and heating continued one more hour. On cooling 0.620 g. (72%) of solid m.p. 148–150° (m) was filtered. After repeated crystallization from acetone-methanol, the melting point was 147–149°.

Anal. Calcd. for $C_{20}H_{18}Br_2$ (418.18): C, 57.44; H, 4.34. Found: C, 58.09, H, 4.59.

5,6-Dihydro-7,12-dimethylbenz(a)anthracene, X. A. *From the dibromo compound* XII. A solution of phenyllithium was prepared in an atmosphere of helium by adding slowly with stirring 1 ml. of bromobenzene to 0.157 g. (0.0227 g.-atom) of lithium suspended in 5 ml. of ether. The freshly prepared phenyllithium solution, followed by an ether wash, was transferred slowly in an atmosphere of helium to a stirred solution of 0.209 g. (0.0005 mole) of the dibromo compound, XII, in 20 ml. of benzene. The mixture was heated at reflux for 30 min., cooled, and decomposed with water and hydrochloric acid. The organic layer was washed with water, dried with sodium sulfate, and the solvent evaporated. The residual phenyl bromide was removed *in vacuo*. The residue was dissolved in cyclohexane and passed through Florisil. Cyclohexane was evaporated from the eluate and the residue crystallized from acetone-methanol to give 0.0671 g. (52%) of colorless[37] solid, m.p. 112–113°. This solid was identical with XII obtained below on the basis of mixed melting point and ultraviolet spectra determinations.

B. *From 7,12-Dimethylbenz(a)anthracene*, I. To a solution of 0.128 g. (0.0005 mole) of 7,12-dimethylbenz[a]anthracene. I, m.p. 122.5–123.1°[c] in 50 ml. of 95% ethanol a small amount of catalyst (5% palladium on strontium carbonate) was added.[38] After several hours the catalyst was filtered and the solution was added to a hydrogenation flask containing 0.064 g. of prereduced catalyst (5% palladium on strontium carbonate); hydrogenation was slow and was continued overnight when 120% of the theoretical amount of hydrogen was absorbed. The catalyst was filtered and the solvent evaporated. The residue after crystallization from acetone-methanol gave 0.076 g. (59%) of colorless solid, m.p. 109–110.5° (m). After repeated crystallization from acetone-methanol and sublimation at 160° at 0.05 mm. the melting point was 112–113° (m.).

Anal. Calcd. for $C_{20}H_8$ (258.35); C, 92.98; H, 7.02. Found; C, 92.67; H, 7.04.

λ_{max} ($\log_{10}\epsilon$); 220 (4.486); 260 (4.918); 268 (4.981); 305 (3.955) λ_{min} ($\log_{10}\epsilon$) 234 (4.217); 264.5 (4.893); 284 (3.894).

In another experiment[39] the hydrogenation of 1.0 g. (0.0039 mole) of I using 50% palladium on strontium carbonate as the catalyst gave 0.731 g. (73%) of X, m.p. 112.3–112.8°. In this experiment the product was obtained subsequent to chromatography (see below) and crystallization from 95% ethanol.

Chromatographic separation of I *and* X. The separation of 1 mg. of I from 1 mg. X was accomplished on 1 g. of a 2:1 mixture of magnesia (Westvaco, Seasorb) and celite (Johns Manville) in an 8 mm. O.D. glass tube, under suction.

Fraction	Eluant		Eluate
1	10 ml. Cyclohexane		Nothing
2	2 ml. Cyclohexane		Nothing
3	10 ml. 1% Chloroform	99% Cyclohexane	X
4	10 ml. 1% Chloroform	99% Cyclohexane	Nothing
5	2 ml. 1% Chloroform	99% Cyclohexane	Nothing
6	10 ml. 20% Chloroform	80% Cyclohexane	I
7	10 ml. 20% Chloroform	80% Cyclohexane	I
8	2 ml. 20% Chloroform	80% Cyclohexane	Nothing

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(37) Repetition of this experiment likely would have given a higher yield.

(38) Prepared by the procedure of D. K. Banerjee, reference (35), footnote 33.

(39) Carried out by E. E. Smith.

[CONTRIBUTION FROM THE RESEARCH DIVISION, ELECTROCHEMICALS DEPARTMENT, E. I. DU PONT DE NEMOURS & CO., INC.]

The Oxidation of Organic Substances by Potassium Peroxymonosulfate

RICHARD J. KENNEDY AND ALBERT M. STOCK

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The reactions of a stable mixture of potassium peroxymonosulfate, potassium hydrogen sulfate, and potassium sulfate with a wide variety of organic substances have been investigated. The reactions with hydrocarbons, hydroxy compounds, carbonyl compounds, amines, nitrogen heterocycles, and with sulfur, phosphorus, and halogen compounds are described and discussed. The utility of peroxymonosulfates in halogenation reactions is also discussed. The behavior of peroxymonosulfates is compared with that of other inorganic peroxygen compounds and organic peroxyacids.

The existence of a peroxygen acid of sulfur was recognized nearly a century ago[1] but it was not until 1898 that Caro[2] demonstrated the existence of two such acids. It was known to Caro that salts of persulfuric acid (peroxydisulfuric acid, $H_2S_2O_8$) converted aniline to an insoluble dye (aniline black). When Caro treated aniline with a solution of ammonium persulfate in concentrated sulfuric acid, he obtained nitrosobenzene, but no aniline black. Three years later, Baeyer and Villiger[3] published conclusive evidence that Caro's acid was peroxymonosulfuric acid (H_2SO_5). It was not until 1910, however, that d'Ans and Friedrich[4] prepared pure, anhydrous peroxymonosulfuric acid.

The oxidation of aniline to nitrosobenzene by peroxymonosulfuric acid has already been cited;

(1) T. S. Price, *Per-Acids and Their Salts*, Longmans, Green and Co., London, 1912, p. 10.

(2) H. Caro, *Z. angew. Chem.*, 845 (1898).

(3) A. Baeyer and V. Villiger, *Ber.* **34**, 853 (1901).

(4) J. d'Ans and W. Friedrich, *Ber.* **43**, 1880 (1910).

this is by no means the only example of the oxidation of an organic substance by peroxymonosulfuric acid or its salts. Peroxymonosulfuric acid and Baeyer's persulfuric reagent ($K_2S_2O_8$, H_2SO_4, and K_2SO_4) have been used in the preparation of lactones from cyclic ketones,[5] esters from ketones[6,7] glycols from olefins,[8] amine oxides from tertiary amines,[9] iodoxybenzene from iodobenzene,[10,11] and nitrosocyclohexane or cyclohexanone oxime from cyclohexylamine.[12]

The preparation of stable salts of peroxymonosulfuric acid has been described in a recent patent.[13] The reactions of a stable mixture of potassium peroxymonosulfate, potassium hydrogen sulfate, and potassium sulfate with a wide variety of organic substances have been investigated. The mixtures used in this investigation contained approximately 5% active oxygen[14] and consisted of approximately two moles of potassium peroxymonosulfate and one mole each of potassium bisulfate and potassium sulfate. Like peroxymonosulfuric acid, the salt mixture is a powerful oxidant with a wide range of application; unlike peroxymonosulfuric acid the mixture can be stored without appreciable loss of active oxygen and handled with negligible hazard to the user.

The mixed salts are moderately soluble in water; solutions approximately 1*M* with respect to potassium peroxymonosulfate can be prepared without difficulty at room temperature. The salt mixture used in our experiments formed strongly acidic solutions (about *p*H 2) because of the presence of the bisulfate ion. The peroxymonosulfate ion is stable in such acidic solutions. As Ball and Edwards[15] have shown, the active oxygen is gradually lost through decomposition reactions in alkaline solution.

Although potassium peroxymonosulfate is not appreciably soluble in common organic solvents, water–ethanol, water–acetic acid and water–ethanol–acetic acid mixtures have been employed successfully as solvents for the $KHSO_5$-$KHSO_4$-K_2SO_4 mixture. A slurry of the mixed salts in glacial acetic acid has also proved to be an effective oxidant.

In addition to solubility, two other factors should be considered in predicting the behavior of peroxymonosulfate toward organic systems. The first of these factors is the oxidation potential of the peroxymonosulfate-bisulfate couple ($E° = 1.44$v). If the standard potential for the organic couple is known, it is possible to predict whether or not the oxidation reaction is thermodynamically feasible. The second factor to be considered is the nature of the free radicals, ionic species, or indefinite intermediate complexes which might be obtained from peroxymonosulfate under various reaction conditions. In free radical reactions, for example, the peroxymonosulfate ion can theoretically liberate a hydroxyl radical and a sulfate ion-radical (Equation 1). One or the other of these radicals can be obtained from an organic peroxyacid, hydrogen peroxide, or peroxydisulfate ion (Equations 2, 3, 4). Thus peroxymonosulfate ion might be

$$HOOSO_3^- \longrightarrow HO\cdot + \cdot OSO_3^- \quad (1)$$

$$RCOOOH \longrightarrow RCOO\cdot + \cdot OH \quad (2)$$

$$HOOH \longrightarrow 2HO\cdot \quad (3)$$

$$(O_3SOOSO_3)^{-2} \longrightarrow 2\cdot OSO_3^- \quad (4)$$

expected to behave somewhat like all of these substances. Differences in behavior might also be expected, as peroxymonosulfate ion is the only one of the four substances capable of generating both an ion-radical and an uncharged radical. These expectations are at least partially confirmed by the fact that the $KHSO_5$-$KHSO_4$-K_2SO_4 mixture effects both the Elbs persulfate oxidation of phenol (peroxydisulfate reaction) and the conversion of a cyclic ketone to a lactone (organic peroxyacid reaction).

An aqueous solution of the salt mixture converts toluene to benzoic acid and diphenylmethane to benzophenone. In both instances, prolonged stirring and heating of the reaction mixture is necessary due to the immiscibility of the aqueous and organic layers. Olefins can be converted to glycols or glycol esters depending upon the solvent system employed. Cyclohexene is converted to *trans*- rather than *cis*-cyclohexanediol. The preferential formation of this isomer may be an indication of *trans* addition by an electrophilic fragment of peroxymonosulfate, but it may also indicate that epoxides are intermediates in this reaction. Attempts to isolate the epoxides, however, have been unsuccessful. A terminal, as well as an internal double bond, can be hydroxylated by the salt mixture if sufficiently vigorous reaction conditions are employed.

(5) A. Baeyer and Villiger, *Ber.* **32**, 3625 (1899).

(6) R. E. Marker, *J. Am. Chem. Soc.*, **62**, 2543 (1940).

(7) For a brief listing of the types of carbonyl compounds oxidized by Caro's acid or related peroxygen compounds, see W. vonE. Doering and L. Speers, *J. Am. Chem. Soc.*, **72**, 5515 (1950).

(8) Y. Ishii, *J. Chem. Soc. Japan, Ind. Chem. Sect.* **54**, 58 (1951).

(9) L. W. Jones and E. B. Hartshorn, *J. Am. Chem. Soc.*, 46, 1840 (1924).

(10) E. Bamberger and A. Hill, *Ber.* **33**, 533 (1900).

(11) I. Masson, E. Race, and F. E. Founder, *J. Chem. Soc.*, 1669 (1935).

(12) I. Okamura and R. Sakurai, *Chem. High Polymers (Japan)*, **8**, 296 (1951).

(13) S. E. Stephanou, U. S. Patent 2,802,722 Aug. 13, 1957.

(14) Active oxygen, as the term is used here, refers to the oxygen in excess of that required to form the bisulfate, *i.e.*, $KHSO_5 \longrightarrow KHSO_4 + [O]$, where [O] = active oxygen. In terms of the structure of the peroxymonosulfate ion, $(HOOSO_3)^-$ the active oxygen is located in the perhydroxyl, *i.e.*, —O—O—H, group.

(15) D. L. Ball and J. O. Edwards, *J. Am. Chem. Soc.* **78**, 1125 (1956).

The $KHSO_5$-$KHSO_4$-K_2SO_4 mixture readily converts 2-propanol to acetone and ethanol to acetic acid (or to ethyl acetate if an excess of ethanol is used). Acetaldehyde and acrolein could not be obtained from the corresponding alcohols despite a report[16] that potassium peroxydisulfate converts allyl alcohol to acrolein.

It appears that the $KHSO_5$-$KHSO_4$-K_2SO_4 composition studied does not effect the cleavage of vicinal glycols; in this respect, it differs from potassium peroxydisulfate, which cleaves vicinal glycols in the presence of silver ions.[17] On the other hand, it does convert phenol to hydroquinone in low yield; in this respect it resembles potassium peroxydisulfate.[18]

Moderate yields of lactones are obtained from the reaction of the salt mixture with cyclic ketones. In this case, its behavior resembles that of organic peroxyacids rather than that of inorganic peroxygen compounds. The latter reagents, including a $K_2S_2O_8$-H_2SO_4 mixture,[19] have a pronounced tendency to convert cyclic ketones to ω-hydroxyacids[20] or polyesters derived from these acids.[19,21]

Simple aromatic aldehydes are easily oxidized to the corresponding acids by the $KHSO_5$-$KHSO_4$-K_2SO_4 mixture, but *o*-hydroxy aromatic aldehydes undergo the Dakin reaction (replacement of a formyl group by a hydroxyl group) when treated similarly. Diaryl ketones can be converted to esters by treatment with the salt mixture.

As expected from the behavior of peroxymonosulfuric acid, the $KHSO_5$-$KHSO_4$-K_2SO_4 mixture readily converts primary aryl amines to nitroso compounds rather than to aniline black. Primary *n*-alkyl amines are oxidized to the corresponding acids by the salt mixture; for example, 2-phenethylamine is converted to phenylacetic acid. The salt mixture converts cyclohexylamine, a typical cycloalkylamine, to the corresponding nitroso compound. Spectroscopic evidence indicates that *t*-butylamine is oxidized to a nitroso or nitro compound, but the identity of the product has not been conclusively proved. Secondary aliphatic amines are apparently unaffected by a solution of the $KHSO_5$-$KHSO_4$-K_2SO_4 mixture in dilute acetic acid. Pyridine is converted to pyridine-1-oxide by a slurry of the salt mixture in glacial acetic acid.

The $KHSO_5$-$KHSO_4$-K_2SO_4 mixture converts alkyl mercaptans to sulfonic acids and diaryl sulfides to sulfones in nearly quantitative yields. Triphenylphosphine is oxidized to triphenylphosphine oxide and iodobenzene is oxidized to iodoxybenzene by the salt mixture.

The free radical polymerization of typical vinyl monomers such as vinyl acetate, ethyl acrylate, and acrylonitrile is initiated by the salt mixture. However, ammonium peroxydisulfate has been found to be superior to $KHSO_5$-$KHSO_4$-K_2SO_4 mixture as an initiator for such polymerizations.

The $KHSO_5$-$KHSO_4$-K_2SO_4 mixture apparently does not bring about the coupling (dehydrodimerization) of compounds such as toluene, acetic acid, and nitriles. This observation is somewhat surprising in view of the fact that both hydrogen peroxide[22] and potassium peroxydisulfate[23] effect the coupling of the above substances.

Toluene can be converted to a benzyl halide by heating with a dry mixture of the $KHSO_5$-$KHSO_4$-K_2SO_4 composition and an alkali metal chloride or bromide. However, such mixtures appear to be indifferent toward most other organic substances, including simple olefins.

EXPERIMENTAL[24,25]

1. *Benzoic acid (from toluene).* Toluene (27.6 g.) was heated under reflux with an aqueous solution of the $KHSO_5$-$KHSO_4$-K_2SO_4 mixture (135 g. in 400 ml. of water) for 22 hr. The organic layer was removed and combined with the ether extracts of the aqueous layer. The ether solution was dried over anhydrous sodium sulfate and filtered. Distillation of the filtrate gave 20.0 g toluene and 5.0 g. of a solid acidic residue. After crystallization from hot water, the acidic solid was identified as benzoic acid, m.p. 121–122°., neut. equiv. 121, 122.

2. *Benzophenone.* The procedure was essentially the same as that employed in the oxidation of toluene, except that the reaction mixture was heated for 30 hr. The ketone was isolated as its 2,4-dinitrophenylhydrazone (m.p. 239–240°) by treating the recovered diphenylmethane with an ethanol solution of 2,4-dinitrophenylhydrazine containing a catalytic amount of hydrochloric acid.

3. *trans-Cyclohexanediol.* Cyclohexene (16.4 g.) was added slowly to a solution prepared by dissolving the $KHSO_5$-$KHSO_4$-K_2SO_4 composition (50.5 g.) in a mixture of glacial acetic acid (75 ml.), water (75 ml.), ethanol (75 ml.), and concd. sulfuric acid (50 ml.). The reaction was maintained at a temperature of 70–80° and stirred vigorously for 3 hr. The mixture was allowed to cool, diluted with water, and extracted with chloroform. The chloroform extract was dried over anhydrous sodium sulfate and filtered. Distillation of the filtrate under reduced pressure (1 mm.) gave 10.2 g. of a liquid (b.p. 75–80°) which solidified on standing. After crystallization from an ethanol–petroleum ether (b.p. 65–110°) mixture, the solid *trans*-cyclohexanediol melted at 79°.

Anal. Calcd. for $C_6H_{12}O_2$: C, 62.1; H, 10.3. Found: C, 61.75, 61.67; H, 10.02, 9.93.

(16) R. L. Datta and J. N. Sen, *J. Am. Chem. Soc.*, **39**, 747 (1917).

(17) F. P. Greenspan and H. M. Woodburn, *J. Am. Chem. Soc.*, **76**, 6345 (1954).

(18) W. Baker and N. C. Brown, *J. Chem. Soc.*, 2303 (1948).

(19) R. Robinson and L. H. Smith, *J. Chem. Soc.*, 371 (1937).

(20) M. Fling, F. N. Minard, and S. W. Fox, *J. Am. Chem. Soc.*, **69**, 2466 (1947).

(21) M. Hudlicky, *Chem. listy*, **45**, 3801 (1952).

(22) D. D. Coffman, E. L. Jenner, and R. D. Lipscomb, *J. Am. Chem. Soc.*, 80, 2864 (1958).

(23) C. Moritz and R. Wolffenstein, *Ber.*, **32**, 2531 (1899).

(24) All melting points are uncorrected.

(25) The stable mixture of $KHSO_5$, $KHSO_4$ and K_2SO_4 used in all reactions was "Oxone" monopersulfate compound containing about 5% active oxygen (E. I. du Pont de Nemours & Co., Inc.).

TABLE I

OXIDATION OF ORGANIC COMPOUNDS WITH $KHSO_5$-$KHSO_4$-K_2SO_4 MIXTURES

Compound	Procedure	Product	Conversion, %[a,c]	Yield, %[b,c]
Toluene	1	Benzoic acid	14	50
Diphenylmethane	2	Benzophenone	2	10
Cyclohexene	3	*trans*-Cyclohexanediol	44	44
1-Dodecene	4	1,2-Dodecanediol	30[d]	37[d]
2-Propanol	5	Acetone	100	100
Ethanol	5	Ethyl acetate	100[e]	100[e]
Phenol	6	Hydroquinone	4	21
Cyclopentanone	7	Valerolactone	35	35
Cyclohexanone	7	Caprolactone	46	46
Benzaldehyde	8	Benzoic acid	70	70
Salicylaldehyde	9	Pyrocatechol	17	70
Benzophenone	10	Phenyl benzoate	69	77
p-Phenylenediamine	11	*p*-Dinitrosobenzene	100	100
2-Phenethylamine	12	Phenylacetic acid	24	24
Cyclohexylamine	13	Nitrosocyclohexane	32	32
Pyridine	14	Pyridine-1-oxide	13	13
Dodecyl mercaptan	15	Dodecylsulfonic acid	100	100
Diphenyl sulfide	16	Diphenyl sulfone	97	97
Triphenylphosphine	17	Triphenylphosphine oxide	100	100
Iodobenzene	18	Iodoxybenzene	72	72

[a] % Conversion = $\frac{\text{moles of product}}{\text{moles of limiting reactant}} \times 100$. [b] % Yield = $\frac{\text{moles of product}}{\text{moles of limiting reactant not recovered}} \times 100$. [c] The yields and conversions reported should not, in all cases, be regarded as the best obtainable. It is felt that many of the reported yields can be improved by modification of the techniques used in isolation of products and recovery of reactants. Some conversions might be improved if more favorable reaction conditions can be found. [d] The glycol was obtained by a two-step process. The yield and conversion reported are based on the glycol-olefin mole ratio. [e] Based on $KHSO_5$.

4. *1,2-Dodecanediol.* A mixture of the $KHSO_5$-$KHSO_4$-K_2SO_4 composition (61.4 g.), glacial acetic acid (75 ml.), ethanol (75 ml.), distilled water (75 ml.), concd. sulfuric acid (50 ml.), and 1-dodecene (33.6 g.) was stirred and heated under reflux for 3 hr. The mixture was allowed to cool and the organic (less dense) layer was removed and washed with four 25-ml. portions of 10% sodium chloride solution. The washed liquid was dried over anhydrous magnesium sulfate, filtered, and distilled, first at atmospheric pressure, then under reduced pressure. Two high-boiling fractions (I, b.p. 120–170°/7 mm., 11.5 g.; II, b.p. 170–235°/7 mm., 5.2 g.) were obtained. The infrared spectra of these fractions indicated that they probably consisted of the mono- and diacetates of 1,2-dodecanediol. A portion (5.8 g.) of Fraction I was boiled under reflux with alcoholic potassium hydroxide (5.0 g. potassium hydroxide, 30 ml. ethanol) for 5 hr. The reaction mixture was then concentrated to a volume of 15 ml. and poured into 350 ml. of hot water. After the mixture cooled, the product (a fragrant oil) was removed by extraction with ether (100 ml. in three portions). The ether solution was dried and filtered; evaporation of the ether left 3.2 g. of an oily residue which solidified on standing overnight. The crude product melted at 52–55° (reported[26] for 1,2-dodecanediol, m.p. 60–61°). Two crystallizations from methanol failed to raise the melting point or narrow the melting range. However, the infrared spectrum of the product left little doubt that it was 1,2-dodecanediol.

Anal. Calcd. for $C_{12}H_{26}O_2$: C, 71.23; H, 12.95. Found: C, 71.81, 71.78; H, 12.59, 12.80.

5. *Acetone.* A 1-l. three necked flask was fitted with a total condensate, variable take-off distilling head, a mechanical stirrer and an addition funnel. The flask was charged with the $KHSO_5$-$KHSO_4$-K_2SO_4 (50.0 g.) and 2-propanol (200 ml.). The stirrer was started and concentrated sulfuric acid added at such a rate that the temperature of the reaction mixture was maintained at about 70°. A liquid, b.p. 57–65°, was distilled from the reaction flask. This liquid was redistilled through an 18-inch, silver mirrored Vigreux column. Aliquots of the distillate were withdrawn periodically and treated with Brady's 2,4-dinitrophenylhydrazine reagent. The resulting 2,4-dinitrophenylhydrazone melted at 127–128° and did not depress the melting point of authentic acetone 2,4-dinitrophenylhydrazone. The distilled acetone obtained weighed 10.2 g.

Ethanol was treated similarly. No acetaldehyde distilled from the reaction flask, but ethyl acetate was recovered from the reaction mixture.

6. *Hydroquinone.* Phenol (18.8 g.) was dissolved in 400 ml. of an aqueous (10%) sodium hydroxide solution. The resulting solution was chilled to 5–10° and stirred vigorously while 250 ml. of an aqueous solution of the $KHSO_5$-$KHSO_4$-K_2SO_4 mixture (61.4 g.) was added. The addition required 3.5 hr.; the reaction mixture was then allowed to come to room temperature (23°) and stand overnight. The reaction mixture was made strongly acidic and extracted with ether. The ether extracts were dried over anhydrous sodium sulfate and filtered. Distillation of the extracts yielded 14.8 g. of unchanged phenol. The acidic reaction mixture was boiled under reflux for 30 min., cooled, and again extracted with ether. The extracts were dried over anhydrous sodium sulfate and filtered. Removal of the ether by distillation gave 1.0 g. of a dark-colored, solid residue. After two crystallizations from dilute hydrochloric acid, the solid melted at 171–173° and did not depress the melting point of an authentic sample of hydroquinone.

7. *ε-Caprolactone.* An aqueous solution (400 ml.) of the $KHSO_5$-$KHSO_4$-K_2SO_4 mixture (150 g.) was added slowly to a cold (0–5°) mixture of cyclohexanone (49 g.) and water (250 ml.). The resulting mixture was stirred for 30 min., then neutralized with an aqueous solution of potassium carbonate. The aqueous layer was extracted with three 100-ml. portions of ether. The ether extracts were combined, dried over anhydrous sodium sulfate and filtered. Distillation of the extracts, first at atmospheric pressure, then under reduced pressure, gave 26 g. crude ε-caprolactone, b.p. 97–110°/14 mm., n_D^{23} 1.450.

The procedure used for the preparation of δ-valerolactone

(26) D. Swern, G. N. Billen, and J. T. Scanlan, *J. Am. Chem. Soc.*, 68, 1504 (1946).

was similar to the above, except that the solvent used was a mixture of water, ethanol and sulfuric acid.

8. *Benzoic acid (from benzaldehyde).* A solution of the $KHSO_5$-$KHSO_4$-K_2SO_4 (25.0 g.) in 150 ml. of distilled water was added cautiously to a solution of benzaldehyde (10.6 g.) in chloroform. Concentrated sulfuric acid was then added slowly to this mixture. The resulting slurry was swirled occasionally over a period of 2 days. The organic layer was removed and combined with the ether extracts of the aqueous layer. The combined extracts were dried over anhydrous sodium sulfate and filtered. The ether was evaporated from the filtrate and the solid residue crystallized from boiling water. The yield of benzoic acid (m.p. 122°, neut. equiv. 120, 119) obtained in this way was 8.4 g.

9. *Pyrocatechol.* One hundred fifty milliliters of a 20% aqueous solution of the $KHSO_5$-$KHSO_4$-K_2SO_4 mixture was added to a solution of 12.2 g. salicylaldehyde in 100 ml. of chloroform. Concentrated sulfuric acid (10 ml.) was added slowly to the vigorously stirred mixture. After addition of the acid, the reaction mixture was stirred for 8 hr., then poured into cold water. The organic layer was removed and combined with the chloroform extracts of the aqueous layer. The chloroform solution was dried over anhydrous sodium sulfate, filtered and distilled, first at atmospheric pressure, then under reduced pressure. Unchanged salicylaldehyde (18.2 g.) was obtained together with 2.1 g. pyrocatechol (m.p. 103°).

10. *Phenyl benzoate.* A thick paste prepared from 25 g. of the $KHSO_5$-$KHSO_4$-K_2SO_4 mixture and 25 ml. of concd. sulfuric acid was added in small portions to a solution of 7.0 g. of benzophenone in 25 ml. of glacial acetic acid. The mixture turned deep red and required intermittent cooling; the temperature was not allowed to exceed 35°. After 30 min., the reaction mixture was poured into a slurry of ice and water and the resulting solution extracted with ether. The extracts were dried in the usual manner. The residue which remained after removal of the ether was distilled under reduced pressure. The distillate was dissolved in warm ethanol, the resulting solution seeded with a crystal of benzophenone and allowed to stand for 48 hr. at 0°. The crystallized benzophenone (0.8 g.) was removed by filtration. The filtrate was heated to boiling, then distilled water was added until turbidity developed. After 24 hr., the crystallized phenyl benzoate (5.2 g., m.p. 67°) was collected. Two crystallizations from ethanol raised the melting point of the ester to 70.0–70.5°.

11. *p-Dinitrosobenzene.* A solution of 25.6 g. of the $KHSO_5$-$KHSO_4$-K_2SO_4 mixture in 200 ml. of water was added slowly, with swirling, to 5.4 g. of *p*-phenylenediamine in 100 ml. of water. The red precipitate of *p*-dinitrosobenzene was removed by filtration and air dried. The product weighed 6.8 g., and showed the characteristic behavior of *p*-dinitrosobenzene[27] when heated (turned brown at 184–186° and black at 243°).

12. *Phenylacetic acid.* A mixture of the $KHSO_5$-$KHSO_4$-K_2SO_4 composition (30 g.), 2-phenethylamine (12.1 g.), and distilled water (150 ml.) was heated under reflux for 24 hr. The mixture was allowed to cool, then extracted with ether. The ether solution was dried over anhydrous sodium sulfate, filtered, and distilled (first at atmospheric pressure, then under reduced pressure). After 3.2 g. of phenylacetic acid (b.p. 90–94°/1 mm.; neut. equiv. 132, 130) had been collected, considerable decomposition occurred leaving a dark, tarry pot residue which weighed 5.1 g. The original reaction mixture was made basic and again extracted with ether. Only a trace of an unidentified dark-colored liquid was isolated from the ether extracts.

13. *Nitrosocyclohexane.* A solution of 25 g. of the $KHSO_5$-$KHSO_4$-K_2SO_4 mixture in 150 ml. of water was added rapidly and with vigorous agitation to a solution of 10.0 g. of cyclohexylamine in 50 ml. ether. An exothermic reaction occurred. The mixture was allowed to cool to room temperature and made basic by the addition of solid sodium carbonate. The ether layer and a yellow solid which had precipitated were separated from the aqueous phase of the mixture. The aqueous solution was extracted continuously with ether for a period of 18 hr. The ether solutions were combined, dried over anhydrous sodium sulfate, filtered, and evaporated to dryness. The crude nitrosocyclohexane (3.7 g., precipitate plus residues from ether solution) thus obtained was recrystallized from ethanol, giving a pale yellow product which melted at 114–115°.

14. *Pyridine-1-oxide.* A vigorously stirred mixture of pyridine (15.8 g.), glacial acetic acid (120 ml.), distilled water (17 ml.), and the $KHSO_5$-$KHSO_4$-K_2SO_4 mixture (61.4 g.) was maintained at 70° for 3 hr. A second portion of the salt mixture (30.7 g.) was added and the stirring continued (at 70°) for 18 hr. The mixture was allowed to cool and the solids were removed by filtration. The liquid portion of the mixture was concentrated to a volume of about 40 ml. by evaporation of the acetic acid under reduced pressure. Distilled water (40 ml.) was added to the mixture, which was again concentrated, this time to a volume of about 10 ml. This final concentrate was made strongly basic by the addition of solid sodium carbonate and a few milliliters of distilled water. The basic mixture was shaken with 100 ml. of chloroform and allowed to stand overnight. The solids were removed by filtration and washed with two 25-ml. portions of chloroform. The combined chloroform solutions were distilled leaving as a residue 2.5 g. of crude pyridine-*1*-oxide. A picrate prepared from the oxide melted at 182.5–183.0° with sintering at 179°.

15. *Dodecylsulfonic acid.* Dodecyl mercaptan (5.0 g.) was shaken with 150 ml. of a 25% aqueous solution of the $KHSO_5$-$KHSO_4$-K_2SO_4 mixture for a period of 30 min. The mixture was then placed in a liquid-liquid extraction apparatus along with 250 ml. of concd. hydrochloric acid. The resulting solution was continuously extracted with ether for 12 hr. The ether layer was removed and dried over anhydrous sodium sulfate. Evaporation of the ether left a residue of 6.2 g. of dodecylsulfonic acid (m.p. 43–44°; neut. equiv. 250).

16. *Diphenyl sulfone.* Diphenyl sulfide (11.0 g.) was added over a 20-min. period to a solution prepared from the following: glacial acetic acid (100 ml.), absolute alcohol (100 ml.), distilled water (100 ml.), concd. sulfuric acid (50 ml.), and the $KHSO_5$-$KHSO_4$-K_2SO_4 mixture (35 g.). The mixture was stirred for 5 hr., then diluted with distilled water. The organic layer was removed and combined with the chloroform extracts of the aqueous layer. The chloroform solution was dried over anhydrous sodium sulfate and filtered. Removal of the chloroform from the filtrate gave 12.5 g. of diphenyl sulfone (m.p. 120–121°). Crystallization from ethanol–petroleum ether (b.p. 65–110°) raised the melting point of the sulfone to 124°.

17. *Triphenylphosphine oxide.* One hundred milliliters of a 20% aqueous solution of the $KHSO_5$-$KHSO_4$-K_2SO_4 mixture was added to a solution of 5.0 g. of triphenylphosphine in 50 ml. of ethanol. The temperature of the mixture rose to 70°, and the rate of addition was adjusted so that this temperature was maintained until the addition was complete. The mixture was stirred briskly for 4 hr., then diluted with cold water and extracted with benzene. Crude triphenylphosphine oxide was obtained in quantitative yield by evaporating the benzene solution to dryness. Crystallization of the crude oxide from a benzene–petroleum ether (b.p. 65–110°) mixture gave a pure product which melted at 156–157°.

18. *Iodoxybenzene.* Iodobenzene (20.0 g.) was added slowly to a mixture prepared by dissolving 35 g. of the $KHSO_5$-$KHSO_4$-K_2SO_4 in a slurry of ice (150 g.) and concd. sulfuric acid (100 g.). The resulting mixture was stirred for 4 hr., then diluted with water. The white precipitate which formed was removed by filtration and recrystallized from boiling water. The yield of iodoxybenzene (m.p. 235°,

(27) D. Bigiavi and F. Franceschi, *Gazz. chim. ital.* **57**, 362 (1927).

explodes!, equivalent weight as oxidizer 67.0, 64.6) thus obtained was 16.0 g.

TABLE II

HALOGENATIONS WITH ALKALI METAL HALIDE $KHSO_5$-$KHSO_4$-K_2SO_4 MIXTURES

Compound	Halide	Procedure	Product	Conversion,[a] %	Yield,[a] %
Toluene	NaCl	19	Benzyl chloride	15[b]	15[b]
Toluene	NaBr	19	Benzyl bromide	21[b]	21[b]
2-Octene	KBr	20	2,3-Dibromooctane (?)	59[c]	59[c]

[a] As defined in Table I. [b] Based on halide. [c] Based on octene.

19. *Benzyl chloride.* An intimate mixture of powdered sodium chloride (11.7 g.), the $KHSO_5$-$KHSO_4$-K_2SO_4 composition (50.5 g.), and toluene was heated under reflux for 15 hr. The solids were removed by filtration and the liquid was distilled through an 18-inch Vigreux column. Four grams of benzyl chloride (b.p. 73–77°/17 mm., m.p. −47° to −45°, n_D^{25} 1.5322) were obtained.

20. *2,3-Dibromooctane.* An aqueous potassium bromide solution (23.8 g. potassium bromide, 50 ml. distilled water) and 2-octene (11.2 g.) were added simultaneously to a stirred solution of 61.4 g. of the $KHSO_5$-$KHSO_4$-K_2SO_4 mixture in 250 ml. of distilled water. The addition required about 30 min.; stirring was continued for 2 hr. after the addition was complete. The excess bromine was destroyed by the addition of solid sodium sulfite and the product extracted with methylene chloride (100 ml. in three portions). The extracts were dried over anhydrous magnesium sulfate, filtered, and distilled, first at atmospheric pressure, then under reduced pressure. The major fraction boiled at 105–12°/11 mm. and was identified as a saturated bromoalkane (presumably 2,3-dibromooctane), as it gave a precipitate when treated with alcoholic silver nitrate, but gave negative tests for active unsaturation.

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NIAGARA FALLS, N. Y.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLLEGE OF ARTS AND SCIENCES OF THE UNIVERSITY OF LOUISVILLE]

Synthesis of Pyrimidine-5-carboxaldehydes by the Reimer-Tiemann Reaction

RICHARD H. WILEY AND YUZURU YAMAMOTO

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A study of the structural requirements for the synthesis of pyrimidine-5-carboxaldehydes by the Reimer-Tiemann reaction has shown that the reaction is successful with two methyl and one hydroxyl substituents in the pyrimidine nucleus. The hydroxyl group may be in either the 2- or 4-position. The reaction fails with 4-hydroxypyrimidine and its 6-methyl derivative indicating the necessity for the electron release characteristics of two methyl groups. Monohydroxydimethyl-, di-, and trihydroxypyrimidines give pyrimidine-5-carboxaldehydes. A variety of carbonyl derivatives of the pyrimidine aldehydes are described.

Pyrimidine aldehydes have not been investigated in detail. Their synthesis from acyclic intermediates[1] has not proved to be useful, but a variety of substituted pyrimidines has been converted to aldehydes by standard reactions. Thus, aldehydes have been obtained by ozonolysis of ethylenic groups,[2] by hydrolysis of nitrosomethyl groups,[3] and by suitable conversions of cyano,[4] carboxy,[5] trichlorohydroxyethyl,[6] and hydroxymethyl[7] groups. Formyl groups, or derivatives thereof, have been introduced directly by acylation reactions[8,9,10] and by the Reimer-Tiemann reaction.[6] The last appears to be the most generally useful reaction yet described. Aldehydes have been prepared from 2-amino or alkylamino-4-hydroxy; 2,4-dihydroxy; and 2-piperidinyl or phenyl-4,6-dihydroxy types.[6] Our study was undertaken to extend the Reimer-Tiemann reaction to additional types and to determine minimum structural requirements for activation of the nucleus by electron releasing groups in this reaction.

The pyrimidines converted to aldehydes in the present study are listed in Table I. The aldehydes were prepared, in 13–42% yields, by treating a water-ethanol solution of the pyrimidine with potassium hydroxide and chloroform at 80° for one hour. The potassium salt of the aldehyde

(1) T. B. Johnson, *et al.*, *J. Am. Chem. Soc.*, **37**, 2144 (1915); **41**, 810 (1919); **51**, 1274 (1929); **53**, 1989 (1931); *J. Biol. Chem.* **26**, 99 (1916).

(2) H. Kondo and M. Yanai, *J. Pharm. Soc. Japan* **57**, 747 (1937); *Chem. Abstr.* **32**, 1723; E. Ochiai and M. Yanai, *J. Pharm. Soc. Japan* **58**, 397 (1938); *Chem. Abstr.* **32**, 6653[4].

(3) F. E. King and T. J. King, *J. Chem. Soc.* 943 (1947).

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(5) D. Price, E. L. May, and F. D. Pickel, *J. Am. Chem. Soc.*, **62**, 2818 (1940).

(6) R. Hull, J. Chem. Soc., 4845 (1957).

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(8) M. Ridi and P. Papini, *Gazz. chim. ital.* **76**, 376 (1946).

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(10) W. Pfleiderer and G. Strauss, *Ann.* **612**, 173 (1958).

TABLE I

SUBSTITUTED PYRIMIDINE-5-CARBOXALDEHYDES

No.	Substituent 2-	4-	6-	Yield, %	Recryst. Solvent[a]	M.P.[b]	Nitrogen, % Calcd.	Found
I	OH	OH	OH	42	W	330	17.95	17.92
II	OH	OH	H	18	M; W	304	20.00[f]	19.82
III	CH_3	OH	OH	29	A	300[c]	16.28[g]	16.24
						300	18.18[h]	18.02
IV	OH	OH	CH_3	14[d]	—	—	—	—
V	SH	OH	CH_3	17	W	300	16.46	16.18
VI	SCH_3	OH	CH_3	14	EW	300	15.21[i]	14.99
VII	OH	CH_3	CH_3	26[e]	—	—	—	—
VIII	CH_3	OH	CH_3	13[e]	—	—	—	—

[a] Solvent for recrystallization: W, water; M, methanol; A, acetic acid; EW, aq. ethanol. [b] Uncorrected, with decomposition. [c] The initial product is yellow and analyzes as the monohydrate; on drying it gives the black product which analyzes as the aldehyde. [d] The aldehyde was not isolated from the potassium salt. The yield is based on the yield of the potassium salt. [e] The aldehyde salt did not precipitate. The yield is based on the yield of the phenylhydrazone prepared from the crude solution from which the aldehyde salt has not precipitated. [f] *Anal.* Calcd. for $C_5H_4N_2O_3$: C, 42.86; H, 2.88. Found: C, 42.84; H, 3.00. [g] *Anal.* Calcd. for $C_6H_6O_3N_2H_2O$: C, 41.86; H, 4.68. Found: C, 42.06; H, 4.80. [h] *Anal.* Calcd. for $C_6H_6O_3N_2$: C, 46.76; H, 3.92. Found: C, 46.54; H, 4.10. [i] *Anal.* Calcd. for $C_7H_8O_2N_2S$: C, 45.65; H, 4.38. Found: C, 45.92; H, 4.44.

usually precipitates from the reaction mixture, at room temperature or above, or on cooling either to ice or subzero temperatures. The potassium salt is converted to the free aldehyde on neutralization with acetic acid. For those aldehydes having only one hydroxyl substituent, the potassium salt does not precipitate from solution. The formation of the aldehyde in these cases was established by conversion to a derivative which could be isolated. The yields given for such aldehydes are those of the derivatives. This nonprecipitation may be due to an increased solubility of the salt. Insufficient aldehyde is formed to exceed its solubility in the reaction mixture. It may also be attributed to variations in chelating properties of the hydroxy (or thiol) substituted *ortho*-hydroxy aldehyde structure present in the aldehydes which precipitate. A more complete characterization of the chelating properties of these aldehydes may clarify this point and establish more effective procedures for isolation of the aldehydes. In other experiments, a low yield (1.5%) of an aldehyde derivative was obtained in the reaction using 4-hydroxy-6-methylpyrimidine. The product did not have an analysis in accord with the structure of the pyrimidinecarboxaldehyde derivative. No aldehyde or derivative at all was obtained from 4-hydroxypyrimidine. Because the method of isolation used is reasonably sensitive, it is believed that if any aldehyde had been formed, its presence would have been detected.

The available data establish that the Reimer-Tiemann reaction is successful for those pyrimidines having, as a minimum, two methyl groups and one hydroxyl substituent. The hydroxy group can be in either the 2- or 4-position. If it is assumed that this reaction procedes *via* a carbene intermediate[11,12] and that carbenes react as electrophilic reagents,[13] it appears that the pyrimidine nucleus requires activation by the combined electron release characteristics of two methyl groups and one hydroxyl for the success of this reaction. Although this provides only an approximate basis for establishing the reactivity of the pyrimidine nucleus in the Reimer-Tiemann reaction, it does provide data consistent with three currently accepted concepts: first, that there is a definite difference in reactivity between the 6-methyl-4-hydroxy- and 2,6-dimethyl-4-hydroxypyrimidine; second, that the pyrimidine nucleus is definitely less reactive than the benzene nucleus; and third, that the reaction involves an electrophilic attack by the reactive species derived from chloroform.

In addition to a variety of carbonyl derivatives listed in Table II, the oxime of 2,4-dihydroxy-6-methylpyrimidine-5-carboxaldehyde has been converted to the nitrile with acetic anhydride or phosphorus oxychloride and to the 2,4-dichloronitrile by phosphorus oxychloride and dimethylaniline. The ease with which the oxime dehydrates suggests that the hydroxyl and hydrogen atoms of the oxime are in the trans configuration. The 2-chloro, or 4-chloro, group is replaced by ethoxyl on recrystallization of this compound from ethanol.

EXPERIMENTAL[14]

Barbituric acid, uracil, 2-methyl-4,6-dihydroxypyrimidine, 6-methyluracil, and 6-methyl-2-thiouracil were commercial materials. 4-Hydroxy-6-methyl-2-methylmercaptouracil,[15] 2-hydroxy-4,6-dimethylpyrimidine,[16] 4-hydroxy-

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(12) H. Wynberg, *J. Am. Chem. Soc.* **76**, 4998 (1954).
(13) R. W. Taft, Jr., N. C. Deno, and P. S. Skell, *Ann. Rev. Phys. Chem.* **9**, 308 (1958).
(14) Melting points are uncorrected. Analyses by Micro Tech Laboratories, Skokie, Illinois.
(15) J. Stanek, *Chem. listy* **52**, 357 (1958); *Chem. Abstr.* **52**, 11072[a] (1958).
(16) T. Matsukawa, *J. Pharm. Soc. Japan* **69**, 489 (1949); *Chem. Abstr.* **44**, 3456g (1950).

TABLE II

DERIVATIVES OF SUBSTITUTED PYRIMIDINE-5-CARBOXALDEHYDES

Aldehyde[a]	Derivative[b]	M.P.	Prepd.[c] From	Recrys.[d] From	Nitrogen, % Calcd.	Nitrogen, % Found
I	P	271–273	A	A	22.76	22.83
I	DP	301–302	A	DMF/E	25.00	24.79
I	M	283–284	K	M	28.27	28.41
I	O	250[e]	K	W	24.56	24.43
II	S	240[e]	A	RP	32.58[f]	32.69
II	P	298–300	A	DMF	24.34	24.20
II	DP	270–272[g]	A	M	30.76	30.62
II	O	260[e]	K	DMF	27.09	27.05
II	DP	[e]	A	DMF/W	26.25	26.21
II	HO	[e]	K	M	20.80[f]	21.87
III	S	205[e]	A	RP	33.17	32.90
III	P	240[e,h]	A	RP	22.94	23.01
III	M	200[e,h]	A	C	28.56	28.37
III	DP	[e,h]	K	DMF/W	25.15	24.97
IV	M	258–259	K	M	27.30[i]	27.30
IV	HO	320	K	M	21.86	21.72
IV	O	260	K	M	24.84	24.58
V	P	276–277	K	M	21.53	21.41
V	M	232–233	A	M	26.39	26.48
VI	S	263	K	RP	29.04	28.92
VI	P	250–251	K	M	20.43	20.44
VI	DP	283–284	K	DMF	23.07	23.21
VI	M	168–170	K	M	24.76	24.61
VI	O	228–229	A	M	21.09	20.82
VII	P	229–231	S	M	23.13	23.32
VIII	P	277–279	S	M	23.13	23.19
VIII	DP	305	S	DMF	23.99[f]	23.93
					25.30	25.12
VIII	S	265–266	S	RP	33.48	33.22
VIII	M	192–193	S	M	28.85	28.56
VIII	O	238–240	S	M	22.69[f]	22.41

[a] The number refers to the aldehyde number in Table I. [b] M, dimethylhydrazone; O, oxime; S, semicarbazone; P, phenylhydrazone; DP,2,4-dinitrophenylhydrazone; HO, di(2-hydroxyethyl)hydrazone. [c] A, aldehyde; K, potassium salt of aldehyde; S, solution of unisolated aldehyde. [d] A, Acetic acid; DMF, dimethylformamide; E, ethanol; M, methanol; W, water; RP, reprecipitated from alkaline solution; C, ethyl acetate. [e] Changes color at this temperature; melts over 330°. [f] For the 1.5 hydrate. [g] Water of crystallization lost at 240°. [h] Unstable to heat and light. [i] For hemihydrate (0.5 H_2O). The crude reaction mixture was evaporated to dryness; extracted with ethyl acetate to remove unreacted pyrimidine.

2,6-dimethylpyrimidine,[17] 4-hydroxy-6-methylpyrimidine,[18] and 4-hydroxypyrimidine[19] were prepared as previously described.

The substituted pyrimidine-5-carboxaldehydes are described in Table I. Experimental details are given for a typical preparation of an aldehyde (II). Only minor deviations from this procedure were made with other pyrimidines. The potassium salt of barbituric aldehyde (I) precipitated from the hot (80°) solution. Additional salt was obtained on cooling. The 4,6-dihydroxy-2-methyl aldehyde (III) salt precipitated in part at 80°; in part at 50°; and in part on cooling. Acidification of the potassium salt gives a yellow product, m.p. 150–208°, which had an analysis corresponding to the aldehyde (III) monohydrate; thorough drying in vacuum at 100° gives a black solid which analyzes as the aldehyde (III). Its derivatives were prepared from the hydrated material. Neutralization of the potassium salt of 2,4-dihydroxy-6-methyl-(IV), 2-hydroxy-4,6-dimethyl-(VII), and 4-hydroxy-2,6-dimethyl-(VIII) aldehydes did not precipitate the corresponding free aldehydes. Derivatives were prepared using the acidified solution of the salt.

The derivatives of the aldehydes are described in Table II. They were prepared by standard procedures from the free aldehyde or its potassium salt with the appropriate reagent either with or without addition of acetic acid. The di(hydroxyethyl)hydrazine was prepared as elsewhere[20] described and the corresponding hydrazone was isolated by evaporation of the reaction mixture to dryness extraction of the residue with ethyl acetate, and recrystallization of the residue left on evaporation of the ethyl acetate extracts. The dimethylhydrazone of VIII was isolated by evaporating the reaction mixture to dryness, extracting the residue with ethyl acetate, subliming the unchanged pyrimidine from the extracts, and recrystallizing the residue. The oxime of VIII was isolated by evaporating the crude reaction mixture to dryness, extracting the residue with hot ethyl acetate to remove unchanged pyrimidine, and recrystallizing the material insoluble in hot ethyl acetate.

2,4-Dihydroxypyrimidine-5-carboxaldehyde. A mixture of 24 ml. (0.333 mole) of chloroform and 56 g. of potassium hydroxide in 60 ml. of water was added to a solution of 22.4 g. (0.2 mole) of 2,4-dihydroxypyrimidine and 11.2 g. of potassium hydroxide in 100 ml. of water and 80 ml. of ethanol at 80° during 20 min. and with stirring. The mixture was refluxed 1 hr., cooled to room temperature, and filtered to separate the precipitated potassium chloride. The filtrate was stored 10 hr. at room temperature to precipitate the crude potassium salt of the aldehyde. This salt was suspended in water and neutralized with acetic acid to precipi-

(17) H. R. Snyder and H. M. Foster, *J. Am. Chem. Soc.* **76**, 121 (1954).

(18) H. M. Foster and H. R. Snyder, *Org. Syntheses* **35**, 80 (1955).

(19) D. G. Brown, *Chem. and Ind.* **69**, 353 (1950).

(20) R. H. Wiley and G. Irick, *J. Org. Chem.*, in press.

tate the crude aldehyde. Recrystallization from methanol gave 2.4 g. (8.6%) of the product as yellow crystals. Addition of phenylhydrazine to the filtrate from which the potassium salt of the aldehyde had precipitated gave an additional 4.3 g. (9.4%) of the phenylhydrazone of the aldehyde.

2,4-Dihydroxy-5-cyano-6-methylpyrimidine. A solution of 0.5 g. of the aldoxime and 10 ml. of acetic anhydride were heated under reflux for 30 min. The hot solution was filtered and cooled to room temperature to precipitate 0.15 g. of crystals, m.p. over 330°; ultraviolet, λ_{max} 273 mμ.

Anal. Calcd. for $C_6H_5N_3O_2$: N, 27.80. Found: N, 27.81. The same product was obtained by refluxing 0.5 g. of the aldoxime with 4.5 ml. phosphoryl chloride. The cooled reaction mixture was poured onto ice-water and the precipitate collected and recrystallized from ethanol to give 0.25 g. (56%) of product.

2,4-Dichloro-5-cyano-6-methylpyrimidine. Dimethylaniline (3 ml.) was added slowly and with cooling to a solution of 0.7 g. of 2,4-dihydroxy-6-methylpyrimidine-5-aldoxime in 6 ml. of phosphoryl chloride. The mixture was refluxed 0.5 hr., cooled, and poured onto ice water. The mixture was extracted with ether and the ether extracts washed with bicarbonate, dried, and evaporated to give a yellow crystalline residue. Recrystallization from petroleum ether (b.p. 60–80°) gave 0.45 g. (57%) of the product, m.p. 93–94°.

Anal. Calcd. for $C_6H_3N_3Cl_2$: N, 22.35. Found: N, 22.54.

2(4?)-Chloro-5-cyano-4(2?)-ethoxy-5-methylpyrimidine. On recrystallization of the 2,4-dichloro compound from ethanol, the 2(4?)-ethoxy compound was obtained as yellow plates, m.p. 134–136°.

Anal. Calcd. for $C_8H_8N_3OCl$: N, 21.27. Found: N, 21.20, 21.42.

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LOUISVILLE, KY.

CONTRIBUTION FROM THE DEPARTMENT OF APPLIED CHEMISTRY, UNIVERSITY COLLEGE OF SCIENCE & TECHNOLOGY, CALCUTTA]

Syntheses of Some Arylamino- and Arylguanidinopyrimidines

DOLLY ROY, SUDHAMOY GHOSH, AND B. C. GUHA

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A number of 6-hydroxy-5-unsubstituted pyrimidines having variously substituted arylamino, or arylguanidino groups at C-2 and/or C-4 positions were synthesized. It has been shown that the condensation of arylamines with 2-methylthio-4-amino-6-hydroxypyrimidine under mild condition yields 2-arylamino-4-amino-6-hydroxypyrimidines and under drastic conditions 2,4-bis(arylamino)-6-hydroxypyrimidines.

Curd and Rose[1] demonstrated that 5-unsubstituted 6-alkyl pyrimidines with amino or substituted amino groups at C-2 and C-4 positions were active as antimalarials. Hitchings,[2] *et al.* showed further that if 2,4-diamino-6-alkylpyrimidines have bulky substituents (for example phenyl, phenoxy, etc.) at the C-5 position, they prove to be strong antagonists of folic acid and some of them possess marked antimalarial[3] and antileukemic[4] properties. In connection with our studies of pyrimidines of potential chemotherapeutic value, it was considered of interest to investigate the biological properties of pyrimidines having hydroxyl group in the 6-position and which had variously substituted amino groups at C-2 and C-4 positions, while C-5 position was kept free. The synthesis of some arylamino- and arylguanidinopyrimidines of this type having various substituents at the *para* position of the benzene ring (I to IV) is being reported here. The pronounced inhibitory effects of some of these compounds on bacterial growth have already been reported in preliminary communications.[5,6]

The pyrimidines of type I were synthesized by the reaction of 2-methylthio-4-amino-6-hydroxypyrimidine[7] (V) with the appropriate arylamines according to the method of Wheeler.[8] The reaction takes place with the elimination of methylthiol when an intimate mixture of equimolecular quantities of V and the corresponding arylamine is heated in an inert atmosphere at a temperature necessary for the mixture to go into solution. This type of displacement was not possible with the compound (VI) in which the C-4 and C-6 positions of pyrimidine ring were occupied by methyl groups (*Cf.* ref. 1). The lability of the methylthio group in compound V may be due to the possibility of tautomerism between V and Va as suggested by Curd and Rose.[1] Apparently this type of reaction does

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(2) G. H. Hitchings, E. A. Falco, H. Vanderwerff, P. B. Russell, and G. B. Elion, *J. Biol. Chem.*, 199, 43 (1952).

(3) E. A. Falco, L. G. Goodwin, G. H. Hitchings, I. M. Rollo, and P. B Russel, *Brit. J. Pharmacol.*, 6, 185 (1951).

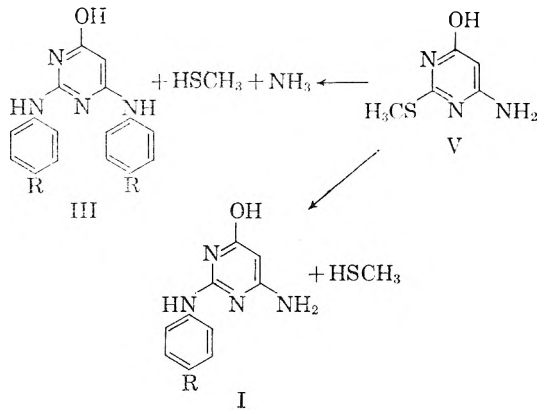
(4) J. H. Burchenal, S. K. Goetchins, C. C. Stock, and G. H. Hitchings, *Cancer Res.*, 12, 255 (1951).

(5) Sudhamoy Ghosh, Dolly Roy, and B. C. Guha, *Nature*, 182, 187 (1958).

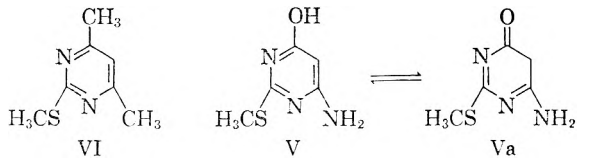
(6) Dolly Roy, S. Ghosh, and B. C. Guha, *Naturwissenschaften*, 45, 392 (1958).

(7) B. T. Johnson and J. O. Carl, *Am. Chem. J.*, 34, 175 (1905).

(8) H. L. Wheeler and G. S. Jamieson, *Am. Chem. J.*, 32, 342 (1904).



not occur with 2-methylthio-4,6-dimethylpyrimidine (VI) as no such tautomerism is possible.



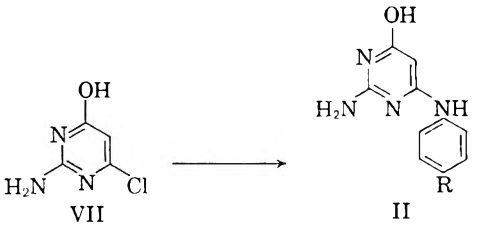
A study of the type of reaction of compound V with the different aromatic amines appears to indicate that a parallelism exists between the basicity of the amine and the yield obtained (Table I). It will be seen that the yields obtained from aniline, *p*-toluidine, and *p*-chloroaniline range in the order of their basicities. No reaction was possible with *p*-nitroaniline and α-naphthylamine apparently owing to their low basicity, the reactants being recoverable unchanged. The failure of reaction in the case of *p*-bromoaniline was due to the instability of this compound. *p*-Bromoaniline decomposed before the reaction could take place.

TABLE I

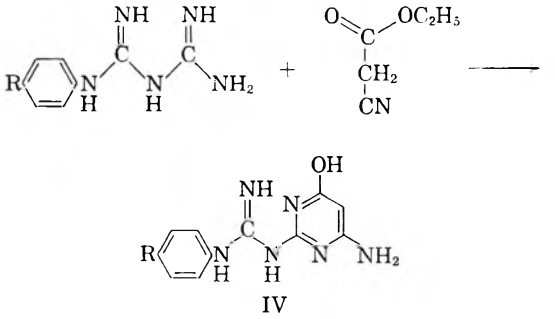
REACTION OF DIFFERENT AROMATIC AMINES WITH V TO PRODUCE COMPOUNDS OF THE TYPE I

Amine	Yield, %	Dissociation Constant (K) of Amine at 25°
p-Toluidine	80	1.5×10^{-9}
p-Bromoaniline	0	1.0×10^{-10}
p-Chloraniline	70	1.5×10^{-10}
Aniline	70	3.5×10^{-10}
p-Nitroaniline	0	3.45×10^{-11}
α-Naphthylamine	0	9.9×10^{-11}

When arylamines in excess were allowed to react with V under more drastic conditions (higher temperature and longer heating period), the formation of 2,4-bis(arylamino)-6-hydroxypyrimidines (type III) was favored. The treatment of 2,4-bis(*p*-chloroanilino)-6-hydroxypyrimidine (IIIc) with phosphorus oxychloride in the usual way gave rise to the corresponding 6-chloro compound (IIId). This shows that the 6-hydroxyl group in IIIc is free. The condensation of the second arylamine to produce compounds of type III is probably due to the presence of amidine structure $-\overset{3}{N}=\overset{4}{C}-NH_2$ in I involving N-3 and C-4 of the pyrimidine ring where the electronically deficient C-4 is vulnerable to nucleophilic attack by aromatic amines.



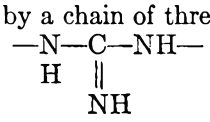
The pyrimidines of type II were synthesized by the condensation of 2-amino-4-chloro-6-hydroxypyrimidine[9] (VII) with the appropriate arylamine in presence of a mineral acid using a modification of the method of Banks.[10]



The compounds of type IV were prepared by the condensation of ethyl cyanoacetate with the corresponding arylbiguanide in absolute ethanol in presence of sodium ethoxide following a modified procedure of Curd and Rose.[1]

The C-5 position of these compounds is free because on treatment of an acidic solution of these pyrimidines with nitrous acid, they give rise to colored precipitates which show that nitrosation occurs in the 5-position. One such nitroso compound (IIIe) has been isolated.

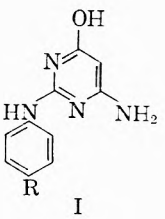
The ultraviolet absorption spectra of these compounds were determined in ethanol. The relevant data are given in Table III. It is known that the simple trisubstituted pyrimidines exhibit a maximum in the region 264 ± 6 mμ. However, in all the compounds listed below except in IVc the positions of the maxima are at higher wave length. This seems to be due to the presence of the phenyl ring near the pyrimidine nucleus. The fact that the compound IVc behaves differently is apparently because the phenyl group is separated from the pyrimidine nucleus by a chain of three atoms:



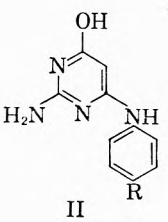
(9) S. Gabriel and J. Coleman, *Ber.*, **36**, 3381 (1903).
(10) C. K. Banks, *J. Am. Chem. Soc.*, **66**, 1127 (1944).

TABLE II

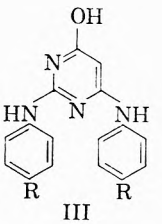
ARYLGUANIDINO- AND ARYLAMINOPYRIMIDINES



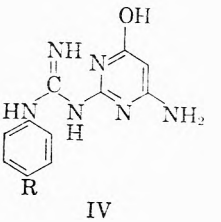
I



II



III



IV

Compounds	R	Yield, %	M.P.[a]	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
Ia	—H	70	274–275	$C_{10}H_{10}N_4O$[b]	59.40	4.95	27.72	59.51	4.91	27.48
Ib	—CH_3	80	272–273	$C_{11}H_{12}N_4O$[b]	61.11	5.55	25.92	61.00	5.60	25.87
Ic	—Cl	70	269–270	$C_{10}H_9N_4OCl$[b]	50.73	3.80	23.67	50.65	3.77	23.71
IIa	—H	63	145	$C_{10}H_{10}N_4O$[c]	59.40	4.95	27.72	59.21	4.82	27.56
IIb	—CH_3	86	152–155	$C_{11}H_{12}N_4O$[d]	61.11	5.55	25.92	61.01	5.46	25.62
IIc	—Cl	95	168–169	$C_{10}H_9N_4OCl$[d]	50.73	3.80	23.67	51.00	3.75	23.67
IIIa	—H	46	214–216	$C_{16}H_{14}N_4O$[d]	69.06	5.03	20.14	69.20	5.03	20.14
IIIb	—CH_3	52	224–226	$C_{18}H_{18}N_4O$[d]	70.58	5.88	18.30	70.56	5.90	18.18
IIIc	—Cl	60	254	$C_{16}H_{12}N_4OCl_2$[b]	55.33	3.45	16.13	55.17	3.47	16.12
IVa	—H	42	151–152	$C_{11}H_{12}N_6O$[e]	54.04	4.91	34.40	54.02	4.88	34.45
IVb	—OCH_3	35	142	$C_{12}H_{14}N_6O_2$[c]	52.55	5.10	30.65	52.50	5.06	30.70
IVc	—CH_3	48	198	$C_{12}H_{14}N_6O$[d]	55.81	5.42	32.55	56.20	5.40	32.48
IVd	—NO_2	50	[f]	$C_{11}H_{11}N_7O_3$[g]	45.68	3.80	33.91	45.59	3.78	34.04
IVe	—Cl	34	221–222	$C_{11}H_{11}N_6OCl$[h]	47.39	3.94	30.16	47.35	4.02	29.88

[a] Melting points are uncorrected. [b] Recrystallized from 90% ethanol. [c] Recrystallized from water. [d] Recrystallized from 60% ethanol. [e] Recrystallized from aqueous acetone. [f] Decomposes above 310° without melting. [g] Recrystallized from *N,N*-dimethylformamide. [h] Recrystallized from acetone.

TABLE III

ULTRAVIOLET ABSORPTION DATA OF ARYLGUANIDINO- AND ARYLAMINOPYRIMIDINES IN ETHANOL

Compound	λ_{max} (mμ)		log ε	
2-(*p*-Chloroanilino)-4-amino-6-hydroxypyrimidine (Ic)	275		4.115	
2-Amino-4-(*p*-chloroanilino)-6-hydroxypyrimidine (IIc)	250	292	4.421	3.639
2,4-Bis(*p*-chloroanilino)-6-hydroxypyrimidine (IIIc)	243	279	4.224	4.510
2-(*p*-Chlorophenylguanidino)-4-amino-6-hydroxypyrimidine (IVc)	265		4.433	

The biological properties of these compounds are under detailed investigation and will be reported elsewhere.

EXPERIMENTAL[11]

2-(p-Chloroanilino)-4-amino-6-hydroxypyrimidine (Ic). 2-Methylthio-4-amino-6-hydroxypyrimidine (5.2 g., 0.033 mole) and *p*-chloroaniline (4.3 g., 0.033 mole) were thoroughly mixed and the mixture was slowly heated on an oil bath in an Erlenmeyer flask provided with an air condenser and an inlet tube through which nitrogen was passed to maintain an inert atmosphere. When the temperature of the bath reached about 160° the mixture started to melt. The reaction mixture was maintained at this temperature until no odor of methylmercaptan was perceptible (about 6 hr.). After cooling and dissolving the mixture in ethanol and subsequent decolorization with charcoal, the product was precipitated with water. The suspension was made acidic (*p*H 3) with hydrochloric acid to dissolve any unchanged starting materials. The precipitate was filtered and washed with water. The product (5.2 g.) was crystallized from 90% ethanol to yield silky white crystals.

2-(Anilino)-4-amino-6 hydroxypyrimidine (Ia) and *2 (p-toluidino)-4-amino-6-hydroxypyrimidine* (Ib) were prepared by the same general method as described for (Ic).

2,4-Bis(p-chloroanilino)-6-hydroxypyrimidine (IIIc). 2-Methylthio-4-amino-6-hydroxypyrimidine (5.2 g., 0.033 mole) and excess *p*-chloroaniline (15 g.) were thoroughly mixed and the mixture was heated on an oil bath in an atmosphere of nitrogen as described in the preparation of Ic. The temperature of the oil bath was slowly raised to 180–190° and maintained at that level until the solid completely melted (about 4 hr.). More *p*-chloroaniline was added at this stage to replenish any loss of it from the reaction mixture by evaporation. The temperature of the bath was lowered to 170–175° and the reaction mixture was further heated for another 4 hr. The mixture was then cooled and taken up in water and the aqueous medium acidified with dilute hydrochloric acid. The suspension was stirred for 2 hr. at room temperature to dissolve unchanged starting materials. This was then filtered and the residue washed well with water. The product was then purified by repeated crystallization from 90% ethanol.

2,4-Bis(anilino)-6-hydroxypyrimidine (IIIa) and *2,4-bis-(p-toluidino)-6-hydroxypyrimidine* (IIIb) were prepared by the same method as described for IIIc.

2,4-Bis(p-chloroanilino)-6-chloropyrimidine (IIId). Compound IIIc (1 g.) was finely powdered and treated with phosphorus oxychloride (15 ml.). When the initial vigor of the reaction subsided, the mixture was slowly heated over

(11) Before analysis the samples were dried *in vacuo* at 110° for about 8 hr. The solvents for crystallization, melting points, and analytical data are given in Table II.

boiling water-bath until all the solid went into solution. The excess oxychloride was removed by distillation under reduced pressure and the oily liquid was poured over crushed ice. A white precipitate appeared immediately which was filtered, washed with water and finally crystallized from aqueous acetone; yield 900 mg. IIId decomposes above 260°.

Anal. Calcd. for $C_{16}H_{11}N_4Cl_3$: C, 52.53; H, 3.00; N, 15.32. Found: C, 52.49; H, 2.90; N, 15.26.

2,4-Bis(p-chloroanilino)-5-nitroso-6-hydroxypyrimidine (IIIe). Compound IIIc was finely pulverized and suspended in 30 ml. of 95% ethanol. Concentrated hydrochloric acid was added to this mixture until the *p*H went down to 3. Sodium nitrite (200 mg.) in 10 ml. of water was added drop by drop with stirring at room temperature maintaining the *p*H of the solution at about 3, until the nitrosation was complete. A deep brown colored precipitate was formed during nitrosation. The reaction mixture was cooled, filtered, and the residue washed thoroughly with water and then with cold alcohol. The product could not be satisfactorily crystallized; yield 850 mg. It does not melt below 310°.

Anal. Calcd. for $C_{16}H_{11}N_5O_2Cl_2$: C, 51.06; H, 2.92; N, 18.61. Found: C, 51.00; H, 2.86; N, 18.57.

2-(p-Nitrophenylguanidino)-4-amino-6-hydroxypyrimidine (IVd). *p*-Nitrophenylbiguanide (9 g., 0.04 mole) was added to a solution of sodium ethoxide (0.92 g., 0.04 mole of sodium in 100 ml. of absolute ethanol), and to this mixture was added slowly with stirring ethyl cyanoacetate (11.3 g., 0.1 mole) while the temperature was maintained below 20°. The mixture was heated under reflux for 16 hr. The mass became deep yellow and some precipitate appeared immediately on refluxing. The reaction mixture was cooled, filtered, and the precipitate washed first with water and then with alcohol. The product could be crystallized from *N,N*-dimethylformamide. The crystals appeared as fine yellow needles.

2-(Phenylguanidino)-4-amino-6-hydroxypyrimidine (IVa). A solution of sodium ethoxide (3 g., 0.13 mole of sodium in 75 ml. of absolute ethanol) was treated with phenylbiguanide hydrochloride (10.7 g., 0.05 mole) in an ice bath. This was shaken well until the reaction was complete. The precipitated sodium chloride was filtered and to the filtrate ethyl cyanoacetate (11.3 g., 0.1 mole) was added with shaking, taking care that the temperature of the mixture did not rise above 30°. Some precipitate appeared immediately and the amount increased on standing. The mixture was left at room temperature (25–28°) for 24 hr. The heavy precipitate formed was filtered and washed with cold absolute alcohol. This was suspended in water when most of the precipitate went into solution. The mixture was acidified with hydrochloric acid, cooled to 2°, filtered, and the residue washed with cold water. The residue could be crystallized from aqueous acetone.

2-(p-Methoxyphenylguanidino)-4 amino 6-hydroxypyrimidine (IVb). A mixture of *p*-anisylbiguanide hydrochloride (12.2 g., 0.05 mole), sodium ethoxide (2.3 g. sodium in 50 ml. absolute ethanol), and ethyl cyanoacetate (5.7 g., 0.05 mole) was refluxed for about 2 hr. The precipitate obtained was washed with alcohol, suspended in water (50 ml.), and neutralized with hydrochloric acid. After cooling, the product was filtered, washed with cold water, and crystallized from water as white needles.

2-(p-Methylphenylguanidino)-4-amino-6-hydroxypyrimidine (IVc). A mixture of *p*-methylphenylbiguanide hydrochloride (11.4 g., 0.05 mole), ethyl cyanoacetate (11.3 g., 0.1 mole) and sodium ethoxide (3.5 g. of sodium in 100 ml. of absolute ethanol) was refluxed for 4 hr. The product obtained was isolated in the same way as described under IVb.

2-(p-Chlorophenylguanidino)-4-amino-6-hydroxypyrimidine (IVe). A mixture of *p*-chlorophenylbiguanide hydrochloride (12.5 g., 0.05 mole), ethyl cyanoacetate (5.7 g., 0.05 mole), and sodium ethoxide (1.3 g. of sodium in 50 ml. of absolute ethanol) was refluxed for 2 hr. The product was then isolated in the same way as described under IVb.

[Added in proof]

2-Amino-4-(p-chloroanilino)-6-hydroxypyrimidine (IIc). A mixture of 2-amino-4-chloro-6-hydroxypyrimidine (2.9 g., 0.02 mole), *p*-chloroaniline, (2.6 g., 0.02 mole), glacial acetic acid (30 ml.), and concentrated hydrochloric acid (0.4 ml.) was heated at refluxing temperature for about 4 hr. The resulting solution was treated with charcoal for decolorization and filtered hot. The desired product precipitated partially on cooling, but for complete precipitation the solution was diluted with 200 ml. of water and then neutralized partially with 20 ml. of 10*N* sodium hydroxide. The precipitate was filtered, thoroughly washed with water, and crystallized from 60% alcohol.

2-Amino-4-(p-toluidino)-6-hydroxypyrimidine (IIb) *and 2-amino-4-(anilino)-6-hydroxypyrimidine* (IIa) were prepared by the same general method as given for IIc.

Acknowledgment. We are grateful to the Council of Scientific & Industrial Research, Government of India, for financing this work. Our thanks are also due to Prof. J. C. Bardhan for valuable discussion.

CALCUTTA, INDIA

[CONTRIBUTION FROM BATTELLE MEMORIAL INSTITUTE AND THE UNIVERSITY OF ALABAMA MEDICAL SCHOOL]

Synthesis of Some Vicinal Trimethoxyphenyl Derivatives of Heterocyclic Nitrogen Bases

F. BENINGTON,[1] R. D. MORIN,[1] AND L. C. CLARK, JR.[2]

Received March 22, 1960

A number of vicinal trimethoxy analogs of compounds possessing psychopharmacological activity were synthesized to examine the influence of vicinal trimethoxy groups on this type of activity.

In a continuation of our investigation of correlations between chemical structure and psychopharmacological activity, we have undertaken the synthesis of several new compounds in which vicinal trimethoxy groups are present on the phenyl rings of a number of useful synthetic drugs which affect mood and behavior of human subjects. It is well known that the presence of vicinal trimethoxy groups on a phenyl ring can alter pro-

(1) Battelle Memorial Institute.

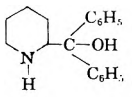
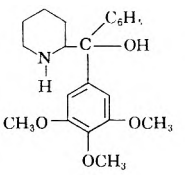
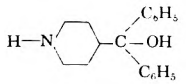
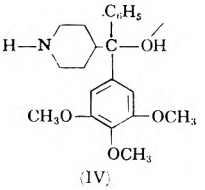
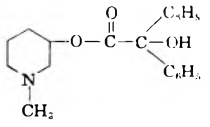
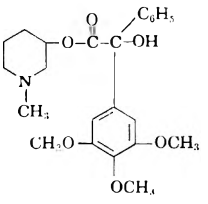
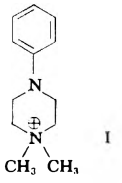
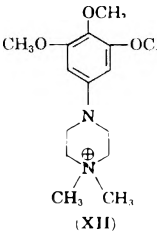
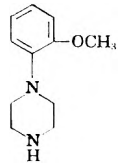
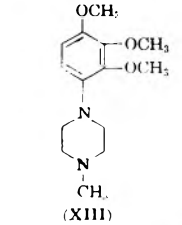
(2) Department of Surgery, University of Alabama Medical School.

foundly the psychopharmacological action of certain amines. For example, 3,4,5-trimethoxy-β-phenethylamine and DL-3,4,5-trimethoxy-β-phenylisopropylamine both exhibit psychotomimetic activity whereas the unalkoxylated amines are inactive in this respect at comparable dose levels.

Table I shows the parent compound, its type of activity, and the structure of the desired trimethoxy analog.

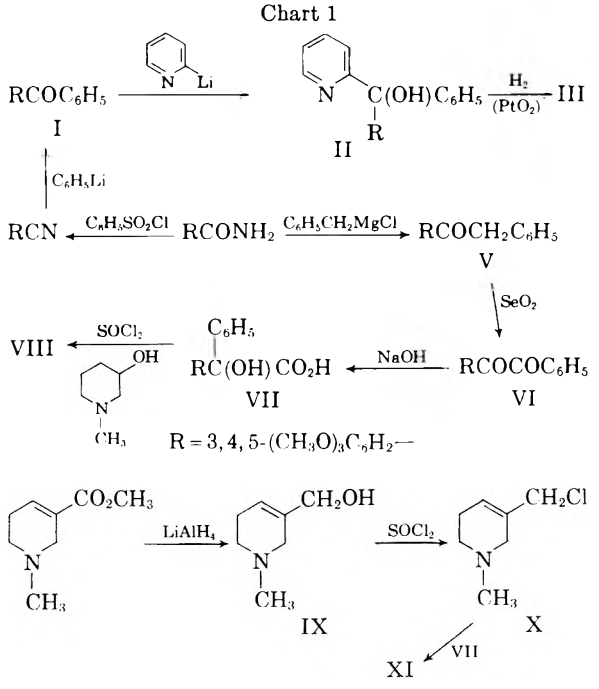
TABLE I

VICINAL TRIMETHOXY DERIVATIVES

Parent Compound	Type of Activity	Desired Trimethoxy Analog
	CNS Stimulant[3]	 (III)
	Ataractic[4]	 (IV)
	Psychotogenic[5]	 (VIII)
 I	Sympathetic ganglian stimulator[6]	 I (XII)
	Antihypotensive causing dream activity[6]	 (XIII)

As shown in Chart 1, 3,4,5-trimethoxybenzonitrile, obtained from the dehydration of the corresponding amide with benzenesulphonyl chloride,[7] reacted readily with a solution of phenyllithium in absolute ether to obtain 3,4,5-trimethoxybenzophenone (I) in 86% yield. Previous work in this laboratory had shown that extensive ether cleavage occurs when the preparation of I is attempted by means of a Friedel-Crafts reaction between 3,4,5-trimethoxybenzoyl chloride and benzene in the presence of aluminum chloride. The preparation of I through the action of phenylmagnesium bromide on 3,4,5-trimethoxybenzonitrile was not attempted because Grignard reagents usually attack the 4-methoxy group and also cause ether cleavage.[8] Our use of the organo - lithium reaction was prompted by the fact that many nitriles give better yields of ketones with this reagent than with organomagnesium halides.[9] 2-Lithiopyridine, obtained from the interchange of *n*-butyllithium with 2-bromopyridine at −50°, was allowed to react with the ketone I to obtain DL-phenyl-2-pyridyl-3,4,5-trimethoxyphenylcarbinol (II) in 72% yield.

Chart 1



Catalytic hydrogenation of II, as a methanol solution containing some hydrochloric acid, in the presence of Adams catalyst[10] brought about the

(3) B. B. Brown and H. W. Werner, *J. Pharmacol. Exptl. Therap.*, **110**, 180 (1954).

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(5) L. G. Abood, A. Ostfeld, and J. H. Biel, *Arch. intern. pharmacodynamie*, **120**, (2), 186 (1959).

(6) I. H. Page, *Science*, 125, 721 (1957).

(7) C. R. Stephens, E. J. Bianco, and F. J. Pilgrim, *J. Am. Chem. Soc.*, **64**, 2085 (1942).

(8) In the preparation of 3,4,5-trimethoxyphenyl isobutyl ketone from the corresponding nitrile and isobutylmagnesium bromide, C. D. Hurd and H. E. Winberg, *J. Am. Chem. Soc.*, **64**, 2085 (1942), found that this cleavage occurred at temperatures above 40°. Although lower reaction temperatures prevented this side reaction, the yield of ketone was unsatisfactory.

(9) H. Gilman, private communication (1957).

(10) H. W. Warner and C. H. Tilford, U. S. Patent **2,624,739** (1953).

selective reduction of the heterocyclic ring and gave the desired DL-phenyl-2-piperidyl-3,4,5-trimethoxyphenylcarbinol (III); this compound was isolated as its water-soluble hydrochloride.

An exploratory attempt to prepare the isomeric DL-phenyl-4-piperidyl-3,4,5-trimethoxyphenylcarbinol (IV) *via* the above route using 4-pyridyllithium was unsuccessful since the latter reagent could not be prepared. When 4-bromopyridine was interchanged with *n*-butyllithium at −75°, the only reaction product which could be isolated was an oil which was identified as 4-*n*-butylpyridine. Wibaut and Heeringa[11] state that 4-pyridyllithium results when the above interchange is carried out at this reaction temperature.

The synthesis of DL-*N*-methyl-3-piperidyl 3,4,5-trimethoxybenzilate (VIII) required DL-3,4,5-trimethoxybenzilic acid (VII) as an intermediate. 3,4,5-Trimethoxybenzamide was first treated with benzylmagnesium chloride to obtain 3,4,5-trimethoxyphenyl benzyl ketone (V) in 41% yield. Oxidation of V to 3,4,5-trimethoxybenzil (VI) by means of selenium dioxide in acetic anhydride as a solvent[12] gave a somewhat lower yield than might have been expected. Clark[13] has pointed out that it is often not advantageous to carry out the oxidation of desoxybenzoins, such as V, in the presence of acetic anhydride because of the formation of high-boiling selenium-containing compounds as side products. The conversion of the benzil VI to a high yield of DL-3,4,5-trimethoxybenzilic acid (VII) was carried out using the anaerobic technique described by Schoenberg and Keller.[14] These workers have shown that alkoxybenzils are converted to undesirable oxidation products when their alkaline solutions are exposed to air under the conditions usually employed in the benzilic acid rearrangement. DL-*N*-Methyl-3-piperidyl 3,4,5-trimethoxybenzilate (VIII) resulted from the reaction of VII with *dl*-1-methyl-3-chloropiperidine in isopropyl alcohol.[15] Treatment of VIII in dry ether solution with anhydrous hydrogen chloride gave an oily salt which could not be induced to crystallize. Accordingly, VIII was isolated as the maleate.

In the course of this investigation, it was desired to obtain DL-*N*-methyl-1,2,5,6-tetrahydro-3-pyridylmethyl benzilate (XI) for making pharmacological comparisons with DL-*N*-methyl-3-piperidyl benzilate. The commercially available alkaloid arecoline was reduced to *N*-methyl-3-hydroxymethyl-1,2,5,6-tetrahydropyridine[16] (IX) by means of lithium aluminum hydride. Treatment of IX with thionyl chloride afforded *N*-methyl-3-chloromethyl-1,2,5,6-tetrahydropyridine (X) hydrochloride, which was subsequently treated with benzilic acid under the conditions already given for the preparation of VIII. The resulting ester base XI was isolated as the hydrochloride.

In an attempt to obtain *N*-(3,4,5-trimethoxyphenyl)-*N'*,*N'*-dimethylpiperazinium iodide (XII), 3,4,5-trimethoxyaniline was first treated with *N*-methyl-bis(β-chloroethyl)amine hydrochloride under the conditions given by Prelog and Driza[17] for aniline. However, none of the expected intermediate *N*-(3,4,5-trimethoxyphenyl)-*N'*-methylpiperazine could be isolated from the tar which formed during the reaction. It was of interest to note, however, that 2,3,4-trimethoxyaniline reacted smoothly with this chloroethylamine derivative to give a 46.5% yield of *N*-(2,3,4-trimethoxyphenyl)-*N*-methylpiperazine (XIII) with no formation of tar. By treating XIII with a limited quantity of methyl iodide, *N*-(2,3,4-trimethoxyphenyl)-*N'*,*N'*-dimethylpiperazinium iodide was obtained in high yield.

Detailed results concerning the psychopharmacology of these compounds will be published elsewhere.

EXPERIMENTAL[18]

3,4,5-Trimethoxybenzophenone (I). To a stirred suspension of 35 g. of 3,4,5-trimethoxybenzamide in 70 ml. of pyridine was added slowly 34.2 g. of benzenesulphonyl chloride. The warm reaction mixture was heated to 70° for 0.5 hr. (stirring), cooled to room temperature, and finally poured into 400 ml. of cold water. The solid product was collected on a Büchner funnel and washed with dilute hydrochloric acid and then with water. After air drying, the crude 3,4,5-trimethoxybenzonitrile amounted to 29.2 g. (91%); m.p. 94–95° (reported,[7] m.p. 90–92°).

To a stirred solution of phenyllithium, prepared from 2.8 g. of lithium wire and 31.4 g. of bromobenzene in 150 ml. of dry ether, was added a solution of 29 g. of 3,4,5-trimethoxybenzonitrile in 125 ml. of dry benzene. The mixture was stirred at room temperature overnight and then hydrolyzed by the addition of water and cold dilute hydrochloric acid. The resulting insoluble ketimine hydrochloride of I was converted to 35 g. (86%) of nearly colorless 3,4,5-trimethoxybenzophenone (I) by boiling with very dilute hydrochloric acid; m.p. 75–76°, after recrystallization from alcohol.

Anal. Calcd. for $C_{16}H_{16}O_4$: C, 70.5; H, 5.9. Found: C, 70.6; H, 5.8.

DL-*Phenyl-2-pyridyl-3,4,5-trimethoxyphenylcarbinol* (II). A solution of *n*-butyllithium was prepared by treating a stirred suspension of 2.8 g. of lithium wire (2-mm. pieces) in 200 ml. of dry ether with 30 g. of *n*-butyl bromide under a dry nitrogen atmosphere. When dissolution of the metal was complete, the solution was cooled to −60° (Dry Ice-acetone bath) and 30 g. of 2-bromopyridine was added at such a rate that the temperature did not rise above −50°. To the re-

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(12) H. H. Hatt, A. Pilgrim, and W. J. Hurran, *J. Chem. Soc.*, 93 (1936).

(13) M. T. Clark, E. C. Hendly, and O. K. Neville, *J. Am. Chem. Soc.*, **77**, 3280 (1955).

(14) A. Schoenberg and K. T. Keller, *Ber.*, **36B**, 1638 (1923).

(15) F. F. Blicke and C. E. Maxwell, *J. Am. Chem. Soc.*, **64**, 428 (1942).

(16) P. Karrer and P. Portmann, *Helv. Chim. Acta*, **31**, 2088 (1948).

(17) V. Prelog and G. J. Driza, *Collection Czechoslov. Chem. Communs*, **5**, 497 (1933).

(18) All melting points uncorrected.

sulting deep-orange solution was added 12.9 g. of I in 25 ml. of dry benzene; during this addition the temperature of the reaction mixture was kept below +10°. After refluxing for 45 min. and cooling to room temperature, the reaction mixture was hydrolyzed by adding 80–90 ml. of water. The organic layer was separated, dried over anhydrous magnesium sulfate, filtered, and quickly evaporated to a small volume. Treatment of the residue with petroleum ether (30–60°) precipitated II (12 g.; 72%) as nearly colorless prisms; m.p. 134–135°. An analytical specimen recrystallized from boiling ether melted at 137–137.5°.

Anal. Calcd. for $C_{21}H_{21}NO_4$: C, 71.9; H, 5.99. Found: C, 71.8; H, 5.8.

DL-*Phenyl-2-piperidyl-3,4,5-trimethoxyphenylcarbinol* (III). To a solution of II (14 g.) in 100 ml. of reagent methanol was added 200 mg. of Adams' catalyst and 20 ml. of 10% aqueous hydrochloric acid. The mixture was shaken with hydrogen in a Parr apparatus at about 60 p.s.i.g. until hydrogen was no longer absorbed (final pressure 56.5 p.s.i.g. after 3.3 hr.). After adding both another 200-mg. portion of catalyst and 5 ml. of 10% hydrochloric acid, the apparatus was repressurized to 60 p.s.i.g. and hydrogenation continued until the total gas uptake had reached that calculated for total hydrogenation of the pyridine ring. The resulting mixture was treated with Norit, filtered, and evaporated *in vacuo*. A sample of the crude free base III thus obtained melted at 169–170°. The residue was taken up in a dry ether-benzene mixture and treated with dry hydrogen chloride to precipitate DL-phenyl-2-piperidyl-3,4,5-trimethoxyphenylcarbinol (III) hydrochloride. Recrystallization from hot ether-ethanol gave 9.5 g. (61%) of the purified salt as colorless prisms, m.p. 265–266°.

Anal. Calcd. for $C_{21}H_{28}ClNO_4$: C, 64.1; H, 7.12; Cl, 9.03. Found: C, 63.8; H, 7.2; Cl, 9.0.

3,4,5-Trimethoxyphenyl benzyl ketone (V). To a stirred solution of benzylmagnesium chloride (prepared from 101 g. of benzyl chloride and 19.4 g. of magnesium turnings) in 500 ml. of dry absolute ether was added 42 g. of finely powdered 3,4,5-trimethoxybenzamide. The mixture was refluxed for 2 hr., allowed to stand overnight, and then poured into 800 g. of an ice-water mixture containing 44 ml. of concd. sulfuric acid. An insoluble precipitate of unchanged amide (20.5 g.; 49% recovery) was collected. The ether layer from the filtrate was washed with 5% aqueous sodium bicarbonate and then with water. After drying over anhydrous magnesium sulfate, and concentrating *in vacuo*, the residue was induced to crystallize by adding an ether–petroleum ether (b.p. 30–60°) mixture. The crude product (20.4 g.) yielded 13.1 g. of 3,4,5-trimethoxyphenyl benzyl ketone (V) as light-yellow prisms, m.p. 97–98°. An additional 4.4 g. of purified V was obtained by treating the recovered amide in suspension in dry benzene with benzylmagnesium chloride. A total yield of 17.5 g. (41%) of pure V was thus obtained.

Anal. Calcd. for $C_{17}H_{18}O_4$: C, 71.3; H, 6.3. Found: C, 71.3; H, 6.2.

3,4,5-Trimethoxybenzil (VI). To a solution of 35 g. of V in 75 ml. of acetic anhydride was added 19.2 g. of selenium dioxide. After refluxing for 3.5 hr., the reaction mixture was poured onto crushed ice and brought to *p*H 8 by the addition of aqueous ammonia. The yellow semisolid precipitate was collected and recrystallized from hot ethanol to give 13 g. (39%) of VI as yellow prisms; m.p. 110–111°; an analytical specimen cut of ethanol-ether melted at 115–116°. No additional benzil could be obtained by evaporating the mother liquor; instead, an intractable orange oil was obtained.

Anal. Calcd. for $C_{17}H_{16}O_5$: C, 68.0; H, 5.34. Found: C, 68.0; H, 5.2.

DL-*3,4,5-Trimethoxybenzilic acid* (VII). A solution of 4.3 g. of sodium hydroxide in a minimum volume of water was first diluted with 45 ml. of absolute ethanol and cooled in an ice bath, and then 9.2 g. of 3,4,5-trimethoxybenzil (VI) was added in one portion. The mixture was placed in a 125-ml. flask and sufficient ether added to fill the neck. After securing a rubber stopper closure by means of a wire, the flask was placed in the refrigerator for 2 days. The resulting solution of the sodium salt of VII was diluted with ice water and extracted with ether to remove traces of unchanged ketone. Upon acidification of the aqueous liquid with hydrochloric acid, the crude benzilic acid (VII) precipitated as an oil which solidified on cooling and scratching. There was obtained 9.2 g. (97%) of DL-3,4,5-trimethoxybenzilic acid as colorless prisms; m.p. 148°. The melting point was unchanged after recrystallization from benzene–petroleum ether.

Anal. Calcd. for $C_{17}H_{18}O_6$: C, 64.2; H, 5.7. Found: C, 64.3; H, 5.7.

DL-*N-Methyl-3-piperidyl 3,4,5-trimethoxybenzilate* (VIII). A mixture of 8.7 g. of *N*-methyl-3-chloropiperidine[16] and 10.6 g. of VII in 50 ml. of isopropyl alcohol was refluxed for 2 days and then the solvent removed by evaporation *in vacuo*. The viscous oily residue was first treated with 10% aqueous sodium carbonate to remove unchanged VII and then extracted with three 50-ml. portions of ether. Treatment of the dried ether extracts with anhydrous hydrogen chloride gave an oily precipitate which did not crystallize, and therefore the base was again liberated by the addition of alkali. The crude base, amounting to 11.1 g. of a colorless oil, was taken up in hot ethyl acetate and treated with a boiling solution of 3.5 g. of maleic acid in the same solvent. Upon cooling and adding ether dropwise, III maleate crystallized from the solution as small colorless needles. Recrystallization from an ethanol–ethyl acetate mixture containing a little water afforded 2.5 g. of the pure salt, m.p. 196–197°.

Anal. Calcd. for $C_{27}H_{33}NO_{10}$: C, 61.0; H, 6.22. Found: C, 60.9; H, 6.5.

N-Methyl-1,2,5,6-tetrahydro-3-pyridylmethyl benzilate (XI). Arecoline alkaloid was reduced by means of lithium aluminum hydride to *N*-methyl-3-hydroxymethyl-1,2,5,6-tetrahydropyridine (IX) in 64% yield by the procedure of Karrer and Portmann.[16] To an ice-cooled solution of 17.9 g. of IX in chloroform was added dropwise with swirling 19 g. of thionyl chloride, and the resulting mixture heated on the steam bath for 0.5 hr. After cooling and dilution with ether, the *N*-methyl-3-chloromethyl-1,2,5,6-tetrahydropyridine (X) hydrochloride was collected and washed with ether. The resulting base hydrochloride was dissolved in a small volume of water and made alkaline with saturated potassium carbonate solution to liberate the free base which in turn was taken up in ether. After drying, the ether solution was evaporated to a yellow oil which exhibited some tendency to dimerize. Accordingly, the free base was immediately dissolved in 100 ml. of isopropyl alcohol containing 22.5 g. of benzilic acid and the resulting solution refluxed for 2.5 days. Evaporation of the isopropanol *in vacuo* left a residue which was first treated with saturated potassium carbonate solution and then extracted with ether. By passing anhydrous hydrogen chloride through the resulting dry ether solution, there was obtained the crude ester hydrochloride as a heavy dark oil which gradually solidified (12 g.; 32%). Recrystallization from ethanol gave 8 g. of pure *N*-methyl-1,2,5,6-tetrahydro-3-pyridylmethyl benzilate (XI) hydrochloride as colorless crystals, m.p. 200–201° dec.

Anal. Calcd. for $C_{21}H_{24}ClNO_3$: C, 67.5; H, 6.64; Cl, 9.5. Found: C, 67.6; H, 6.6; Cl, 9.4.

N-(2,3,4-Trimethoxyphenyl)-N'-methylpiperazine (XIII). A mixture of 20 g. of *N*-methylbis(β-chloroethyl)amine hydrochloride,[19] 39 g. of 2,3,4-trimethoxyaniline and 90 ml. of methanol was stirred and refluxed for 17 hr. The solvent was removed at diminished pressure leaving a solid residue which was taken up in a minimum volume of hot methanol. Upon cooling there was deposited 14.1 g. (47%) of pure XIII hydrochloride as small colorless needles, m.p. 239–240° dec.

(19) K. A. Jensen and F. Lundquist, *Dansk. Tiddskri Farm.*, 15, 201 (1941).

Anal. Calcd. for $C_{14}H_{23}ClN_2O_3$: C, 55.5; H, 7.6; Cl, 11.7. Found: C, 55.2; H, 7.4; Cl, 11.9.

N-(2,3,4-Trimethoxyphenyl)-N',N'-dimethylpiperazinium iodide (XIV). The free base was liberated by treating 10.5 g. of XIII hydrochloride with aqueous alkali and extracting with ether. After drying over anhydrous magnesium sulfate, the ether solution was concentrated to a volume of 25 ml. and treated with 5.7 g. of methyl iodide. A white precipitate began to form almost immediately. After standing overnight, the solid product was collected on a suction filter, washed with ether, and air dried. The resulting XIV weighed 15 g. (93%); m.p. 170–171°.

Anal. Calcd. for $C_{15}H_{25}IN_2O_3$: C, 44.2; H, 6.1; I, 31.2. Found: C, 44.1; H, 6.3; I, 30.9.

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BATTELLE MEMORIAL INSTITUTE
COLUMBUS 1, OHIO

THE UNIVERSITY OF ALABAMA MEDICAL SCHOOL
DEPARTMENT OF SURGERY
BIRMINGHAM 3, ALA.

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, UNION CARBIDE CHEMICALS CO.]

n-Butyl 5-Chloro-2-pyrimidoxyacetate—A Plant Growth Regulator Analog

DONALD G. CROSBY AND ROBERT V. BERTHOLD

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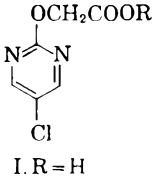
In order to provide a further comparative test of the present theories concerning the relation of structure to chemical stimulation of plant growth, *n*-butyl 5-chloro-2-pyrimidoxyacetate was prepared as an analog of the active 4-chlorophenoxyacetic ester. Although very similar in shape and physical properties to the phenyl compound, the analog was inactive as a growth stimulant.

The stimulation of plant growth by substituted phenoxyacetic acids was first reported by Zimmerman and Hitchcock in 1942.[1] Since then these compounds have received much attention in an attempt to correlate the position and type of substituent with observed effects on growth. The results of the many investigations directed toward elucidation of the mechanism of growth regulator action have been resolved into three general theories.

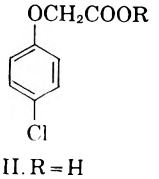
One theory[2] supposes that the regulator undergoes a chemical reaction with appropriate groups, probably nucleophilic, at some site within the cell with the resulting formation of new covalent bonds. The most probable point of reaction on the phenyl ring is indicated to be at a position *ortho* to the ether oxygen. Another theory[3,4] ascribes major importance to the shape of the regulator molecule and the specificity of its fit onto some receptor within the plant. In this case, the phenyl nucleus with its substituents acts as a whole at a locus or point of attachment, and chemical reactions at the ring are considered unlikely. The third and most recent theory,[5,6] unlike the other two, is not particularly concerned with the relation of the regulator to an active site. It holds, instead, that the growth-regulating activity of a compound is primarily associated with its ability to chelate metal ions such as calcium or magnesium.

In order to offer a further test of these hypotheses, it was thought desirable to attempt the synthesis of an analog of a simple aromatic growth-promoting compound in which the possibility of reaction at the positions *ortho* to the side chain was negligible. The compound chosen was 5-chloro-2-pyrimidoxyacetic acid (I) which, although expected to be very similar in many respects to the powerful growth stimulant 4-chlorophenoxyacetic acid (II), would not be susceptible to the usual form of nucleophilic attack at the *ortho* positions.

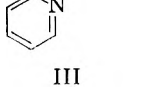
For our purposes, it was not only desirable but necessary for the chlorine and nitrogens to have this particular structural relationship to each other and to the side chain, as the 5-position is the only one



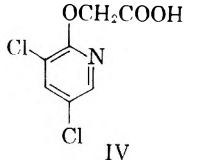
I. R = H
Ia. R = *n*-C_4H_9



II. R = H
IIa. R = *n*-C_4H_9



III



IV

(1) P. W. Zimmerman and A. E. Hitchcock, *Contribs. Boyce Thompson Inst.*, **12**, 321 (1942).
(2) R. M. Muir and C. H. Hansch, *Ann. Rev. Plant Physiol.*, **6**, 157 (1955).
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(5) O. V. S. Heath and J. E. Clark, *Nature*, **178**, 600 (1956).
(6) E. J. Johnson and A. R. Colmer, *Nature*, **180**, 1365 (1957).

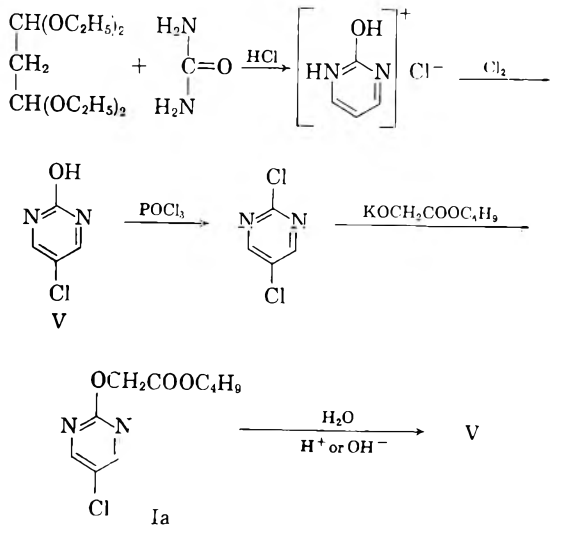

Fig. 1. Preparation of *n*-butyl 5-chloro-2-pyrimidoxyacetate (Ia)

on the pyrimidine nucleus in which a halogen substituent could be expected to be inert under the conditions of bioassay.

Consideration of satisfactory synthetic routes to the pyrimidine led to the conclusion that an ester would be more convenient to prepare and handle than the acid itself. The *n*-butyl ester was chosen because of the ease with which these derivatives are made and the high degree of plant growth stimulation previously shown by *n*-butyl 4-chlorophenoxyacetate (IIa).

The reaction sequence followed for the preparation of *n*-butyl 5-chloro-2-pyrimidoxyacetate (Ia) is shown in Fig. 1.

2-Hydroxypyrimidine hydrochloride was obtained by reaction of a malonaldehyde derivative such as 1,1,3,3-tetraethoxypropane or 1,3,3-triethoxy-1-propene with urea in the presence of alcoholic hydrogen chloride. The reaction mixture must be boiled in order for the desired compound to be formed. Otherwise, the only product isolated was a high-melting material which, from analysis and infrared spectrum, appeared to be identical with the complex substance obtained by Dornow and Peterlein[7] from the reaction of triethoxypropene with two equivalents of urea. The preparation of 2-hydroxypyrimidine from tetraethoxypropane and urea at room temperature in the presence of aqueous hydrochloric acid, described by Protopopova and Skoldinov[8] during the course of our work, could not be repeated. Under conditions satisfactory for our synthesis of 2-hydroxypyrimidine hydrochloride, sulfuric acid provided a good yield of 2-hydroxypyrimidine bisulfate, while syrupy phosphoric acid gave monobasic 2-hydroxypyrimidine phosphate. Both the bisulfate and the phosphate were readily converted to free 2-hydroxypyrimidine.

2-Hydroxypyrimidine hydrochloride was converted into 2-hydroxy-5-chloropyrimidine by reaction with chlorine in aqueous solution, analogous to the chlorination of 2-aminopyrimidine reported in the literature.[9] A large excess of chlorine was very detrimental to the yield of the desired product. In a similar manner, 2-hydroxy-5-bromopyrimidine was prepared by bromination of 2-hydroxypyrimidine in aqueous solution. The monochloropyrimidine formed 2,5-dichloropyrimidine upon heating with phosphoryl chloride,[10] and the product was recovered by steam distillation.

The preparation of 2-alkoxypyrimidines by reaction of 2-chloropyrimidine with the appropriate sodium alkoxide has been reported previously.[11,12] Reaction of 2,5-dichloropyrimidine with the potassium or sodium alkoxide of *n*-butyl glycolate in dry toluene provided a 52% yield of an almost colorless liquid product which was assumed to be the desired ester Ia.

The compound contained the anticipated amounts of carbon, hydrogen, and nitrogen corresponding to the formula $C_9H_{13}ClN_2O_3$. Its ultraviolet spectrum was typical of simple 2,5-disubstituted pyrimidines,[11] as shown in Table I.

TABLE I

PYRIMIDINE SPECTRA[a]

Compound	*p*H	λ_{max}	log ϵ
(Ia)	—[b]	219, 282	4.10, 3.55
	0.7	218, 281	4.08, 3.54
	5.0	218, 281	4.03, 3.54
	13.0	222, 283	4.05, 3.52
2,5-Dichloropyrimidine[11]	—[c]	219, 268	4.20, 3.49
	7.0	219, 272	4.23, 3.51
2-Methyl-5-bromopyrimidine[11]	7.0	219, 267	4.09, 3.48

[a] Spectra measured in a Cary Model 11 spectrophotometer. [b] Anhydrous methanol solution. [c] Ethanol solution.

The wave length of maximum absorption and the extinction coefficients were not greatly affected by changes in *p*H of the solvent, indicating a probably low order of basicity in the nitrogen atoms.

The infrared spectrum was consistent with the proposed structure and exhibited absorption bands characteristic of the pyrimidine ring (795 cm.$^{-1}$, 1560 cm.$^{-1}$), ester (1748 cm.$^{-1}$), and ether (1270 cm.$^{-1}$). Although thermal rearrangement of alkoxypyrimidines and alkoxypyridines to the corresponding *N*-alkylated pyrimidinones and pyri-

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(12) D. J. Brown and L. N. Short, *J. Chem. Soc.*, 331 (1953).

TABLE II

COMPARATIVE PROPERTIES OF (Ia) AND (IIa)

Compound	Mol. Wt.	M.P.	B.P./1 Mm.	n_D^{45}	Ring	Halogen
n-Butyl 5-chloro-2-pyrimidoxyacetate (Ia)	244.7	14°	119–125°	1.492	Planar	Aromatic
n-Butyl 4-chlorophenoxyacetate (IIa)	242.7	41°	122–123°	1.501	Planar	Aromatic

dones has been reported on several occasions,[13,14] the possibility of such a reaction having taken place in the present instance to give butyl 5-chloro-2-pyrimidinone-1-acetate is removed by the absence of any infrared absorption attributable to this type of amide (1600–1700 cm.$^{-1}$ in 5-chloro-2-pyrimidinone). Brown and Short[12] have discussed this difference in the case of 2-pyrimidinone (2-hydroxypyrimidine) and 2-methoxypyrimidine.

In a closely analogous reaction, Hill and McGraw[15] obtained ethyl 2-pyridoxyacetate from 2-bromopyridine and sodium ethyl glycoxide. The structure of their ester was confirmed by synthesis of both it and the corresponding *N*-substituted compound from 2-hydroxypyridine and ethyl diazoacetate.[16] However, unlike the pyridine derivative, butyl 5-chloro-2-pyrimidoxyacetate was not converted to the free acid upon hydrolysis. Instead, 2-hydroxy-5-chloropyrimidine was produced in the presence of either hot alkali or hot acid, offering further evidence of *O*-alkylation rather than *N*-alkylation.

The similarity between butyl *p*-chlorophenoxyacetate and its pyrimidine analog is shown in Fig. 2 and Table II. Molecules of the two substances are of almost identical shape and size. Although the pyrimidine must differ slightly in shape from the benzene derivative,[17] the difference may be considered negligible for most purposes. Dipole moment measurements on pyrimidine and 2,5-disubstituted pyrimidines[18] indicate that the ring is planar, as it is in the phenoxy acid. The halogen in position 5 is similar in its reactivity to a phenyl halogen, and the reactivity of the ester would not be expected to differ appreciably from that of the same group in butyl 4-chlorophenoxyacetate.

The plant growth regulatory activities of the *n*-butyl esters of 4-chlorophenoxyacetic acid and 5-chloro-2-pyrimidoxyacetic acid were measured by Dr. A. J. Vlitos of the Boyce Thompson Institute for Plant Research, Inc., in Yonkers, N. Y. Four different bioassays were employed: elongation of wheat and oat (*Avena*) coleoptiles, elongation of oat first internodes,[19] and curvature of slit pea stems. In each test, the phenoxy derivative was highly active while the pyrimidine was completely inactive.[20]

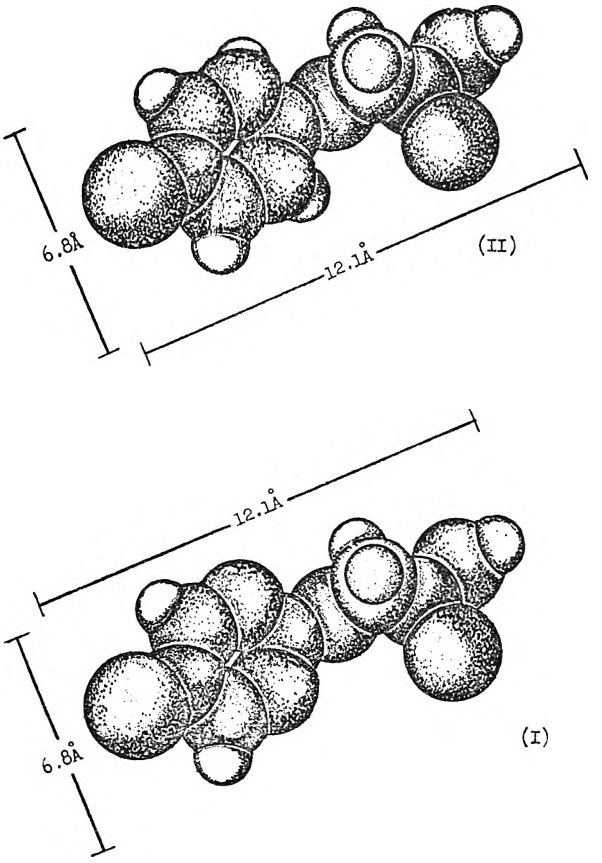

Fig. 2. Similarity between *p*-chlorophenoxyacetate acid (II) and its pyrimidine analog (I)

Gorter[21] has demonstrated the high degree of growth stimulation provided by 2-pyridoxyacetic acid (III) and 3,5-dichloro-2-pyridoxyacetic acid (IV), both of which also are closely related to our pyrimidine. Although the pyridine derivatives were tested as free acids, no difficulty in the *in vivo* hy-

(13) D. J. Brown, E. Hoerger, and S. F. Mason, *J. Chem. Soc.*, 211 (1955).
(14) H. Meyer, *Monatsh.*, 28, 47 (1907).
(15) A. J. Hill and W. J. McGraw, *J. Org. Chem.*, 14, 783 (1949).
(16) J. Maas, G. B. R. de Graaff, and H. J. den Hertog, *Rec. trav. Chim.*, 74, 175 (1955).
(17) R. B. Corey, *Ann. Rev. Biochemistry*, 20, 131 (1951).
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(19) J. P. Nitsch and Colette Nitsch, *Plant Physiol.*, 31, 94 (1956).
(20) D. G. Crosby and A. J. Vlitos, *Science*, 128, 480 (1958).
(21) C. J. Gorter, *Physiol. Plantarum*, 10, 858 (1957).

drolysis of the pyrimidoxy ester Ia to the corresponding acid would be anticipated.

According to the proposal of Hansch, *et al.*,[22] which has received recent theoretical support by Fukui,[23] the pyridines III and IV could derive their biological activity through displacement of hydride ion and chloride ion, respectively, from the the 3-position by some cellular nucleophilic agent. The complete absence of growth-promoting ability in butyl 5-chloro-2-pyrimidoxyacetate, a substance which appears to possess many spatial and chemical characteristics closely resembling those of the corresponding phenyl and pyridyl analogs, strongly suggests that the availability of the positions *ortho* to the side chain toward nucleophilic reaction indeed bears an important relation to growth stimulation by compounds of the phenoxy acid series.

EXPERIMENTAL[24]

2-Hydroxypyrimidine hydrochloride. Urea (360 g., 6.0 moles) was added to 2 l. of dry methanol, and the mixture was chilled to 0° and saturated with hydrogen chloride. While the temperature was maintained at 0°, 1,1,3,3-tetraethoxypropane (1320 g., 6.0 moles) was added dropwise over a period of 1.25 hr. with constant stirring. After standing overnight, the mixture was boiled for 1 hr. under reflux with stirring, cooled, and the product removed by filtration in 88% yield. Crystallization from ethanol gave tan needles, m.p. 205–210° dec. (lit.,[25] m.p. 200–205° dec.).

Under similar conditions, substitution of concd. sulfuric acid for the hydrogen chloride provided a 90% yield of *2-hydroxypyrimidine bisulfate*, which, after crystallization from dilute acetic acid, was recovered as white needles, m.p. 188.5–189°.

Anal. Calcd. for $C_4H_6N_2O_6S$: C, 24.7; H, 3.11; N, 14.4. Found: C, 24.9; H, 3.23; N, 14.6.

Likewise, use of 86% phosphoric acid provided an 80% yield of monobasic *2-hydroxypyrimidine phosphate*, m.p. 179° dec.

Anal. Calcd. for $C_4H_7N_2O_5P$: C, 24.8; H, 3.63; N, 14.4. Found: C, 24.9; H, 3.63; N, 14.6.

2-Hydroxy-5-chloropyrimidine. 2-Hydroxypyrimidine hydrochloride (9.0 g., 0.068 mole) was dissolved in 1 l. of 0.1*M* aqueous chlorine solution and heated to 70° for 30 min. After cooling and standing at room temperature overnight, the crude product was isolated by removal of solvent under reduced pressure at steam-bath temperature. Recrystallization from ethanol afforded a 54% yield of pale yellow crystals m.p. 236° dec. (lit.[9] m.p. 237–238°).

Anal. Calcd. for $C_4H_3ClN_2O$: C, 36.8; H, 2.32; N, 21.5. Found: C, 37.1; H, 2.17; N, 21.3.

2-Hydroxy-5-bromopyrimidine. Free 2-hydroxypyrimidine was prepared by dissolving 20 g. (0.1 mole) of its bisulfate in 150 ml. of water, adding a solution of an equivalent quantity of barium acetate in 200 ml. water, treatment with carbon dioxide, and filtration. The filtrate was evaporated to dryness to provide an 87% yield of pure 2-hydroxypyrimidine, m.p. 180–181°.

This product (5 g., 0.05 mole) was added with stirring to a solution of 9 g. (0.056 mole) bromine in 2 l. water. Solvent was removed under vacuum and the residue was crystallized from 90% aqueous ethanol. The yield of 2-hydroxy-5-bromopyrimidine, m.p. 234–235° dec., was 5 g. (55%).

Anal. Calcd. for $C_4H_3BrN_2O$: C, 27.5; H, 1.73; N, 16.0. Found: C, 27.8; H, 1.83; N, 16.3.

2,5-Dichloropyrimidine was prepared by the method of English, *et al.*,[10] by reaction of 2-hydroxy-5-chloropyrimidine with excess phosphoryl chloride. The yield of product melting at 58.5–59.5° (lit. m.p. 57–57.5°) was 47%.

n-Butyl glycolate. Glycolic acid (300 g., 4 moles), *n*-butyl alcohol (600 g., 8 moles), 300 ml. of dibutyl ether, and 5 g. of tetrabutyl titanate were mixed and heated to boiling under reflux in apparatus permitting the separation of water as it distilled azeotropically. After about 5 hr., the theoretical volume of water had been collected. The ether solution was washed with water and distilled to give an almost quantitative yield of product, b.p. 56–59° (5 mm.), n_D^{30} 1.4225.[26]

Butyl (5-chloro-2-pyrimidoxy)acetate. Metallic potassium (5.9 g., 0.15 mole) in the form of sand was suspended in 300 ml. of dry toluene under a nitrogen atmosphere. Butyl glycolate (22.8 g., 0.17 mole) was added dropwise over a period of 45 min. with rapid stirring, and stirring was continued for 3 hr. after the ester addition was complete. A solution of 22 g. (0.15 mole) 2,5-dichloropyrimidine was then added dropwise, the mixture was boiled under reflux for 1 hr., and, when cool, it was treated with 25 ml. of absolute ethanol. After washing with water, the dark toluene solution was dried over anhydrous sodium sulfate, filtered, and the solvent was removed under reduced pressure. The residual oil was distilled to give 18 g. (52%) of colorless liquid, b.p. 119–125° (1 mm.).

Redistillation gave an analytically pure sample, b.p. 110° (0.8 mm.), n_D^{20} 1.4998, n_D^{45} 1.492, m.p. 10–14°.

Anal. Calcd. for $C_{10}H_{13}ClN_2O_3$: C, 49.1; H, 5.35; N, 11.5. Found: C, 49.2; H, 5.49; N, 11.5.

Hydrolysis of butyl (5-chloro-2-pyrimidoxy)acetate. The ester (9.0 g., 0.037 mole) was heated with stirring at about 95° for 1 hr. with 10% aqueous sodium hydroxide solution, cooled, and acidified with hydrochloric acid. The precipitated solid was filtered, washed with water, and dried in air to give 5.0 g. (84%) of yellowish crystals of 2-hydroxy-5-chloropyrimidine. After recrystallization from ethanol, the compound melted at 236.5–237.5°.

Anal. Calcd. for $C_4H_3ClN_2O$: C, 36.8; H, 2.32; N, 21.5. Found C, 37.0; H, 2.32; N, 21.5.

Hydrolysis with dilute aqueous hydrochloric acid at 95° resulted in the same product.

Butyl p-chlorophenoxyacetate. Commercial *p*-chlorophenoxyacetic acid was esterified with *n*-butyl alcohol in the presence of a catalytic amount of *p*-toluenesulfonic acid, and water was removed azeotropically with toluene. Distillation provided a 93% yield of the desired ester boiling at 122–123° (1 mm.), m.p. 41°, n_D^{45} 1.501.

Anal. Calcd. for $C_{12}H_{15}ClO_3$: C, 59.4; H, 6.23. Found: C, 59.7; H, 6.05.

Acknowledgment. We wish to express our gratitude to Mr. Quentin Quick and his group for infrared spectra and microanalyses, Dr. A. J. Vlitos and his group for bioassays, and Mr. F. G. Bollinger and Miss Celeste Holswade for their assistance.

SOUTH CHARLESTON, W. VA.

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(26) The authors are indebted to Mr. T. F. Carruthers for the preparation of this compound.

[CONTRIBUTION FROM THE MIDWEST RESEARCH INSTITUTE]

Potential Growth Antagonists. I. Hydantoins and Disubstituted Glycines[1,2]

LOUIS H. GOODSON, IRWIN L. HONIGBERG, J. J. LEHMAN,[3] AND W. H. BURTON

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Several 2,2-disubstituted glycines were prepared by the hydrolysis of the intermediate hydantoin in either sulfuric acid or barium hydroxide solution. Acid hydrolysis was satisfactory for the preparation of the dialkyl glycines but led to decomposition during the hydrolysis of the aryl substituted glycines. This route to the synthesis of these amino acids is considered superior to that of the Strecker method.

Preliminary anticancer screening of these amino acids containing no *alpha* hydrogen atom has shown them to be inactive, and therefore, unlike their structural analogue, 1-aminocyclopentanecarboxylic acid.

The present paper is concerned with the synthesis of disubstituted glycines of the type $RR'C(NH_2)$-COOH. Compounds of this type were expected to be metabolic antagonists of value in the chemotherapy of cancer.

A number of compounds belonging to this class have already been prepared and shown to possess biological activity. *In vitro* and *in vivo* studies of disubstituted glycine have revealed wide differences between these compounds and the corresponding natural amino acids. 2-Methylalanine appears incapable of being metabolized.[4] 2-Methyl-DL-tryptophan is an antagonist of tryptophan and has shown activity against staphylococcic infections.[5] 3-(3,4-Dihydroxyphenyl)-2-methyl-DL-alanine (α-methyl-DOPA) is a potent inhibitor of mammalian DOPA decarboxylase *in vitro* but is inactive *in vivo*.[6] 2-Methyl-DL-glutamic acid inhibits the decarboxylation of glutamic acid by glutamic decarboxylase.[7] 2-Methyl-DL-methionine is a potent antagonist of methionine and also blocks the action of D-amino acid oxidase on phenylalanine;[7] it is also reported to be active against Newcastle virus disease.[8] 2-Methylalanine, 2-methyl-DL-serine and 2-hydroxymethyl-DL-serine are accumulated in the rat liver after intraperitoneal injection, but they are not degraded.[9] The *alpha* hydrogen of serine appears to be necessary for the reaction with pyridoxal and its subsequent conversion to glycine.[9] *N*-Carbamoyl-2-methyl-DL-glutamic acid did not catalyze the conversion of ornithine to citrulline as did *N*-carbamoyl-DL-glutamic acid.[10] 2-Methyl-DL-serine does not undergo oxidative deamination in the presence of L- or D-amino oxidase.[11] 2-Methyl-DL-valine inhibits penicillin synthesis from lactose, but this inhibition is reversed by valine.[12]

Compounds which inhibit specific metabolic reactions can also be expected to possess selective toxicity and therefore are obvious candidates for trial in cancer chemotherapy. A few members of this group have been screened for their effects upon experimental tumors. 2-Amino-2-methylbutyric acid did not inhibit the growth of mouse Sarcoma-180, Carcinoma-755, or Leukemia-1210.[13] On the other hand, 2-methylalanine, 1-amino-cyclohexanecarboxylic acid, and 1-amino-cyclopentanecarboxylic acid inhibited the development of the Novikoff hepatoma in the rat.[14] The latter compound has also been found to be active on at least one of the mouse tumors mentioned above.[14] 1-Aminocyclohexanecarboxylic acid, 1-amino-1,2,3,4-tetrahydro-1-naphthoic acid, and 2-amino-1,2,3,4-tetrahydro-2-naphthoic acid were inactive in inhibiting the growth of transplanted Walker rat carcinoma; however, 1-aminocyclopentanecarboxylic acid as well as its N- and C-terminal peptides with glycine were very effective in retarding growth in this same system.[15]

Two general methods were considered for the preparation of the disubstituted glycines: the Strecker reaction, *i.e.*, the reaction of a ketone with an alkali cyanide and ammonium chloride to give the amino nitrile followed by hydrolysis to the

(1) This research was supported by Contract No. SA-43-ph-2394 with the Cancer Chemotherapy National Service Center, National Cancer Institute of the National Institutes of Health, Bethesda, Md.

(2) Presented in part at the 136th National Meeting of the American Chemical Society, September 13–18, 1959.

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(13)(a) J. Leiter and M. A. Schneiderman, *Cancer Research*, 19, No. 3, Part II, Cancer Chemotherapy Screening Data II, p. 112 (1959); (b) p. 31 for screening method.

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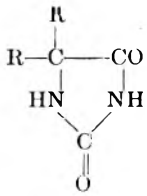
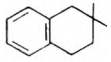
TABLE I 5,5-DISUBSTITUTED HYDANTOINS

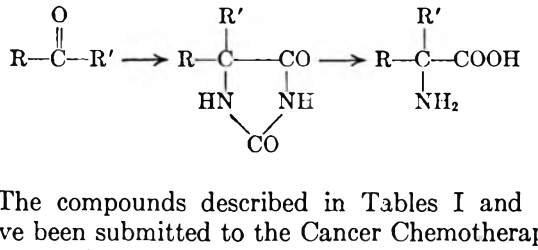


No.	R	R′	Molecular Formula	M.P.	Reported M.P.	Method	Reaction Time, hr.	Yield, %	Calcd. C, %	Calcd. H, %	Calcd. N, %	Found C, %	Found H, %	Found N, %
1	CH_3	n-C_4H_9	$C_8H_{14}N_2O_2$	113–114	107.5–108.5[a]	A	3	58			16.5			17.2
2	CH_3	n-C_6H_{13}	$C_{10}H_{18}N_2O_2$	106–108.5	107.5–108[a]	A	3	92						
3	CH_3	n-C_7H_{15}	$C_{11}H_{20}N_2O_2$	101–102		A	3	55			13.2			12.8
4	CH_3	n-C_9H_{19}	$C_{13}H_{24}N_2O_2$	110–112	115[b]	A	3	93						
5	CH_3	CH_2=CH—CH_2—CH_2	$C_8H_{12}N_2O_2$	118–119	119.5–120.5[c]	A	3	62	57.1	7.19	16.7	57.9	7.30	16.7
6	CH_3	CH_2=$CH(CH_2)_8$	$C_{14}H_{24}N_2O_2$[d]	88–89		A	3	78			11.1			11.3
7	CH_3	Cyclo C_6H_{11}	$C_{10}H_{16}N_2O_2$	210–211	214.6–215.8[e,f]	A	3	84						
8	CH_3	$C_6H_5CH_2$—CH_2	$C_{12}H_{14}N_2O_2$	176–177	179–180[g]	A	3	87						
9	CH_3	p-F—C_6H_4	$C_{10}H_9FN_2O_2$	205–206	206–207[h]	A	3	55	57.7	4.36	13.5	57.5	4.55	13.5
10	CH_3	2-Thienyl	$C_8H_8N_2O_2S$	136.5–138	138.5–140[i]	B	24	60						
11	C_2H_5	iso-C_3H_7	$C_8H_{14}N_2O_2$	163–165	115–116[j]	A	3	46	56.5	8.29	16.5	56.4	8.23	16.4
12	C_2H_5	p-F—C_6H_4	$C_{11}H_{11}FN_2O_2$	209–210		A	3	67	59.5	4.99	12.6	59.3	5.02	12.4
13	C_6H_5	p-CH_3—C_6H_4	$C_{16}H_{14}N_2O_2$	225–226	229–230[k]	C	24	52						
14	C_6H_5	$C_6H_5CH_2$	$C_{16}H_{14}N_2O_2$	210–211	210–211[l]	A	8	85						
15	C_6H_5	p-Cl—$C_6H_4CH_2$	$C_{16}H_{13}ClN_2O_2$	212–213		C	24	73	63.9	4.36	9.32	63.7	4.58	9.33
16	C_6H_5	$C_6H_5CH_2CH_2$	$C_{17}H_{16}N_2O_2$	195–197	201[j]	A	15	74						
17	$C_6H_5CH_2$	$C_6H_5CH_2$	$C_{17}H_{16}N_2O_2$	320–321	305[l]	A	3	78	72.8	5.75	9.99	72.3	5.98	10.0
	R and R′ Combined													
18			$C_{11}H_{10}N_2O_2$	239–240	240[a]	B	24	69	65.3	4.98	13.9	65.1	4.96	13.7
19			$C_{12}H_{12}N_2O_2$	267–268	268[m]	A	3	79						
20			$C_{12}H_{12}N_2O_2$	241–242.5		A	8	52	66.7	5.59	13.0	66.6	5.73	12.9
21			$C_9H_{14}N_2O_2$	215.5–216.5	215.5–216[a]	A	3	81						

[a] H. R. Henze and R. J. Speer, *J. Am. Chem. Soc.*, **64**, 523 (1942). [b] M. Tiffeneau, *et al.*, *Bull. soc. chim. France* **1947**, 445. [c] The ketone, 11-dodecene-2-one, was prepared according to the method of Cason [J. Cason, *J. Am. Chem. Soc.*, **68**, 2078 (1946)]. Semicarbazone m.p. 113–114°; reported m.p. 112–113° [N. Polgar and R. Robinson, *J. Chem. Soc.*, 389 (1945). [d] H. R. Henze, L. M. Long, R. J. Speer, and T. R. Thompson, *J. Am. Chem. Soc.*, **65**, 324 (1943). [e] The ketone, cyclohexyl methyl ketone, was prepared according to the method of Cason [J. Cason, *J. Am. Chem. Soc.*, **68**, 2078 (1946)]. B.p. 180–181°. [f] R. M. Herbst and T. B. Johnson, *J. Am. Chem. Soc.*, **54**, 2467 (1932). [g] J. J. Spurlock, *J. Am. Chem. Soc.*, **75**, 1115 (1953). [h] A compound of this reported structure was prepared from an amino acid and potassium cyanate; however, no analysis was given. [Kuo-Hao Lin, Liang Li, and Yao-Tseng Huang, *Sci. and Technol. China*, **1**, 5 (1948)]. [i] H. R. Henze and A. F. Isbell, *J. Am. Chem. Soc.*, **76**, 4152 (1954). [j] K. H. Slotta, R. Behnisch, and G. Szyska, *Ber.*, **67B**, 1529 (1934). [k] H. R. Henze and L. M. Long, *J. Am. Chem. Soc.*, **63**, 1936 (1941). [m] W. C. J. Ross and T. A. Connors, private communication. [n] G. Quadbeck and E. Röhm, *Arzneimittel-Forsch.*, **6**, 531 (1956). [o] F. J. Marshall, *J. Am. Chem. Soc.*, **78**, 3696 (1957).

amino acid; and the synthesis of an amino acid by the hydrolytic cleavage of a hydantoin. From preliminary experiments it was seen that for the preparation of the dialkyl substituted amino acids, either the Strecker method or the hydantoin method gave comparable yields of the amino acid. The hydantoin method was selected as the preferred route for several reasons. The reactions, in the case of the hydantoin method, proceeded with less decomposition. Even where the reactions were incomplete, the unchanged starting material was easily recovered from the reaction mixture. Furthermore, the hydantoins are readily purified and relatively stable, while the amino nitriles are neither stable nor easily purified. Finally, it was found easier to apply forcing conditions to the preparation and hydrolysis of the hydantoins of hindered ketones, *e.g.*, 4-methylbenzophenone, rather than to use the Strecker reaction.

The hydantoins (Table I) were prepared from the appropriate ketones by the Bucherer-Berg reaction, a method that has been adequately reviewed by Ware[16] and refined by Henze[17] in the last few years. The hydrolysis of the dialkyl hydantoins in 60% sulfuric acid gave good yields of the amino acids. The hydrolyses of the aryl substituted hydantoins were much less successful in acid due to their low solubility in the reaction solutions and the large amount of decomposition which accompanied the reaction. As a result, the the use of barium hydroxide under autoclave conditions was instituted. This method proved satisfactory for the hydrolysis of both the aryl substituted hydantoins and the unsaturated alkyl substituted hydantoins. The preferred reaction sequence is illustrated below and the disubstituted glycines are shown in Table II, where R and R′ = alkyl and aryl. Reaction conditions are more fully described in the experimental section.



The compounds described in Tables I and II have been submitted to the Cancer Chemotherapy National Service Center for screening.[13b] Preliminary results indicate that these compounds are neither capable of producing significant inhibition of the growth of Sarcoma-180 or Carcinoma-755 nor do they increase the survival time of mice bearing Leukemia L-1210. Detailed screening results of these compounds will be published by the National Institutes of Health at a later time.

(16) E. Ware, *Chem. Revs.*, **46**, 403 (1950).

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EXPERIMENTAL[18]

Preparation of hydantoins. The hydantoins were synthesized from commercially available ketones according to methods described by Henze and co-workers.[17] In cases where the ketones were not available, they were prepared as noted in Table I. The three methods used for the preparation of the hydantoins are illustrated as follows:

Method A.[17a] *5-Ethyl-5-p-fluorophenylhydantoin.* In a three-necked flask equipped with a mercury-seal stirrer, a dropping funnel, and reflux condenser were placed 46 g. (0.33 mole) of 4′-fluoropropiophenone, 100 g. of reagent grade ammonium carbonate, and 550 ml. of 60% ethanol. The mixture was stirred and warmed to 50°, at which time 17 g. (0.35 mole) of sodium cyanide dissolved in 50 ml. of water was added over a period of 5 min. The reaction mixture was then stirred for 3 hr. at temperatures between 56° and 60°. The reflux condenser was then replaced by an air condenser and the temperature raised to 85° for 1 hr. to remove the excess ammonium carbonate. The reaction solution was cooled, acidified to *p*H 6, and chilled to 0° for 24 hr. The precipitate was collected and washed with several portions of cold water. The product was then purified by dissolving it in 300 ml. of 5% aqueous sodium hydroxide solution, the solution filtered, and the filtrate washed with three 50-ml. portions of ether to remove unchanged ketone. The aqueous layer was then cooled and acidified to *p*H 6 and the precipitate collected and recrystallized from 95% ethanol; yield, 44 g., m.p., 209–210.5°.

Anal. Calcd. for $C_{11}H_{11}FN_2O_2$: C, 59.45; H, 4.99; N, 12.61. Found: C, 59.32; H, 5.02; N, 12.44.

Method B.[19] *Spiro[imidazolidine-4,1′-indan]-2,5-dione.* Forty-four grams (0.33 mole) of 1-indanone was mixed with 33 g. (0.5 mole) of potassium cyanide and 114 g. of reagent grade ammonium carbonate. The solids and 350 ml. of 70% ethanol were placed in a stainless steel reaction vessel, sealed, and heated to 110° for 24 hr. The bomb was cooled, the contents removed, filtered and diluted with 100 ml. of water. The reaction solution was then heated to boiling for 15 min. to remove the excess ammonium carbonate, cooled, and acidified to *p*H 6. The resulting precipitate was filtered and recrystallized from 95% ethanol; yield, 46 g., m.p., 239–240°.

Anal. Calcd. for $C_{11}H_{10}N_2O_2$: C, 65.33; H, 4.98; N, 13.86. Found: C, 65.09; H, 4.96; N, 13.68.

Method C.[17b] *5-(p-Chlorobenzyl)-5-phenylhydantoin.* Twenty-three grams (0.10 mole) of 2-(*p*-chlorophenyl)-acetophenone, 7 g. (0.11 mole) of potassium cyanide, 34 g. of reagent grade ammonium carbonate and 250 g. of fused acetamide were intimately mixed and then placed in a stainless steel reaction vessel which was sealed and heated to 110° for 24 hr. After cooling, the contents were removed by washing with 500 ml. of boiling water in several portions. The reaction product was then filtered and washed several times with cold water. The crude hydantoin was decolorized with activated charcoal in hot 95% ethanol, precipitated by cooling, and recrystallized a second time from ethanol; yield, 22 g., m.p., 212–213°.

Anal. Calcd. for $C_{16}H_{13}ClN_2O_2$: C, 63.89; H, 4.36; N, 9.32. Found: C, 63.70; H, 4.57; N, 9.33.

Preparation of amino acids. The hydrolysis of the hydantoins listed in Table I was carried out in both acid and basic solution. Conditions for the preparation and isolation of the amino acids (Table II) are illustrated by the following examples:

Method A. Acid hydrolysis.[20] *2-Amino-2-methylnonanoic*

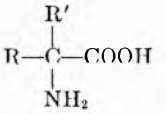
(18) All melting points are uncorrected; analyses were performed by Galbraith Microanalytical Laboratories and Micro-Tech Laboratories.

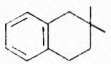
(19) E. Campaigne and H. L. Thomas, *J. Am. Chem. Soc.*, **77**, 5365 (1955).

(20) H. T. Bucherer and W. T. Steiner, *J. prakt. Chem.*, **140**, 291 (1934).

TABLE II

Disubstituted Glycines



No.	R	R′	Molecular Formula	M.P., dec Sealed Tube	Method	Reaction Time, hr.	Yield, %	Calcd. C, %	Calcd. H, %	Calcd. N, %	Found C, %	Found H, %	Found N, %
1	CH_3	n-C_4H_9	$C_7H_{15}NO_2$	308–309	A	72	60			9.63			9.44
2	CH_3	n-C_6H_{13}	$C_9H_{19}NO_2$	280–284	A	72	72			8.08			7.58
3	CH_3	n-C_7H_{15}	$C_{10}H_{21}NO_2$	296–300	A	72	58			7.48			7.33
4	CH_3	n-C_9H_{19}	$C_{12}H_{25}NO_2$	284–286	A	72	66			6.50			6.29
5	CH_3	CH_2=$CHCH_2CH_2$	$C_7H_{13}NO_2$	312–314	B	0.5	87	58.7	9.15	9.78	58.9	8.97	9.86
6	CH_3	CH_2=$CH(CH_2)_8$	$C_{13}H_{25}NO_2$	258–260	B	2.5	81			6.16			6.20
7	CH_3	Cyclo C_6H_{11}	$C_9H_{17}NO_2$	308–309	A	72	57			8.18			8.04
8	CH_3	$C_6H_5CH_2CH_2$	$C_{11}H_{15}NO_2$	287–289	A	72	36			7.25			6.99
9	CH_3	p-F—C_6H_4	$C_9F_{10}FNO_2$	271–272	B	6	69	59.0	5.50	7.65	59.0	5.53	7.53
10	CH_3	2-Thienyl	$C_7H_9NO_2S$	205.5–206.5[a]	B	0.5	77	49.1	5.30	8.18	48.9[a]	5.38	8.14
11	C_2H_5	*iso*-C_3H_7	$C_7H_{15}NO_2$	178–179	A	72	43	57.9	10.4	9.65	57.9	10.4	9.81
12	C_2H_5	p-F—C_6H_4	$C_{10}H_{12}FNO_2$	253–254	B	3	81	60.9	6.14	7.10	60.9	6.15	7.05
13	C_6H_5	p-CH_3—C_6H_4	$C_{15}H_{15}NO_2$	244.5–245.0	C	24	75	74.66	6.27	5.81	74.70	6.32	5.75
14	C_6H_5	$C_6H_5CH_2$	$C_{15}H_{15}NO_2$	268–269	A	72	20	74.7	6.22	5.80	74.6	6.26	5.68
15	C_6H_5	p-Cl—$C_6H_4CH_2$	$C_{15}H_{14}ClNO_2$	263–264	C	24	73	65.34	5.12	5.08	65.45	5.14	5.25
16	C_6H_5	$C_6H_5CH_2CH_2$	$C_{16}H_{17}NO_2$	268–269	B	1.5	18	75.3	6.71	5.49	74.7	6.83	5.48
17	$C_6H_5CH_2$	$C_6H_5CH_2$	$C_{16}H_{17}NO_2$	307–308	B	7	35	75.3	6.71	5.49	75.3	6.86	5.59
18	CH_3	n-C_5H_{11}	$C_8H_{17}NO_2$	318–319	Strecker[b]		44			8.81			8.76
19	CH_3	p-CH_3—C_6H_4	$C_{10}H_{13}NO_2$	279–280	Strecker[b]		29			7.82			8.09
	R and R′ Combined												
20			$C_{10}H_{11}NO_2$	225–227	B	5	82	67.78	6.26	7.91	67.73	6.23	8.01
21			$C_{11}H_{13}NO_2$	301–302	B	6	59	69.0	6.85	7.32	69.1	6.79	7.24
22			$C_{11}H_{13}NO_2$	231–232	B	6	67	69.00	6.85	7.32	68.90	7.00	7.28
23			$C_8H_{15}NO_2$	304–305	A	72	64	61.12	9.62	8.91	61.07	9.73	8.84

[a] This is the melting point of the hydrate. The analysis shown was obtained on a sample dried to constant weight at 150°. [b] R. E. Steiger, *Org. Syntheses*, 24, 9 (1944).

acid. In a three-necked flask fitted with a reflux condenser and nitrogen inlet tube were placed 45 g. (0.02 mole) of 5-heptyl-5-methylhydantoin and 104 g. (0.6 mole) of 60% sulfuric acid. The mixture was then heated at 130° for 72 hr. under a nitrogen atmosphere. The clear, straw-colored solution was then cooled and a precipitate, consisting of amino acid sulfate and unchanged hydantoin, was filtered. The precipitate was dissolved in 300 ml. of hot water, decolorized with activated charcoal, and filtered. The filtrate was cooled and adjusted to *p*H 6 with 10% aqueous ammonia, which precipitated the free amino acid. The mother liquor from the reaction mixture was diluted with 200 ml. of water, decolorized with charcoal, filtered, and the free amino acid precipitated by the addition of 10% aqueous ammonia to *p*H 6. Both crops of amino acid were combined and recrystallized, first, from 50% ethanol and then from acetic acid–water. Finally the product was dried for 24 hr. *in vacuo* at 50°; yield, 23 g., m.p., 296–300° (sealed tube).

Anal. Calcd. for $C_{10}H_{21}NO_2$: N, 7.48. Found: N, 7.33.

Method B. Base hydrolysis.[21] *2-Amino-2-methyl-5-hexenoic acid.* In a stainless steel reaction vessel were placed 30.2 g. (0.18 mole) of 5-(3-butenyl)-5-methylhydantoin, 85 g. (0.27 mole) of barium hydroxide and 485 ml. of water. The bomb was flushed with nitrogen, sealed, and heated to 165° for 30 min. After cooling to room temperature, the alkaline reaction mixture was diluted with 300 ml. of water, then aerated and heated to drive off the ammonia formed in the reaction. The solution was then acidified with concd. sulfuric acid to *p*H 1–2, the barium sulfate filtered, and the *p*H readjusted to 6 with lead carbonate. The solution was filtered free of lead sulfate and then treated with hydrogen sulfide to remove the excess lead ion. The aqueous solution was next heated to boiling, decolorized with charcoal, filtered, and the filtrate concentrated to give three crops of the free amino acid; total yield 22.5 g., m.p., 312–314°. A sample for analysis was recrystallized from 70% ethanol.

Anal. Calcd. for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.91; H, 8.97; N, 9.86.

Several of the amino acids hydrolyzed by this method were insoluble enough in water to be isolated by concentrating the acidic solution to half volume after removing the precipitated barium sulfate and adjusting the *p*H to 6 with concd. ammonium hydroxide. The amino acid was then filtered and washed with several portions of distilled water.

Method C. Base hydrolysis. 2-Phenyl-2-p-tolylglycine. A stainless steel reaction vessel containing 22.6 g. (0.085 mole) of 5-phenyl-5-*p*-tolylhydantoin and 370 ml. of a 20% sodium hydroxide solution was flushed with nitrogen, sealed, and heated to 165° for 24 hr. The cooled reaction mixture was diluted with 1 l. of water and the *p*H adjusted to <1 with concd. hydrochloric acid. The solution was then treated with charcoal, filtered, and the *p*H readjusted to 6 with ammonium hydroxide; yield, 15 g., m.p., 244.5–245° (sealed tube).

Anal. Calcd. for $C_{15}H_{15}NO_2$: C, 74.66; H, 6.27; N, 5.81. Found: C, 74.70; H, 6.32; N, 5.75.

KANSAS CITY 10, MO.

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[CONTRIBUTION FROM THE DEPARTMENT OF NUCLEAR MEDICINE AND BIOPHYSICS OF THE MEDICAL CENTER, UNIVERSITY OF CALIFORNIA AT LOS ANGELES, THE CHEMISTRY DEPARTMENT, FRESNO STATE COLLEGE, AND THE CHEMISTRY DEPARTMENT, LONG BEACH COLLEGE]

Behavior of Certain Pyridines, Quinolines, and Isoquinolines with Amino or Hydrazino Substituents Toward *N*-Acylamino Acids Under the Influence of Papain Catalysis

JOHN LEO ABERNETHY[1] AND WARREN KILDAY[2]

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3-Aminoquinoline and 3-hydrazinoquinoline have been found to undergo reactions with hippuric acid, carbobenzoxyglycine, and carbobenzoxy-L-alanine in the formation of amide-like products. Also, they both effectively resolve carbobenzoxy-DL-alanine and benzoyl-DL-alanine under papain catalysis. When benzoyl-L-alanine is used alone, however, neither of the amino-containing bases undergoes a papain-catalyzed reaction with this single antipode. A number of aminopyridines, aminoquinolines, 4-aminoisoquinoline, and 2-hydrazinoquinoline failed to react, under papain catalysis, with this same selected group of N-acylamino acids.

Papain catalysis of the formation of peptide-like linkages from N-acyl amino acids and aniline or phenylhydrazine was demonstrated in the original research of Max Bergmann and Heinz Fraenkel-Conrat.[3] Groundwork was thereby laid for a diversity of studies[4] which brought forth much informa-

(1) To whom correspondence should be directed relative to this paper at the Department of Nuclear Medicine and Biophysics of The Medical Center, University of California at Los Angeles.

(2) California Heart Association Undergraduate Research Fellow, Summer, 1958; the principal contents of this paper were presented upon invitation and won first prize and a scroll in the Fresno State College Sigma Xi Club undergraduate research contest, May, 1959; present address, Graduate School, Washington State University, Pullman, Washington.

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tion concerning the specificity of this enzyme, particularly with regard to amine structures and the ability of the enzyme to resolve a variety of *N*-acylamino acids. Usually a preference is shown by the enzyme for an L-acylamino acid in such catalysis, although this is not always the case.[4] Most of the early research was focussed on variations in the amino acids structure and the acyl radical bonded to the α-amino group. Little was done in extending the basic, amino-containing reactant to other varieties of structures. Among the few amino-containing compounds used were an aliphatic type of amine, benzylamine,[4,5] and a secondary amine, methylaniline.[5] Neither underwent a reaction with an *N*-acylamino acid. Phenylhydroxylamine[5] was also employed, but this likewise gave negative results. However, in the majority of instances studied, substituted anilines with many kinds of substituents did give rise effectively to hippuric substituted anilides.[4]

Still further extension was then made in incorporating an asymmetric center[6] in the amino-containing molecule, as in *m*-(1-hydroxyethyl)aniline. With hippuric acid the reaction went well, but the resultant hippuric *m*-(1-hydroxyethyl)anilide was racemic. Attention was then turned to hydrazides, which contain a basic amino group.[4] Effective resolutions of *N*-acylamino acids occurred during the formation of N^{α},N^{β})-diacylhydrazines. However, resolution of DL-mandelic hydrazide did not occur in its reaction with hippuric acid, nor did ethylmalonic hydrazide undergo a partial asymmetric synthesis in its reaction with hippuric acid. Racemic products resulted.

The present investigation was undertaken to incorporate nitrogen in a six-membered ring involving a resonance hybrid, rather than using a benzene ring, with amino or hydraazino groups attached to the heterocyclic nucleus. Pyridine, quinoline, and isoquinoline nuclei were used. The specific compounds chosen were 2-aminopyridine, 4-methyl-2-aminopyridine, 3-aminopyridine, 4-aminopyridine, 2-aminoquinoline, 3-aminoquinoline, 5-aminoquinoline, 6-aminoquinoline, 8-aminoquinoline, 4-aminoisoquinoline, 2-hydrazinoquinoline and 3-hydrazinoquinoline. *N*-Acylamino acids selected were hippuric acid, carbobenzoxyglycine, carbobenzoxy-L-alanine, carbobenzoxy-DL-alanine, benzoyl-L-alanine, and benzoyl-DL-alanine because of their reasonably moderate solubility.

The investigation was divided into the following phases of study: (1) Determination of the dependence of yield on *p*H for a very few reactions served as a guide for an appropriate *p*H to be utilized for an entire group of closely related syntheses. (2) Each amino-containing compound was subjected to reactions with the chosen series of *N*-acyl amino acids. Papain was the catalyst and L-cysteine the promotor at 40° and the established *p*H. Removal of the reaction product was carried out at appropriate intervals of time. (3) Tests were made for resolution when racemic *N*-acylamino acids were utilized by determination of the optical activity of the reaction product.

EXPERIMENTAL

Activation of papain. The papain in these experiments was obtained from the Wallerstein Laboratories, New York City. Activation was carried out according to the procedure of Grassmann[7] and of Bennett and Niemann[8] with certain simplifications.[4] The resultant light tan product was crushed lightly and stored in stoppered vials in a brown bottle fitted with a screw cap and was refrigerated at 5°.

Preparation of intermediates. It was necessary to prepare some of the reactants for these studies in papain catalysis. 3-Aminopyridine was synthesized from nicotinamide by a Hofmann hypobromite reaction.[9] The preparation of 2-aminoquinoline involved a Chichibabin reaction using sodium amide and quinoline in boiling xylene.[10] Care was taken to employ freshly opened lump sodium amide,[11] which was cautiously ground to a powder under a dry nitrogen atmosphere in a dry box. The solid melting at 129–130° after recrystallization from toluene was used in the papain-catalyzed syntheses.

The preparation of 4-aminoisoquinoline[12] was effected by conversion of isoquinoline to 4-bromoisoquinoline[13] and subsequent conversion to 4-aminoisoquinoline[14] by concd. ammonium hydroxide and copper sulfate in a heated, shaking, autoclave. The 4-aminoisoquinoline was then converted to the solid hydrochloride with a stream of dry hydrogen chloride.

The synthesis of carbobenzoxyglycine, carbobenzoxy-DL-alanine, and carbobenzoxy-L-alanine was accomplished by the method of Carter, Frank, and Johnston[15] from benzyl chloroformate and the appropriate amino acids.

Dependence of yield on pH for the papain-catalyzed reactions between 3-aminoquinoline and hippuric acid to form 3-hippuramidoquinoline. It was necessary to perform exploratory experiments to find a wide range of *p*H values over which there was sufficient solubility of both hippuric acid and 3-aminoquinoline and also insolubility of 3-hippuramidoquinoline to determine satisfactorily the dependence of yield on *p*H. For the *p*H range from 4.0 to 6.0, with 0.5 unit increments of *p*H for the study and 0.01 mole each of hippuric acid and 3-aminoquinoline in 125 ml. of total buffered solution, a precipitate was given only at *p*H 5.5. When the quantities of hippuric acid and 3-aminoquinoline were increased to

(5) Unreported experimental work performed at the California State Polytechnic College, San Luis Obispo, and at Fresno State College.

(6) J. L. Abernethy and Bro. Myron Collins, *J. Org. Chem.*, 1558.

(7) W. Grassmann, *Biochem. Z.*, **279**, 131 (1935).

(8) E. L. Bennett and C. Niemann, *J. Am. Chem. Soc.*, **72**, 1789 (1950).

(9) C. F. H. Allen and C. N. Wolf, *Org. Syntheses*, **30**, 3 (1950).

(10) D. A. Shirley, *Preparation of Organic Intermediates* John Wiley and Sons, New York (1951), p. 16.

(11) Fisher Scientific Company Chemicals, lump sodium amide.

(12) D. A. Shirley, *Preparation of Organic Intermediates*, John Wiley and Sons, New York (1951), p. 50.

(13) F. W. Bergstrom and J. H. Rodda, *J. Am. Chem. Soc.*, **62**, 3031 (1940).

(14) D. A. Shirley, *Preparation of Organic Intermediates*, John Wiley and Sons, New York (1951), p. 11.

(15) H. E. Carter, R. L. Frank, and H. W. Johnston, *Org. Syntheses*, Coll. Vol. III, 158 (1955).

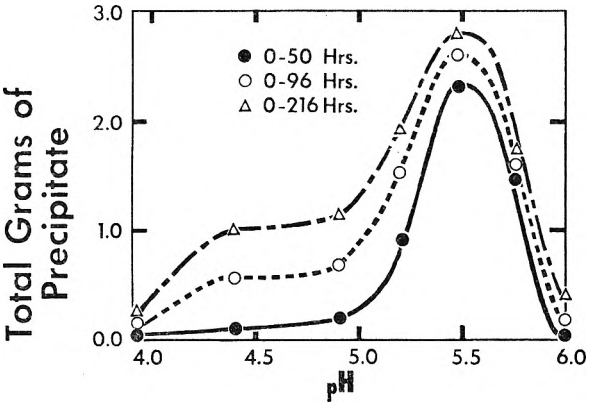


Fig. 1. Dependence of yield on *p*H for the papain-catalyzed formation of 3-hippuramidoquinoline from hippuric acid and 3-aminoquinoline

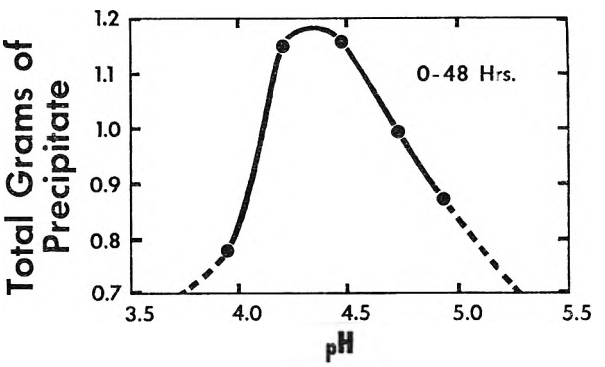


Fig. 2. Dependence of yield on *p*H for the formation of hippuric 3-quinolylhydrazide from hippuric acid and 3-hydrazinoquinoline

0.02 mole each for this same volume of solution, a considerable amount of undissolved reactant remained at the higher pH values. Satisfactory solution was brought about for the entire *p*H range studied by using 0.0200 mole of hippuric acid and 0.0100 mole of 3-aminoquinoline, 0.500 g. of L-cysteine hydrochloride, 0.500 g. of activated Wallerstein papain, and enough buffer to make 125 ml. total of buffered solution. After mixing and filtering, the solutions were adjusted to the exact *p*H desired, with the aid of a *p*H meter. The solutions were incubated at 40° and the precipitates were collected at the end of 50, 96, and 216 hr., with readjustment of the *p*H to its original value after each filtration. Precipitates were dried and weighed. Results are plotted in Fig. 1. Total yields in percent for 216 hr. of incubation were: *p*H 6.01, 13.1%; *p*H 5.75, 55.9%; *p*H 5.47, 93.0%; *p*H 5.22, 66.1%; *p*H 4.92, 37.4%; *p*H 4.40, 33.4%; *p*H 3.95, 7.1%.

Dependence of yield on pH for the reaction between 3-hydrazinoquinoline and hippuric acid to form hippuric 3-(quinolyl)-hydrazide. Preliminary experiments showed that effective results could be obtained by employing 1.161 g. (0.00500 mole) of 3-hydrazinoquinoline, 3.583 g. (0.0200 mole) of hippuric acid, 0.500 g. of L-cysteine hydrochloride, and 0.500 g. of activated Wallerstein papain in sufficient buffer to make 125 ml. of solution. Filtration was carried out before incubation was started. Some insoluble substrate was noted. Incubation was conducted at 40° followed by collection of the precipitates at the end of 48 hr. for each of the *p*H values used. The results are shown graphically in Fig. 2. Percent yields at the end of 48 hr. were: *p*H 3.95, 22.8%; *p*H 4.23, 34.0%; *p*H 4.49, 34.2%; *p*H 4.73, 29.7%; *p*H 4.95, 25.6%.

Experiments with aminopyridines. A number of experiments were tried with 2-aminopyridine, 3-aminopyridine, and 4-methyl-2-aminopyridine. Both hippuric acid and carbobenzoxyglycine were used as the amido acids, with L-cysteine hydrochloride as the promotor and activated Wallerstein papain as the catalyst. The *p*H was varied from about 3.5 to 6.0 at increments of about 0.5 *p*H units. After 5 days or more, no evidence was given for a reaction in any of the situations studied, when incubation was carried out at 40°.

Experiments using 2-aminoquinoline, 5-aminoquinoline, 8-aminoquinoline and 4-aminoisoquinoline with hippuric acid, carbobenzoxyglycine, carbobenzoxy-DL-alanine and carbobenzoxy-L-alanine. These experiments were conducted over a range of *p*H values from 4 to 6 at 0.5 units of *p*H. In all cases the amino compounds were quite insoluble at high *p*H values. At the end of 264 hr. of incubation no precipitate of product had been obtained when incubated at 40°, with activated Wallerstein papain as the catalyst and L-cysteine hydrochloride as the promotor.

Experiments with 3-aminoquinoline and hippuric acid, carbobenzoxyglycine, carbobenzoxy-L-alanine, carbobenzoxy-DL-alanine, benzoyl-L-alanine and benzoyl-DL-alanine. All of these experiments were carried out in 125 ml. total buffered solution at *p*H 5.5 and incubated at 40°. In each case 0.0100 mole of 3-aminoquinoline was employed with 0.500 g. of activated Wallerstein papain and 0.500 g. of L-cysteine hydrochloride. The amounts of *N*-acylamino acids employed for the separate reactions were: 0.0150 mole of hippuric acid; 0.0150 mole of carbobenzoxyglycine; 0.0150 mole of carbobenzoxy-L-alanine; 0.0150 mole of benzoyl-L-alanine; 0.0300 mole of carbobenzoxy-DL-alanine; 0.0300 mole of benzoyl-DL-alanine. Precipitates were collected at the end of 18, 44, and 264 hr. of incubation and were dried and weighed. After recrystallization from an ethanol and water mixture, melting points were determined. Following each filtration, the filtrate was readjusted to *p*H 5.5 before incubation was continued. Specific rotations were determined in approximately 2% solutions in pyridine. Results are given in Table I. No product was given with benzoyl-L-alanine.

Experiments between 3-hydrazinoquinoline and hippuric acid, carbobenzoxyglycine, benzoyl-L-alanine, benzoyl-DL-alanine, carbobenzoxy-L-alanine, and carbobenzoxy-DL-alanine. These reactions were all conducted at *p*H 4.5 and 40°. 3-Hydrazinoquinoline dihydrochloride (0.0100 mole) was employed with 0.0300 mole of hippuric acid, carbobenzoxyglycine, carbobenzoxy-L-alanine, or benzoyl-L-alanine or with 0.0600 mole of carbobenzoxy-DL-alanine or benzoyl-DL-alanine. A total of 250 ml. of buffered solution was utilized with 1.000 g. of activated Wallerstein papain and 1.000 g. of L-cysteine hydrochloride. Results are tabulated in Table II. No product was given with benzoyl-L-alanine. Precipitates were collected at the end of 18, 44, and 168 hr., dried and weighed. The filtrates were readjusted to *p*H 4.5 before incubation was continued. As zero rotation was shown in each case in pyridine, rotations were determined in chloroform or methanol.

Rotations of α-(benzyloxycarbonylamino)propionic 3-quinolylhydrazide and α-benzamidopropionic 3-quinolylhydrazide in pyridine. Both of these 3-quinolylhydrazides displayed zero rotation when dissolved in pyridine, which suggested possible racemization. α-(Benzyloxycarbonylamino)propionic 3-quinolylhydrazide showed $[\alpha]_D^{25°} = -25.3°$ in chloroform. When the chloroform was removed by evaporation and the solid was dissolved in pyridine, zero rotation was obtained. When the pyridine was then evaporated and this solid was redissolved in chloroform, zero rotation was obtained.

On the other hand, α-benzamidopropionic 3-quinolylhydrazide exhibited $[\alpha]_D^{25°} = +40.0°$ in methanol. Upon removal of the methanol and redissolving the solid in pyridine, zero rotation was shown. Removal of the pyridine and

TABLE I

REACTIONS OF 3-AMINOQUINOLINE WITH *N*-ACYLAMINO ACIDS AT *p*H 5.5 AND 40°

Amido Acids[a]	Product	M.P.[b]	$[\alpha]_D^{25°}$ 2% in pyridine	Yield, g. 0–18 Hr.	Yield, g. 18–44 Hr.	Yield, g. 44–264 Hr.	N Calcd.	N Found
HA	3-Hippuramidoquinoline	218–220°		0.997	0.446	0.631	13.76	13.76
CBG	3-Carbobenzoxyglycyl-amidoquinoline	237–238°		2.707	0.245	0.369	12.53	12.49
C-L-A	3-Carbobenzoxy-L-alanylamidoquinoline	179–180°	−77.9°	3.262	0.762	0.209	12.61	12.79
C-DL-A	3-Carbobenzoxyalanyl-amidoquinoline	180–182°	−73.9°	1.326	0.797	0.151	12.61	12.62
B-DL-A	3-Benzoylalanylamido-quinoline	204–205°	−46.55°	2.533	0.264	0.125	13.16	13.15

[a] Hippuric acid (HA); carbobenzoxyglycine (CBG); carbobenzoxy-L-alanine (C-L-A); carbobenzoxy-DL-alanine (C-DL-A); benzoyl-L-alanine (B-L-A), no reaction; benzoyl-DL-alanine (B-DL-A). [b] Recrystallized from ethanol and water.

TABLE II

REACTIONS OF 3-HYDRAZINOQUINOLINE WITH *N*-ACYLAMINO ACIDS AT *p*H 4.5 AND 40°

Amido Acid[a]	Product	M.P.[b]	$[\alpha]_D^{25°}$ 2% in solvent	Yield, g. 0–18 Hr.	Yield, g. 18–44 Hr.	Yield, g. 44–264 Hr.	N Calcd.	N Found
HA	Hippuric 3-quinolylhydrazide	213–214°		1.320	0.019	0.040	17.49	17.69
CBG	Benzyloxycarbonylamino-acetic 3-quinolylhydrazide	179–180°		1.290	0.020	0.000	16.00	15.99
C-L-A	L-α-(Benzyloxycarbonyl-amino)propionic 3-quinolylhydrazide	197–198°	−25.3° in $CHCl_3$	1.197	0.183	0.000	15.38	15.32
C-DL-A	α-(Benzyloxycarbonyl-amino)propionic 3-quinolylhydrazide	195–196°	−25.1° in $CHCl_3$	1.511	0.273	0.019	15.38	15.36
B-DL-A	α-Benzamidopropionic 3-quinolylhydrazide	228–230°	+40.0° in CH_3OH	1.928	0.466	0.086	16.76	16.61

[a,b] See footnotes for Table I.

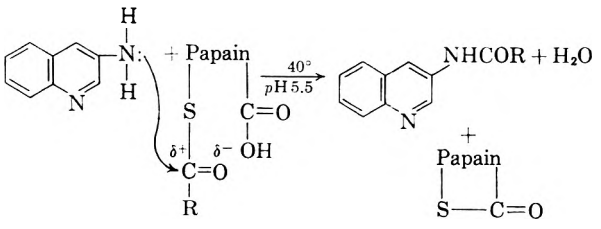
redissolving in methanol gave substantially the same rotation that was given before in methanol.

DISCUSSION

3-Aminoquinoline and 3-hydrazinoquinoline were two compounds containing the quinoline nucleus and, incorporating a basic amino group in their structures, that underwent reactions with hippuric acid, carbobenzoxyglycine, carbobenzoxy-DL-alanine, carbobenzoxy-L-alanine, and benzoyl-DL-alanine. No products were formed when 2-aminopyridine, 3-aminopyridine, 4-methyl-2-aminopyridine, 2-aminoquinoline, 5-aminoquinoline, 8-aminoquinoline, and 4-aminoisoquinoline were each studied with hippuric acid, carbobenzoxyglycine, carbobenzoxy-DL-alanine, and carbobenzoxy-L-alanine. Solubilities of reactants and also of products play a determining role. Relative basicities of amino groups are important contributing factors. Resonance withdrawal of the electron pair on amino nitrogen, particularly when enhanced by the heterocyclic nitrogen, would be significant in reducing the basicity of amino nitrogen. Besides this, coulombic attraction of the hetero nitrogen atom for this electron pair on amino nitrogen would reduce the availability of the pair and therefore the basic properties of the amido group.

The failure of any of the aminopyridines to respond might, in part, also be attributed to relatively high solubilities of anticipated products of reaction. Generally speaking, one of the driving forces of these reactions is the insolubility of the products, which can keep the essentially steady-state equilibria disturbed in favor of these desired substances.

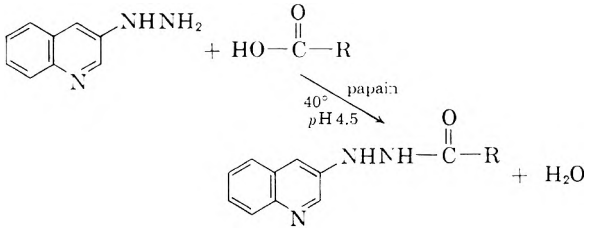
3-Aminoquinoline contains an additional benzene ring, which would decrease the solubility of the reaction product. It has an appropriately situated amino radical for enhancing its basicity and ability to react with the papain-amido acid substrate intermediate.



Enzyme–Substrate Intermediate

The possibility of assistance in the reaction by an imidazolyl radical of an L-histidine residue, if spaced appropriately between an L-cysteine residue and an L-glutamic acid residue of the papain polypeptide chain, has been discussed in detail in connection with previous work.[6,7] These reactions of 3-aminoquinoline show that an amino substituent can be bonded to a heterocyclic ring and undergo a reaction similar to an amino group bonded to a benzene ring. It should be pointed out that an investigation of the dependence of yield on pH for the reaction product of the reaction between hippuric acid and 3-aminoquinoline showed a relatively high optimum *p*H of about 5.5, for the conditions employed.

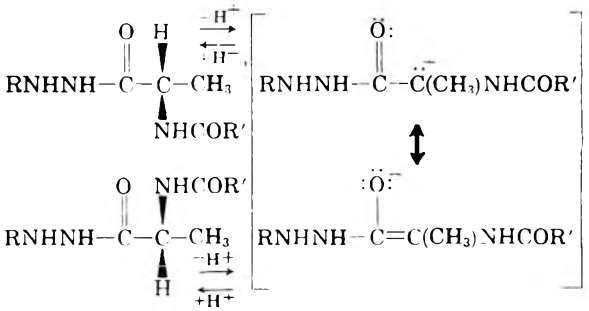
In contrast with this, 3-hydrazinoquinoline undergoes a reaction with hippuric acid at an optimum of about 4.5.



This is the first hydrazino group bonded to something besides a benzene ring or a carbonyl group that has been demonstrated to take part in such a reaction. 4-Aminoisoquinoline did not undergo a reaction with any of the acylated amino acids of this investigation.

A very peculiar situation has consistently arisen with benzoyl-DL-alanine and benzoyl-L-alanine throughout these and previous experiments.[4,6] In all instances where a reaction did occur with benzoyl-DL-alanine and appropriate amino-containing compounds under papain-catalysis, resolution of the racemic *N*-acylamino acid resulted. When benzoyl-L-alanine was used alone no reaction took place. This is not readily explained on the basis of the compounds. Perhaps some inhibitor is present in the benzoyl-L-alanine. Further investigation is planned for this puzzling situation.

The zero rotation of α - (benzyloxycarbonylamino)propionic 3-quinolylhydrazide α-benzamidopropionic 3-quinolylhydrazide in pyridine suggested that racemization might have occurred in this basic solvent. This explanation may apply to



the α-benzyloxycarbonyl derivative (see Experimental) but cannot apply to the α-benzamido derivative, which gave a rotation in methanol, both before and after the measurement of (zero) rotation in pyridine.

Acknowledgment. Funds for this research were generously provided by the Fresno County Heart Association, the California Heart Association, the Sigma Xi Society and RESA, and the Research Corporation. Dr. Kendall Holmes, Dr. Robert D. Beech, Dr. Clell Gray, and Mrs. Joyce Richardson of the Fresno County Heart Association, and Dr. John J. Sampson, Dr. Robert H. Maybury, and Miss Phyllis Hecker of the California Heart Association were instrumental in securing Heart Association grants. Mr. William Woods of the Research Corporation was particularly helpful in working with state college administrators in securing permission to carry out the research before state policy was established.

LOS ANGELES CALIF.

(7) T. C. Bruice, *J. Am. Chem. Soc.*, 81, 5444 (1959).

[CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION OF G. D. SEARLE & CO.]

3-Imidomethyloxazolidines

MAX J. KALM

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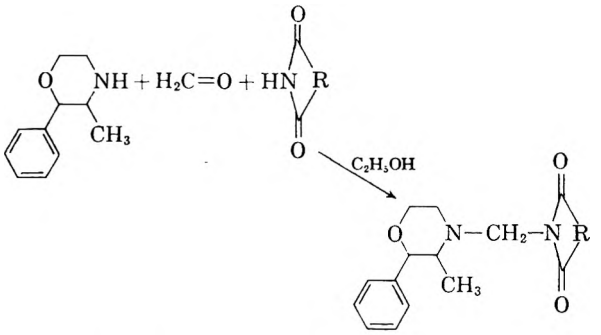
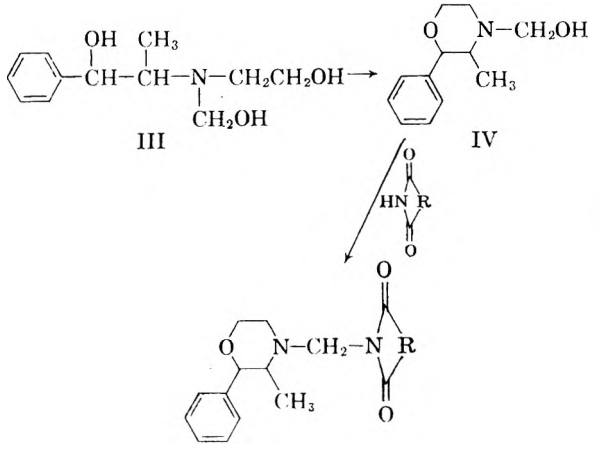
Several 4,5-disubstituted oxazolidines have been prepared and these have been converted to a variety of 4,5-disubstituted 3-imidomethyloxazolidines. In the case of the 4-methyl-5-phenyloxazolidines, both racemic diastereoisomers were prepared and converted to the imidomethyloxazolidines. The reactions leading to these compounds are stereospecific and a number of the optically active isomers were prepared by the use of resolved starting materials. These compounds exhibit a variety of interesting biological activities.

It had been shown in these laboratories that two imidomethyl derivatives of 2-phenyl-3-methylmorpholine (Preludin) had potent appetite inhibitory activity.[1,2] These compounds were prepared by reaction of 2-phenyl-3-methylmorpholine with formaldehyde and an imide, according to the procedure of Moore and Rapala.[3]

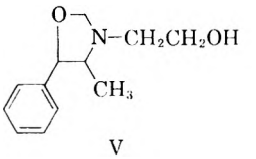


I. R = $-CH_2CH_2-$ II. R = 

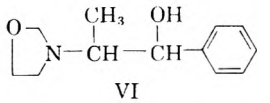
It became desirable to find an alternate route of preparation for these compounds; one which would bypass 2-phenyl-3-methylmorpholine as an intermediate. It had previously been shown that hydroxymethylamines react with imides to give imidomethylamines.[4] An attempt was therefore made to prepare 2-phenyl-3-methyl-4-hydroxymethylmorpholine (IV) by ring closure of *N*-β-hydroxyethyl-*N*-hydroxymethylnorephedrine (III).



Reaction of *N*-β-hydroxyethylnorephedrine with aqueous formaldehyde followed by ring closure with concentrated sulfuric acid gave a yellow oil which on reaction with succinimide gave I identical with the material prepared by reaction of 2-phenyl-3-methylmorpholine with formaldehyde and succinimide. Although it was first thought that the reaction between *N*-β-hydroxyethylnorephedrine and formaldehyde had led to the formation of *N*-β-hydroxyethyl-*N*-hydroxymethylnorephedrine (III), there was doubt about the structure of this intermediate because the literature states that reaction of β-hydroxyethylamines with carbonyl compounds leads to the formation of either the Schiff base or an oxazolidine.[5] The original assignment of the triol (III) for this intermediate was made because reaction was achieved by simply shaking the amine with aqueous formaldehyde, conditions felt to be too mild for anything but the addition of an amine across the double bond of formaldehyde. Analysis, however, showed the hydrochloride of this compound to have the empirical formula which corresponds to either the Schiff base or the oxazolidine, while infrared spectral analysis showed no band in the 1670 cm.$^{-1}$ region characteristic of the —CH=N— absorption of aliphatic Schiff bases.[6] It was now necessary to find additional methods for identifying this intermediate, as it was necessary to prove with certainty that the compound was the oxazolidine and because two isomeric oxazolidines (V) and (VI) can be postulated as the product of the reaction between formaldehyde and *N*-β-hy-



V



VI

(1) Belgian Patent No. 567,664, Nov. 14, 1958.
(2) South African Patent No. 1627/58, Sept. 23, 1959.
(3) M. B. Moore and R. T. Rapala, *J. Am. Chem. Soc.*, 68, 1657 (1946).
(4) W. I. Weaver, J. K. Simons, and W. E. Baldwin, *J. Am. Chem. Soc.*, 66, 222 (1944).
(5) E. D. Bergmann, *Chem. Revs.*, 53, 309 (1953).
(6) L. Kahovec, *Acta Phys. Austriaca*, 1, 307 (1948); *Chem. Abstr.*, 42, 6665 (1948).

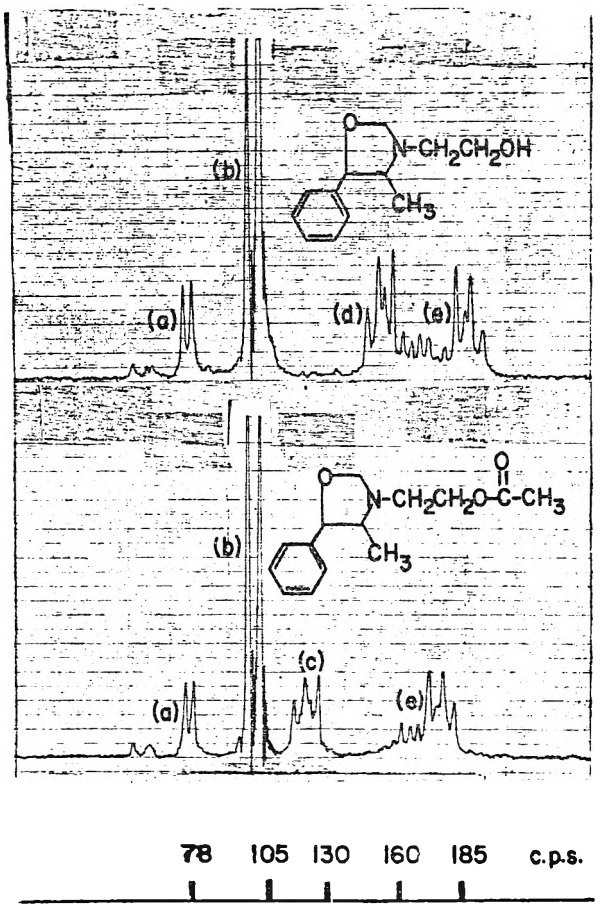


Fig. 1. N.M.R. spectra of 3-β-hydroxyethyl-4-methyl-5-phenyloxazolidine and 3-β-acetoxyethyl-4-methyl-5-phenyloxazolidine in D_2O.

(a) C_6H_5—*CH*, (b) —O*CH*$_2$—N,
O
‖
(c) —*CH*$_2$—O—C—CH_3 (d) —*CH*$_2$OH,
(e) —CH_2—N—

droxyethylnorephedrine, depending on which hydroxyl group participates in the reaction.

Nuclear magnetic resonance spectroscopy served as an excellent tool both for confirming the oxazolidine structure of the product and for establishing which isomer had been formed. The oxazolidine was converted to the acetate and the NMR spectra of both the carbinol and its acetate in the form of their hydrochlorides were compared. The oxazolidine structure was confirmed by the presence of a —O—CH_2—N— band at 100 c.p.s. and the compounds were shown to possess structure V by a shift of the —CH_2OH bands at 160 c.p.s. to 130 c.p.s. for the —CH_2OAc bands. On the other hand the C_6H_5—CH band at 77 c.p.s. was not displaced in going from the free alcohol to the acetate as would be the case if structure VI were correct. Portions of these NMR spectra are reproduced in Fig. 1.

It now became of interest to see if the reaction with aqueous formaldehyde were a general one for β-hydroxyethylamines. To test this the reaction was run with *d,l*-norephedrine to prepare the 3-unsubstituted oxazolidine. This compound had been prepared previously[7] but the reaction conditions had been much more vigorous. The reaction between *d,l*-norephedrine and aqueous formaldehyde yielded an oil which had no absorption at 1670 cm.$^{-1}$ attributable to the Schiff base structure[6] but had a very weak absorption band at 1610 cm.$^{-1}$. There were in addition bands at 1092 cm.$^{-1}$, 1130 cm.$^{-1}$, and 1177 cm.$^{-1}$, a region which is supposed to contain a triplet of bands due to the —O—C—N— structure. It is therefore believed that this reaction also led to the formation of an oxazolidine as the major product. A crystalline hydrochloride was obtained and this also lacked absorption in the 1670 cm.$^{-1}$ region.

No additional structure work was done on the *N*-unsubstituted oxazolidines, as the major interest lay in the preparation of 3-imidomethyloxazolidines, oxazolidine analogs of I and II. Such compounds, if formed, must possess the oxazolidine structure even if the precursors are in equilibrium between the oxazolidine and Schiff base structure.

Using a variety of imides a number of 3-imidomethyloxazolidines were prepared by the method of Moore and Rapala.[3] These compounds are stable crystalline solids with analyses and infrared spectra consistent with the proposed structures. The compounds prepared are given in Table I.

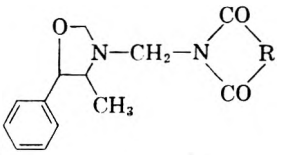
The next step was to investigate the preparation of the diastereoisomeric compounds from norpseudoephedrine. Pfanz and Kirchner[7] had shown that the oxazolidines from norpseudoephedrine had the *threo* configuration and that this isomer was more stable as a ring than the *erythro* isomer from norephedrine. It was therefore not surprising that the product from reaction of norpseudoephedrine with formaldehyde readily formed a variety of 3-imidomethyloxazolidines which differed in their physical properties from the corresponding derivatives prepared from norephedrine. These compounds are described in Table II.

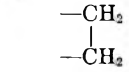
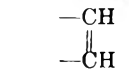
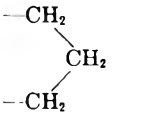
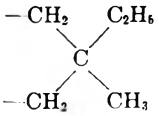
In an attempt to prepare some 2-substituted oxazolidines, norephedrine was allowed to react with acetaldehyde and with *n*-heptaldehyde. In both instances, the intermediate 3-unsubstituted oxazolidine was not purified or characterized, but was carried directly to the 3-imidomethyloxazolidine. The products thus obtained were not the 2-substituted oxazolidines but were identical with the imidomethyloxazolidines prepared from norephedrine and formaldehyde. Two possible explanations for the formation of these compounds are that either the reaction between norephedrine and alkyl aldehydes gives predominantly the Schiff base and that further reaction with the imide and formaldehyde causes first aldehyde interchange followed by ring closure, or that the greater stability of the 2-unsubstituted ring leads to ring opening followed by

(7) H. Pfanz and G. Kirchner, *Ann.*, **614**, 149 (1958)

TABLE I

IMIDOMETHYLOXAZOLIDINES DERIVED FROM *d,l*-NOREPHEDRINE

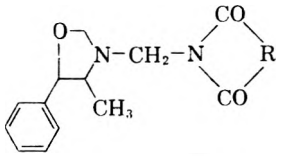


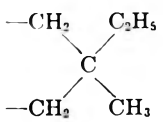
No.	R	Formula	M.P.	Carbon, %		Hydrogen, %		Nitrogen, %	
				Calcd.	Found	Calcd.	Found	Calcd.	Found
VII		$C_{15}H_{18}N_2O_3$	132.0–134.0[a]					10.22	10.01
VIII		$C_{15}H_{16}N_2O_3$	99.0–102.0[a]					10.29	10.13
IX		$C_{16}H_{20}N_2O_3$	92.0–94.0[b]	66.64	66.70	6.99	7.06	9.72	9.58
X		$C_{19}H_{26}N_2O_3$	76.0–78.0[b]					8.48	8.35
XI		$C_{19}H_{24}N_2O_3$	82.0–84.0[b]	69.49	69.51	7.37	7.43	8.53	8.25
XII		$C_{19}H_{22}N_2O_3$	98.5–100.5[a]	69.91	69.83	6.80	7.02		
XIII		$C_{19}H_{18}N_2O_3$	111.0–113.0[a]	70.79	70.98	5.63	5.79	8.69	8.52

[a] Crystallized from absolute ethanol. [b] Crystallized from ethanol and water.

TABLE II

IMIDOMETHYLOXAZOLIDINES DERIVED FROM *d,l*-NORPSEUDOEPHEDRINE

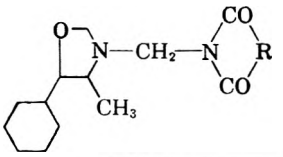


No.	R	Formula	M.P.	Nitrogen, %	
				Calcd.	Found
XIV		$C_{15}H_{18}N_2O_3$	70.5–73.0[a]	10.22	10.22
XV		$C_{15}H_{16}N_2O_3$	92.0–96.0[a]	10.29	10.21
XVI		$C_{19}H_{26}N_2O_3$	86.0–88.0[b]	8.48	8.55
XVII		$C_{19}H_{22}N_2O_3$	92.5–95.0[b]	8.59	8.53
XVIII		$C_{19}H_{18}N_2O_3$	91.5–94.5[a]	8.69	8.73

[a] Crystallized from absolute ethanol. [b] Crystallized from ethanol and water.

TABLE III

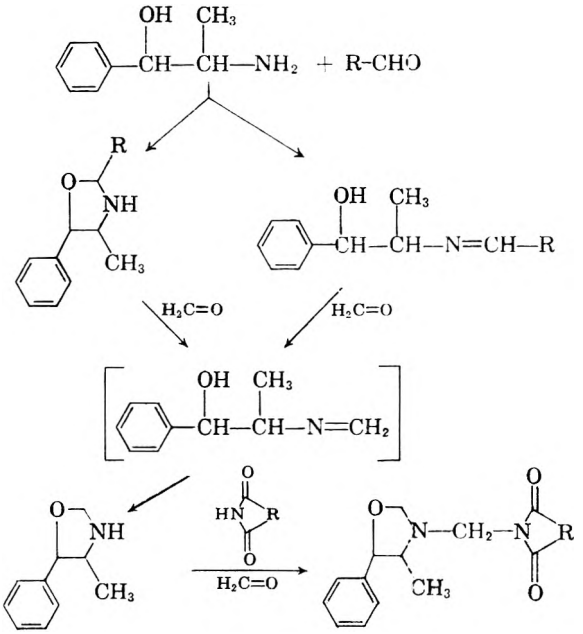
3-IMIDOMETHYL-4-METHYL-5-CYCLOHEXYLOXAZOLIDINES



No.	R	Formula	M.P.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
XIX		$C_{15}H_{24}N_2O_3$	73.0–75.0[b]	64.26	64.66	8.63	8.63		
XX		$C_{15}H_{22}N_2O_3$	82.5–88.0[a]					10.07	9.92
XXI		$C_{19}H_{24}N_2O_3$	90.5–93.0[a]	69.49	69.19	7.37	7.30	8.53	8.34

[a] Crystallized from absolute ethanol. [b] Crystallized from ethanol and water.

aldehyde interchange and reclosing of the ring. Since excess formaldehyde is used in the imidomethylation step the aldehyde interchange is possible. The two possible reaction mechanisms are shown below.



Although 2-substituted 3-imidomethyloxazolidines could not be formed by this method, various modifications in the substituent at C_5 did not affect or alter the course of the reaction. Hexahydronorephedrine, which had previously been prepared by reduction of 1-cyclohexyl-2-nitro-1-propanol,[8] was prepared by reduction of norephedrine with ruthenium oxide. This was readily converted to 4-methyl-5-cyclohexyloxazolidine, which could be transformed into a variety of 3-imidomethyloxazolidines. The *p*-chloro-[9] and *p*-methoxynorephedrines[10] were also prepared. These were converted to their respective oxazolidines by reaction with aqueous formaldehyde and a variety of 3-imidomethyloxazolidines were prepared from them. The compounds are shown in Tables III, IV, and V.

All the substances so far discussed possessed a wide spectrum of biological activities. The compounds prepared from norpseudoephedrine showed a separation of biological properties from those prepared from norephedrine. It therefore was of interest to determine if such a separation of activities also occurred in the case of the individual enantiomorphs. At the same time the preparation of the enantiomorphs would provide information about the stereospecificity of the reactions involved.

As the imidomethyloxazolidines from norephedrine showed the greatest biological activity, it was decided to prepare the enantiomorphs of several of these compounds. Resolution of *d,l*-norephedrine with *d*-tartaric acid yielded after hydrolysis the *d*-isomer of norephedrine. Hydrolysis of the mother liquors from this resolution gave the *l*-isomer in impure form which could be completely resolved by the use of *l*-tartaric acid. The conditions used for these resolutions were a modification[11] of the method of Kanao and Nagai.[12] The *d*- and *l*-norephedrines thus obtained served as starting materials for the stereospecific syntheses of some of the compounds shown in Table I.

The enantiomorphic norephedrines were each

(8) R. R. Burtner and W. M. Selby, U. S. Patent No. 2,586,512, Feb. 19, 1952.

(9) B. L. Zenitz and W. H. Hartung, *J. Org. Chem.*, **11**, 444 (1946).

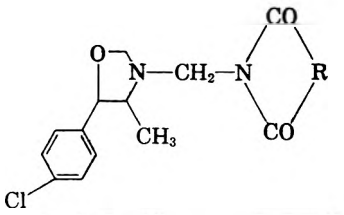
(10) W. H. Hartung, J. C. Munch, E. Miller, and F. Crossley, *J. Am. Chem. Soc.*, **53**, 4149 (1931).

(11) The conditions used for resolving *d,l*-norephedrine constitute unpublished results communicated to me by Dr. Gordon A. Alles of Pasadena, California. I am greatly indebted to Dr. Alles for this information as well as for conditions for isomerizing *d,l*-norephedrine to *d,l*-norpseudoephedrine and the resolution of the latter compound.

(12) S. Kanao and W. N. Nagai, *Ann.*, **470**, 157 (1929).

TABLE IV

3-IMIDOMETHYL-4-METHYL-5-*p*-CHLOROPHENYLOXAZOLIDINES

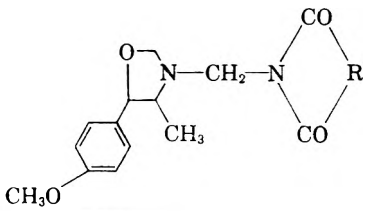


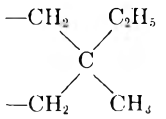
No.	R	Formula	M.P.	Nitrogen, % Calcd.	Nitrogen, % Found
XXII	$-CH_2-CH_2-$	$C_{15}H_{17}ClN_2O_3$	113.0–115.5[a]	9.08	9.24
XXIII	$-CH=CH-$	$C_{15}H_{15}ClN_2O_3$	97.0–99.5[a]	9.14	9.35
XXIV		$C_{19}H_{17}ClN_2O_3$	115.0–118.0[a]	7.85	7.98

[a] Crystallized from absolute ethanol.

TABLE V

3-IMIDOMETHYL-4-METHYL-5-*p*-METHOXYPHENYLOXAZOLIDINES



No.	R	Formula	M.P.	Nitrogen, % Calcd.	Nitrogen, % Found	Nitrogen,[a] % Calcd.	Nitrogen,[a] % Found	Methoxyl, % Calcd.	Methoxyl, % Found
XXV	$-CH_2-CH_2-$	$C_{16}H_{20}N_2O_4$	103.0–105.0[b]	9.21	9.06	4.60	4.66	10.20	10.23
XXVI	$-CH=CH-$	$C_{17}H_{18}N_2O_4$	116.0–119.0[b]	9.27	9.28	4.63	4.70	10.26	10.01
XXVII		$C_{20}H_{28}N_2O_4$	61.5–63.0[c]	7.77	7.90	3.89	4.02		
XXVIII		$C_{20}H_{20}N_2O_4$	127.0–129.0[b]	7.95	7.92	3.97	4.04		

[a] Nonaqueous titration of amino nitrogen. [b] Crystallized from absolute ethanol. [c] Crystallized from ethanol and water.

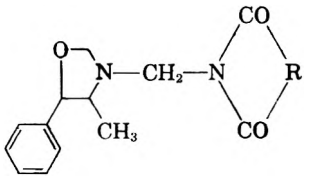
ring closed to the corresponding oxazolidines by treatment with aqueous formaldehyde and the oxazolidines were in turn converted to imidomethyloxazolidines shown in Tables VI and VII. In the case of the compounds where both isomers were prepared the rotations indicated that absolute optical purity was not achieved in some instances and this may well have been the result of slight racemization during ring closure or during the formation of the imidomethyl derivatives.

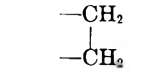
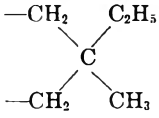
The *d,l*-norpseudoephedrine was also resolved[11] but only one imidomethyl derivative was prepared. This compound was the 3-succinimidomethyl derivative of the oxazolidine obtained from *l*-norpseudoephedrine.

The compounds described have shown activity as appetite inhibitors, diuretics, anti-inflammatory agents, antibacterial agents, and antifungal agents. A brief summary of some of these biological activities is shown in Table VIII.

TABLE VI

IMIDOMETHYLOXAZOLIDINES DERIVED FROM *d*-NOREPHEDRINE

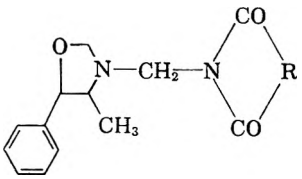


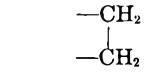
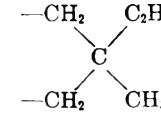
No.	R	Formula	M.P.	α_D	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Caled.	Nitrogen, % Found
XXIX		$C_{15}H_{18}N_2O_3$	99.0–101.0[a]	+8.7°	65.67	65.77	6.61	6.78	10.22	10.33
XXX		$C_{19}H_{26}N_2O_3$	93.0–95.0[b]	+28.3°					8.48	8.31
XXXI		$C_{19}H_{18}N_2O_3$	108.0–110.0[a]	−7.5°					8.69	8.57

[a] Crystallized from absolute ethanol. [b] Crystallized from ethanol and water.

TABLE VII

IMIDOMETHYLOXAZOLIDINES DERIVED FROM *l*-NOREPHEDRINE



No.	R	Formula	M.P.	α_D	Carbon, % Caled.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Caled.	Nitrogen, % Found
XXXII		$C_{15}H_{18}N_2O_3$	101.0–103.0[a]	−7.1°	65.67	65.78	6.61	6.89	10.22	10.50
XXXIII		$C_{19}H_{26}N_2O_3$	91.0–94.0[b]	−23.2°	69.06	68.83	7.93	8.15	8.48	8.49
XXXIV		$C_{19}H_{24}N_2O_3$	55.0–62.0[a]	−2.1°					8.53	8.30
XXXV		$C_{19}H_{18}N_2O_3$	106.5–108.5[a]	+6.2°	70.79	70.45	5.63	5.80	8.69	8.60

[a] Crystallized from absolute ethanol. [b] Crystallized from ethanol and water.

EXPERIMENTAL[13]

N-β-Hydroxyethylnorephedrine. Two methods which differ from the procedures in the literature[14,15] were used for the preparation of this compound.

A. A solution of 151 g. (1.0 mole) of *d,l*-norephedrine and 44.0 g. (1.0 mole) of ethylene oxide in 1000 ml. of absolute ethanol was placed in a 2-l. Parr hydrogenation bomb and was heated at 60° with stirring for 18 hr. The solvent was stripped at reduced pressure and the residue was triturated with anhydrous ether to yield 104 g. (53.3%) of the product as a white crystalline solid, m.p. 110–111.5°; lit.,[15] m.p. 109°.

B. A solution of 113.5 g. (0.75 mole) of *d,l*-norephedrine in 100 ml. of absolute ethanol was treated with 79.6 g. (0.75 mole) of benzaldehyde and the mixture was stirred until Schiff base formation was completed. The material was transferred to a 2-l. Parr hydrogenation bomb with 525 ml. of absolute ethanol and approximately 2.7 g. of commercial Raney Nickel catalyst was added. The material was hydrogenated at 70° using a pressure of 700 p.s.i., uptake being 93% of theory.

After removal of catalyst and addition of 36.2 g. (0.825 mole) of ethylene oxide the solution was heated at 60° for 18 hr. in a hydrogenation bomb. After the solution had cooled to room temperature, 20 g. of 5% palladium on charcoal catalyst was added. The debenzylation was carried out at 50° at a pressure of 800 p.s.i., hydrogen uptake being

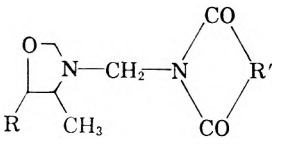
(13) All melting points are uncorrected. Rotations were determined at 26 ± 1° at a concentration of 1.2% in methanol unless otherwise specified.

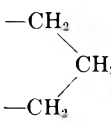
(14) R. H. F.Manske and T. B. Johnson, *J. Am. Chem. Soc.*, 51, 1906 (1929).

(15) A. Skita and F. Keil, *Ber.*, 63B, 34 (1930).

TABLE VIII

BIOLOGICAL ACTIVITIES OF 3-IMIDOMETHYLOXAZOLIDINES



No.	R	R′	Appetite Inhibition: % of Std.[f]	Appetite Inhibition: Dose, mpK in Rats	Appetite Inhibition: Route	Diuresis,[h] Rat: M.E.D., mpK I.G.	Anti-inflammatory Ankle Edema: M.E.D. Mg./rat	Anti-inflammatory Ankle Edema: Route
VII[a]	C_6H_5		50	150	I.G.	6	40	I.G.[g]
XIV[b]	C_6H_5		54	150	I.G.	24[i]	5	I.G.
XXIX[c]	C_6H_5		225	20	I.G.	12	Inactive[g]	
XXXII[d]	C_6H_5	$-CH_2-$	50	150	I.G.	3	<10	S.C.[g]
XXXVI[e]	C_6H_5	$-CH_2-$	53	150	I.G.	Inactive	<10	S.C.
XIX	C_6H_{11}	$-CH_2-$	50	150	I.G.	Inactive	Inactive	
XXII	p-ClC_6H_4	$-CH_2-$	30	150	I.G.	Inactive	5	I.G.
XXV	p-$CH_3OC_6H_4$	$-CH_2-$	40	20	S.C.	12	<10	S.C.
VIII[a]	C_6H_5	$-CH=$	40	150	I.G.[g]	12	<10	S.C.
XV[b]	C_6H_5	$-CH=$	30	20	S.C.	Inactive	<10	S.C.
XX	C_6H_{11}	$-CH=$	Inactive			Inactive	7.5	I.G.
XXIII	p-ClC_6H_4	$-CH=$	20	20	S.C.	Inactive	11	I.G.
XXVI	p-$CH_3OC_6H_4$	$-CH=$	50	20	S.C.	Inactive	<10	S.C.
IX[a]	C_6H_5		100	150	I.G.	6	5	I.G.[g]
X[a]	C_6H_5	$-CH_2-C(C_2H_5)_2-CH_2-$	85	20	S.C.[g]	6	Inactive	
XVI[b]	C_6H_5	$-CH_2-C(C_2H_5)_2-CH_2-$	325	20	I.G.	24[i]	2	I.G.
XXX[c]	C_6H_5	$-CH_2-C(C_2H_5)_2-CH_2-$	180	50	I.G.[g]	24	Inactive	
XXXIII[d]	C_6H_5	$-CH_2-C(C_2H_5)_2-CH_2-$	75	20	S.C.[g]	6	<40	I.G.
XXVII	p-$CH_3OC_6H_4$	$-CH_2-C(C_2H_5)_2-CH_2-$	51	20	S.C.	—	<10	I.G.
XI[a]	C_6H_5		45	20	S.C.	6	<20	I.G.
XXXIV[d]	C_6H_5		34	150	I.G.	6	Inactive[g]	
XII[a]	C_6H_5		Inactive			12	Inactive	
XVII[b]	C_6H_5		20	20	S.C.	Inactive	11	I.G.
XIII[a]	C_6H_5		40	150	I.G.	6	1	I.G.
XVIII[b]	C_6H_5		82	150	I.G.	Inactive	2	I.G.
XXXV[d]	C_6H_5		50	150	I.G.	6	Inactive	
XXXI[c]	C_6H_5		25	20	S.C.	Inactive	1	I.G.
XXI	C_6H_{11}		Inactive			Inactive	Inactive	
XXIV	p-ClC_6H_4		56	150	I.G.	Inactive	Inactive	
XXVIII	p-$CH_3OC_6H_4$		38	20	I.G.	24	<10	S.C.

[a] From *d,l*-norephedrine. [b] From *d,l*-norpseudoephedrine. [c] From *d*-norephedrine. [d] From *l*-norephedrine. [e] From *l*-norpseudoephedrine. [f] Preludin was used as the standard. [g] Compounds showed some lethality in this test. [h] C. G. Van Armen, *Gen. Pharm. and Exptl. Therap.*, 111, 285 (1954). [i] Active as sodium excretor only.

95% of theory. After removal of catalyst the solvent was stripped at reduced pressure and the residue was recrystallized from 300 ml. of benzene. The white crystalline product melted at 105–107°. The yield varied between 67 and 85% based on *d,l*-norephedrine.

3-β-Hydroxyethyl-4-methyl-5-phenyloxazolidine (V). To a suspension of 19.5 g. (0.1 mole) of *N*-β-hydroxyethylnorephedrine in 50 ml. of water in a separatory funnel was added 8.75 g. (0.105 mole) of 36% aqueous formaldehyde. The mixture was shaken vigorously for 5 min. followed by extraction of the product with two 100-ml. portions of chloroform. The extracts were dried over anhydrous sodium sulfate and evaporation of solvent gave 19.1 g. (84.9%) of a yellow oil. The crude base was then converted to the *hydrochloride:* Solution of 19.0 g. of the base in 25 ml. of absolute ethanol followed by treatment with 1 equivalent of hydrogen chloride in 2-propanol (0.25 g./ml.) gave the salt which was crystallized by addition of anhydrous ether to turbidity. Recrystallization from ethanol and ether gave the product as a white crystalline solid, m.p. 107–110°.

Anal. Calcd. for $C_{12}H_{18}ClNO_2$: C, 59.12; H, 7.44; N, 5.75; Cl, 14.55. Found: C, 59.03; H, 7.44; N, 5.72; Cl, 14.40.

3-β-Acetoxyethyl-4-methyl-5-phenyloxazolidine. To a stirred solution of 40.7 g. (0.197 mole) of 3-β-hydroxyethyl-4-methyl-5-phenyloxazolidine in 100 ml. of pyridine was added, dropwise, 21.6 g. (0.21 mole) of acetic anhydride. The solution was allowed to stir overnight. The solvent was removed by distillation at reduced pressure giving as the product an orange oil. The crude base was then converted to the *hydrochloride:* A solution of 10 g. of base in 20 ml. of absolute ethanol was treated with 1 equivalent of hydrogen chloride in 2-propanol (0.25 g./ml.) and the salt was crystallized by addition of anhydrous ether. Recrystallization from ethanol and ether gave 7.75 g. (67.7%) of the product in the form of white needles, m.p. 134–138° with decomposition.

Anal. Calcd. for $C_{14}H_{20}ClNO_3$: C, 58.84; H, 7.06; N, 4.90; Cl, 12.41. Found: C, 58.77; H, 7.44; N, 4.93; Cl, 12.23.

d,l-Norpseudoephedrine.[11] *d,l*-Norephedrine hydrochloride (94 g., 0.5 mole) was added in portions to 146 ml. (2.0 moles) of thionyl chloride with stirring. The mixture was then warmed to 45°, at which point the reaction began, as evidenced by gas evolution. When gas evolution had ceased the mixture was heated at 50–60° for 20 min., stirring being discontinued. While an internal temperature of 50–60° was maintained, 200 ml. of water was slowly added, stirring being resumed after the addition of about 100 ml. This was followed by rapid addition of 800 ml. of water and the resulting solution was heated under reflux for 2 hr. There was added 10 g. of Darco G-60 and the mixture was allowed to cool to room temperature. The Darco was removed by filtration and the filtrate was neutralized with 160 ml. of 18*N* sodium hydroxide. The product crystallized on cooling in an ice bath, and filtration followed by washing with ice water gave 37.6 g. (49.8%) of a white crystalline solid with m.p. 73–78°; lit.,[12] m.p. 71°.

Resolution of d,l-norephedrine.[13] A solution of 302.4 g. (2.0 moles) of *d,l*-norephedrine in 600 ml. of hot methanol was added to a solution of 300 g. (2.0 moles) of *d*-tartaric acid in 1000 ml. of hot methanol. The product crystallized overnight and was twice recrystallized from 1600 ml. of methanol to yield 139.9 g. of *d*-norephedrine-*d*-bitartrate, m.p. 153–163°, α_D +31.8° (2% in water).

The above bitartrate was dissolved in 280 ml. of warm water and was made basic with 113 ml. of 18*N* sodium hydroxide. Extraction with three 200-ml. portions of benzene followed by removal of solvent gave 61.7 g. of *d-norephedrine*, α_D +14.0°; lit.,[12] is α_D +14.8°.

The combined filtrates from the crystallization of the *d*-bitartrate were stripped of solvent at reduced pressure and the residue extracted with 4000 ml. of boiling ethanol. On cooling, the ethanol solution gave a gel-like precipitate which was filtered, washed, and dried to give 374.8 g. of solid with α_D +8.2° (2% in water). This material was dissolved in 750 ml. of water and was made basic by addition of 300 ml. of 18*N* sodium hydroxide. The base was extracted with benzene and solvent removed at reduced pressure.

The residual base was dissolved in 400 ml. of hot methanol and was treated with a solution of 168 g. of *l*-tartaric acid in 400 ml. of hot methanol. This gave 191.2 g. of *l*-norephedrine-*l*-bitartrate, m.p. 149–156° which on recrystallization from 1500 ml. of methanol yielded 118.6 g. of the bitartrate, m.p. 156–160° and α_D −34.6° (2% in water).

Liberation of the free base as described for the *d*-isomer using 95 ml. of 18*N* sodium hydroxide gave 49.2 g. of *l-norephedrine*, α_D −14.5°; lit.,[12] is α_D −14.6°.

l-Norpseudoephedrine. To a solution of 118.2 g. (0.784 mole) of *d*-tartaric acid in 275 ml. of hot water was added 118.7 g. (0.784 mole) of *d,l*-norpseudoephrine. This yielded 78.3 g. of crude bitartrate which on recrystallization from 250 ml. of water gave 65.5 g. of pure product, m.p. 201–202° and α_D −12.0° (2% in water). The salt was dissolved in 250 ml. of hot water and made basic with 18*N* sodium hydroxide, and the product was extracted with benzene to yield 29.2 g. of *l-norpseudoephedrine*, m.p. 75–78° and α_D −30.9°; lit.,[12] m.p. 77.5–78°, α_D −32.6°.

Hexahydronorephedrine. A solution of 250 g. (1.65 moles) of *d,l*-norephedrine in 750 ml. of 95% ethanol was reduced at 83° using 2.5 g. of ruthenium oxide catalyst. Uptake of the theoretical amount of hydrogen required 6.5 hr. After filtration of the catalyst the solvent was stripped at reduced pressure and the residue was suspended in 250 ml. of water. Sufficient concentrated hydrochloric acid was added to make the solution acid and this was filtered to remove some colloidal catalyst. The filtrate was made basic with 6*N* sodium hydroxide and the product was extracted with chloroform to yield 185.5 g. (71.6%) of a crystalline solid. The crude base was converted to the *hydrochloride:* A 5.0-g. sample of the base in 20 ml. of absolute ethanol was treated with 1 equivalent of hydrogen chloride in 2-propanol (0.25 g./ml.) and the salt was crystallized by addition of anhydrous ether. Recrystallization from ethanol and ether gave the product as a white crystalline solid, m.p. 218–219°.

Anal. Calcd. for $C_9H_{20}ClNO$: N, 7.23; Cl, 18.31. Found: N, 7.20; Cl, 18.14.

General procedure for the preparation of 4-methyl-5-substituted oxazolidines. To a suspension of 0.1 mole of the appropriate norephedrine in 50 ml. of water in a separatory funnel is added 0.105 mole of 36% aqueous formaldehyde and the mixture is shaken vigorously for 5–10 min. The product is extracted with several portions of chloroform and the extracts are dried over anhydrous sodium sulfate. Evaporation of solvent gives as a residue the crude oxazolidine. The *hydrochloride* can be prepared by solution of the base in absolute ethanol and conversion to the salt by addition of one equivalent of hydrogen chloride in 2-propanol. The product is crystallized by addition of anhydrous ether and is recrystallized from ethanol and ether. In some cases the products were not fully characterized but were used as intermediates in the crude form.

A. 4-Methyl-5-phenyloxazolidine. The various isomers were prepared by the above procedure in yields varying between 89 and 99%.

(*1*) *From d,l-norephedrine.* The product was a colorless oil.

Anal. Calcd. for $C_{10}H_{13}NO$: N, 8.58. Found: N, 8.41. Hydrochloride salt, m.p. 143–148°.

Anal. Calcd. for $C_{10}H_{14}ClNO$: N, 7.02; Cl, 17.76. Found: N, 7.04; Cl, 17.80.

(*2*) *From d,l-norpseudoephedrine.* The product was a pale green oil.

(*3*) *From d-norephedrine.* The product was a colorless oil, α_D +17.9°; hydrochloride salt, m.p. 170–172° and α_D +47.5°.

Anal. Calcd. for $C_{10}H_{14}ClNO$: N, 7.02. Found: N, 7.33.

(*4*) *From l-norephedrine.* The product was a colorless oil, α_D −16.9°.

(*5*) *From l-norpseudoephedrine.* The product was a colorless oil, α_D −59.7°.

B. 4-Methyl-5-cyclohexyloxazolidine was prepared by the general procedure above giving a near quantitative yield of the product; hydrochloride salt, m.p. 137.5–140°.

Anal. Calcd. for $C_{10}H_{20}ClNO$: C, 58.38; H, 9.80; N, 6.81; Cl, 17.24. Found: C, 58.28; H, 9.58; N, 6.43; Cl, 16.86.

C. 4-Methyl-5-p-chlorophenyloxazolidine was prepared from *p*-chloronorephedrine[9,16] by the above general procedure, giving a near quantitative yield of the oxazolidine.

D. 4-Methyl-5-p-methoxyphenyloxazolidine was prepared from *p*-methoxynorephedrine[10] by the above general procedure in 97% yield. The product, a yellow oil, was crystallized from ethanol to yield a white solid, m.p. 106–110°.

Anal. Calcd. for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.83; N, 7.25. Found: C, 68.65; H, 7.87; N, 7.71.

General procedure for the preparation of 3-imidomethyl-4-methyl-5-substituted oxazolidines. To a solution of 0.03 mole of the appropriate 3-unsubstituted oxazolidine in 25–50 ml. of absolute ethanol is added 0.0306 mole of the desired imide and the mixture is warmed to give a clear solution. To this is added 0.06 mole of 36% aqueous formaldehyde and the resulting solution is heated for 15 min. at the boiling point of ethanol. The hot solution is filtered and the product crystallizes on cooling in an ice bath, in some cases addition of water to turbidity being necessary. Recrystallization from ethanol or ethanol and water affords the pure products. Compounds VII to XXXV were prepared in this manner and the physical properties and analyses are given in Tables I to VII.

A. 3-Succinimidomethyl-4-methyl-5-phenyloxazolidine from l-norpseudoephedrine (XXXVI). This imidomethyloxazolidine was prepared by the above procedure using 4.89 g.

(16) W. H. Hartung, J. C. Munch, and F. S. Crossley, *J. Am. Chem. Soc.*, **57**, 1091 (1935).

(0.03 mole) of 4-methyl-5-phenyloxazolidine (from *l*-norpseudoephedrine), 3.02 g. (0.0306 mole) of succinimide, 5.0 g. (0.06 mole) of 36% aqueous formaldehyde, and 35 ml. of absolute ethanol. Crystallization from absolute ethanol gave the product as a white crystalline solid, m.p. 74–77.5° and α_D −57.6°.

Anal. Calcd. for $C_{15}H_{18}N_2O_3$: C, 65.67; H, 6.61; N, 10.22. Found: C, 65.99; H, 6.56; N, 10.18.

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CHICAGO 80, ILL.

[CONTRIBUTION FROM THE RADIUM INSTITUTE, UNIVERSITY OF PARIS]

Some Reactions of 5H-Benzo[b]carbazole

PHILIPPE MABILLE* AND N. P. BUU-HOÏ

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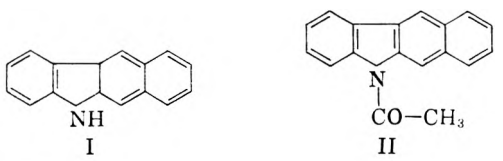
Chrysene obtained from commercial sources, even purified by recrystallization, has been found to contain from 10 to 12% 5H-benzo[b]carbazole. This heterocycle, especially in dilution with chrysene, readily undergoes Friedel-Crafts diacylations with aliphatic and aromatic acid chlorides.

In the course of an investigation on potential antileukemic agents derived from chrysene,[1] large quantities of chrysene were submitted to various chemical reactions, especially Friedel-Crafts acylations. The product used was commercial chrysene purified by recrystallization from toluene and treated with maleic anhydride to remove naphthacene, and was thus obtained as a colorless material having the melting point indicated in the literature. Friedel-Crafts acetylation of this substance yielded, as reported earlier,[1a] 6-acetylchrysene. It is now shown that it is possible to isolate in sizable amounts, from the mother liquors of this ketone, a new compound containing nitrogen, whose composition corresponds to the formula $C_{20}H_{15}NO_2$; it was therefore suspected to arise from a nitrogen-containing impurity that must have been present in appreciable quantities in the starting chrysene. Such an impurity could be one of the benzocarbazoles known to exist in coal tar,[2] for instance, 5H-benzo[b]carbazole (I). Should this be so, the compound $C_{20}H_{15}NO_2$ would be a product of Friedel-Crafts diacetylation of I. Indeed, the same compound was obtained, although in very low yield, along with the known 5-acetyl-5H-benzo[b]carbazole (II), when 5H-benzo[b]carbazole was submitted to acylation under similar conditions. That the compound $C_{20}H_{15}NO_2$ was a diketone, *i.e.*, that the —NH— group was not acetylated, was proven by its ready conversion into a diethyl-5H-benzo[b]-carbazole by means of a Wolff-Kishner reaction. The ultraviolet spectrum of this reduction product closely resembles that of 5H-benzo[b]carbazole itself (see Fig. 1).



I II

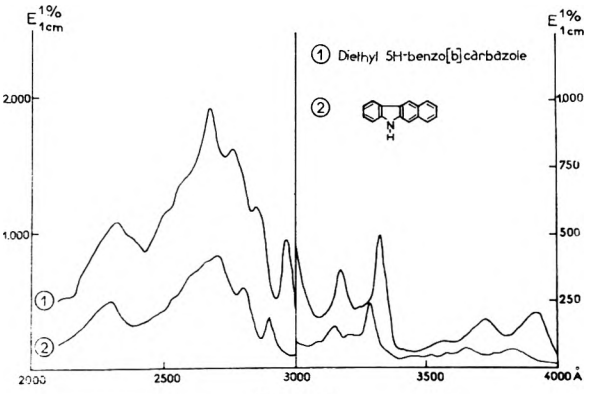


Figure 1

As so little is known of the chemistry of 5H-benzo[b]carbazole, the sites occupied by the substituents in the molecule of its diacetyl compound could not be established, but in view of the rules governing substitution in carbazole itself,[3] one of

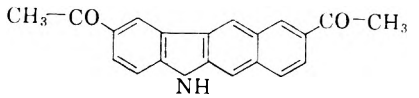
(*) Present address: Institut National d'Hygiène, 21 rue de l'Ecole de Medecine, Paris, France.

(1) (a) P. Mabille and N. P. Buu-Hoï, *J. Org. Chem.*, **25**, 216 (1960). (b) P. Mabille and N. P. Buu-Hoï, *J. Org. Chem.*, **25**, 1092 (1960). (c) P. Mabille and N. P. Buu-Hoï, *J. Org. Chem.*, **25**, 1094 (1960).

(2) S. Kikkawa, *J. Chem. Soc. Japan (Ind. Chem. Section)*, **54**, 631 (1951).

(3) For a review of this subject, see N. P. Buu-Hoï and R. Royer, *Rec. trav. chim.*, 66, 533 (1947).

the acetyl groups could perhaps be assumed to occupy position 2; the other substituent might be placed either in position 6 or in position 9 (as, for instance, in Formula III). It is interesting to note



III

that the yield of the diacetyl compound was considerably higher when the reaction was performed with 5H-benzo[b]carbazole diluted in chrysene (shown by nitrogen determinations to contain 10 to 12% of I) than when the heterocycle was used in the pure state.

In the benzoylation of chrysene which, as is shown, was heavily polluted with I, an x,y-dibenzoyl-5H-benzo[b]carbazole could be isolated from the mother liquors of crystallization of 6-benzoylchrysene.[1b] This diketone underwent Wolff-Kishner reduction to x,y-dibenzyl-5H-benzo[b]carbazole. Similarly, an x,y-di-(*o*-toluoyl)-5H-benzo[b]-carbazole and an x,y-di(2,4-dimethylbenzoyl)-5H-benzo[b]carbazole could be isolated from the mother liquors of crystallization of 6-(*o*-toluoyl)- and 6-(2,4-dimethylbenzoyl)-chrysene, respectively. The first of these two could be reduced to x,y-di(*o*-methylbenzyl)-5H-benzo[b]carbazole.

Chrysene could be freed of 5H-benzo[b]carbazole by treatment with acetic anhydride in the presence of zinc chloride, which converted the impurity into its *N*-acetyl derivative (II), a compound more soluble in acetic acid than chrysene.

EXPERIMENTAL

The chrysene used in this work was prepared by purification of commercial chrysene, m.p. 252°, by refluxing its toluene solution with maleic anhydride, removal of the adduct of maleic anhydride and naphthacene by alkaline treatment, and crystallization from toluene. The chrysene thus purified melted at 256–258° and was practically colorless, but its solutions in sulfuric acid showed a slight yellow halochromism. Its nitrogen content was 0.77%, which corresponds to *circa* 12% of 5H-benzo[b]carbazole.

x,y-Diacetyl-5H-benzo[b]carbazole. The acetylation of 100 g. of the above chrysene with acetyl chloride, performed in methylene chloride as already reported,[1a] afforded 92 g. of 6-acetylchrysene after recrystallization from acetone. Concentration of the mother liquors of this operation furnished 9 g. of a yellow, crystalline precipitate, m.p. 185–188°, which on recrystallization from 300 ml. of acetone afforded 6 g. of short, golden yellow needles, m.p. 189°. This compound gave an orange-yellow halochromism in sulfuric acid; its solutions in sulfuric acid with traces of nitric acid gave a green coloration characteristic of carbazole derivatives.

Anal. Calcd. for $C_{20}H_{15}NO_2$: C, 79.7; H, 5.0; N, 4.7; O, 10.6. Found: C, 79.9; H, 5.1; N, 4.8; O, 10.8.

Acetylation of pure 5H-benzo[b]carbazole. To a stirred solution of 4 g. of aluminum chloride in 100 ml. of anhydrous methylene chloride containing 5 ml. of acetyl chloride, a suspension of 5 g. of 5H-benzo[b]carbazole in 70 ml. of methylene chloride was added portionwise. The brown mixture was left to stand at room temperature for 3 hr., then refluxed for 3 hr., and finally left again to stand for 12 hr. at room temperature. After decomposition with ice and hydrochloric acid, methylene chloride was added and the organic layer washed with 5% aqueous sodium hydroxide, then with water, and dried over sodium sulfate. The resinous brown mass remaining after evaporation of the solvent was taken up in ethanol (charcoal), and after standing for several days in the refrigerator, it formed a pale yellow, crystalline precipitate, m.p. 100–110°. Fractional crystallization of this from acetone furnished 0.5 g. of x,y-diacetyl-5H-benzo[b]carbazole, m.p. 189–190°, showing no depression of melting point when mixed with a sample prepared as above. Evaporation of the mother liquors left a residue which was extracted with hexane; concentration of the hexane solution afforded 0.5 g. of *5-acetyl-5H-benzo[b]carbazole* (II), which crystallized from ethanol in two forms, either colorless leaflets, m.p. 117–118°, or colorless needles, m.p. 120°. The literature,[4] gives m.p. 117° and 121°, respectively.

x,y-Diethyl-5H-benzo[b]carbazole. A mixture of 1.4 g. of the diketone, 2 g. of 98% hydrazine hydrate, and 30 ml. of diethylene glycol was refluxed for 9 hr. with 1.5 g. of potassium hydroxide. After cooling, dilute hydrochloric acid was added, and the precipitate was collected. Crystallization first from hexane, then from ethanol, yielded 0.7 g. of almost colorless needles, m.p. 129°. Sulfuric acid produced a brownish halochromism.

Anal. Calcd. for $C_{20}H_{19}N$: C, 87.9; H, 7.0. Found: C, 87.9; H, 7.3.

x,y-Dibenzoyl-5H-benzo[b]carbazole. Benzoylation of chrysene was effected in the usual way,[1b] and the mother liquors from the preparation of 6-benzoylchrysene were evaporated, leaving 5 g. of a solid residue. This was treated with hot carbon tetrachloride, leaving 1 g. of undissolved material, which on recrystallization from acetic acid afforded silky yellow needles, m.p. 232°, giving a blood-red halochromism in sulfuric acid.

Anal. Calcd. for $C_{30}H_{19}NO_2$: C, 84.7; H, 4.5; N, 3.3; O, 7.5. Found: C, 84.7; H, 4.8; N, 3.5; O, 7.2.

x,y-Dibenzyl-5H-benzo[b]carbazole. One gram of the foregoing diketone was reduced with 1.5 g. of hydrazine hydrate and 1 g. of potassium hydroxide in 25 ml. of diethylene glycol as above. The reaction product crystallized from a mixture of benzene and ethanol in fine colorless prisms (0.5 g.), m.p. 191–192°. Its solutions in sulfuric acid were brownish.

Anal. Calcd. for $C_{30}H_{23}N$: C, 90.7; H, 5.8; N, 3.5. Found: C, 90.4; H, 5.7; N, 3.8.

x,y-Di-(o-toluoyl)-5H-benzo[b]carbazole. This compound was obtained as a by-product in the preparation of 6-(*o*-toluoyl)chrysene,[1c] from which it could easily be separated because of its greater solubility in carbon tetrachloride. Recrystallization from acetic acid afforded golden-yellow needles, m.p. 249°, giving an orange-red halochromism in sulfuric acid; yield, 1.5 g. (from 22.8 g. of chrysene).

Anal. Calcd. for $C_{32}H_{23}NO_2$: C, 84.7; H, 5.1; O, 7.1. Found: C, 85.0; H, 5.3; O, 7.3.

x,y-Di-(o-methylbenzyl)-5H-benzo[b]carbazole was obtained by reduction of 1 g. of the foregoing ketone with 1.5 g. of hydrazine hydrate and 1 g. of potassium hydroxide in 35 ml. of diethylene glycol; the reaction was considerably slower than in the previous cases, and the mixture had to be refluxed for 12 hr. The product crystallized from acetic acid in almost colorless needles (0.7 g.), m.p. 236°.

Anal. Calcd. for $C_{32}H_{29}N$: C, 89.9; H, 6.8; N, 3.3. Found: C, 90.0; H, 6.4; N, 3.3.

x,y-Di-(2,4-dimethylbenzoyl)-5H-benzo[b]carbazole. Obtained from the mother liquors of crystallization of 6-(2,4-dimethylbenzoyl)chrysene,[1c] this diketone crystallized from acetic acid or acetone in shiny yellow needles, m.p. 222°, giving an orange halochromism in sulfuric acid; yield, 0.2 g. (from 22.8 g. of chrysene).

Anal. Calcd. for $C_{34}H_{27}NO_2$: C, 84.8; H, 5.7; O, 6.6. Found: C, 84.8; H, 5.7; O, 6.7.

(4) F. Kehrmann, A. Oulévay, and F. Régis, *Ber.*, 46, 3713 (1913).

Separation of 5H-benzo[b]carbazole from chrysene. A mixture of 50 g. of commercial chrysene purified as described above, 500 ml. of acetic anhydride, 2 g. of finely powdered anhydrous zinc chloride, and 2500 ml. of acetic acid was gently refluxed for 1 hr. After cooling, the precipitate of pure chrysene (42 g.) was filtered, washed with acetic acid, and recrystallized from toluene. A sample of this hydrocarbon gave no coloration in sulfuric acid. Dilution of the filtrate with water to a volume of 6000 ml. produced a precipitation of 4 g. of less pure chrysene. Dilution of the second filtrate to a volume of 10 l. yielded 4 g. of 5-acetyl-5H-benzo[b]carbazole, from which the nonacetylated heterocycle could be recovered by treatment with potassium hydroxide in ethanol. 5H-benzo[b]carbazole gave a brown-yellow halochromism in sulfuric acid.

Acknowledgment. This work was carried out with the financial aid of The Anna Fuller Fund, New Haven, Connecticut; the authors express their gratitude to Professor William U. Gardner and the Trustees of the Fund.

PARIS (V^e^), FRANCE

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF IRWIN, NEISLER & CO.]

Pyridylethylation of Skatole, Benzotriazole, and Benzimidazole

ALLAN P. GRAY, HAROLD KRAUS, AND DONALD E. HEITMEIER

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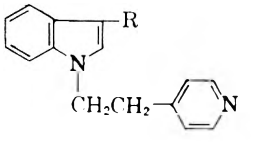
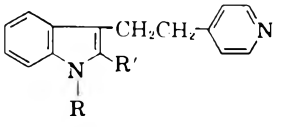
Skatole, 2-methylindole, benzimidazole, and benzotriazole have been pyridylethylated. Under alkaline conditions skatole yielded the 1-substituted derivative, 4-(3-methyl-1-indolylethyl)pyridine. The same product was obtained, in poor yield, when the reaction was carried out in boiling glacial acetic acid. Base catalyzed pyridylethylations of benzotriazole afforded mixtures of two, separable products. Ultraviolet spectral evidence indicates these to be the corresponding 1- and 2-substituted benzotriazole derivatives.

An earlier report[1] from these laboratories was concerned with the pyridylethylation of indole, *N* substitued indoles, and indene. The finding that certain of the derived indolylethylpyridines displayed an interestingly selective spectrum of central depressant effects[2] has stimulated further work in this area. The present paper deals with some aspects of this work, and in particular examines the course of the pyridylethylation reaction with related ring systems.

It is well known that indoles undergo substitution by electrophilic reagents preferentially at the 3-position—no doubt owing to the necessary participation of quinoid forms in the α-substitution process—but the orientation of further substituents is not so clear. Thus, apparently rate control in the Mannich reaction under either acidic or basic conditions results in the order of substitution, 3, *N*, 2[3]—except when stability of the product (as in the intramolecular Mannich-type cyclizations of tryptamines to tetrahydro-β-carbolines) overridingly directs reaction to the 2-position. On the other hand, presumably equilibrium control in Erlich-like reactions with aldehydes under more strongly acid conditions causes substitution to occur at the 3- and then the 2-position, the nitrogen being apparently unaffected.[4] Perhaps more pertinent is the report that skatole reacted with methyl vinyl ketone in a mixture of acetic acid and acetic anhydride to give (in poor yield) the more stable 2-substituted adduct.[5] It was, therefore, of interest to examine the pyridylethylation of skatole. Under alkaline conditions (sodium ethoxide in ethanol) skatole reacted with 4-vinylpyridine to yield 4-(3-methyl-1-indolylethyl)pyridine (I). The structural assignment is unequivocal in view of the re-



I. R = CH_3



II. R = H, R′ = CH_3
III. R = C_2H_5, R′ = H

action of indole under the same conditions to give I(R = H)[1] and of analogous experience with base catalyzed cyanoethylation (see references cited[1]). It would appear that the indole anion is involved in the rate determining step of these base catalyzed reactions. More interesting was the finding that the acid, boiling glacial acetic acid, catalyzed reaction of skatole with 4-vinylpyridine also afforded I, although in poor yield and accompanied by large

(1) A. P. Gray and W. L. Archer, *J. Am. Chem. Soc.*, **79**, 3554 (1957).

(2) J. H. Mirsky, H. D. White, and T. B. O'Dell, *J. Pharmacol. Exptl. Therap.*, **125**, 122 (1959).

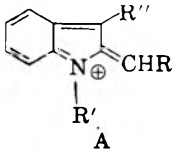
(3) (a) S. Swaminathan and S. Ranganathan, *J. Org. Chem.*, **22**, 70 (1957); *J. Org. Chem.*, **23**, 707 (1958); (b) J. Thesing and P. Binger, *Chem. Ber.*, **90**, 1419 (1957); (c) F. Troxler and A. Hofmann, *Helv. Chim. Acta*, **40**, 1706 (1957).

(4) (a) H. v. Dobeneck and G. Maresch, *Hoppe-Seyler's Z. physiol. Chem.*, **289**, 271 (1952) [*Chem. Abstr.*, **49**, 5432 (1955)]; (b) H. v. Dobeneck and J. Maas, *Chem. Ber.*, **87**, 455 (1954); (c) A. Treibs and E. Hermann, *Hoppe-Seyler's Z. physiol. Chem.*, **299**, 168 (1955) [*Chem. Abstr.*, **50**, 943 (1956)]; (d) W. E. Noland and D. N. Robinson, *Tetrahedron*, **3**, 68 (1958).

(5) J. Szmuszkovicz, *J. Am. Chem. Soc.*, **79**, 2819 (1957).

quantities of tarry, polymeric materials. The fact that the 1-substituted product is obtained under acidic or basic conditions suggests that pyridylethylation, like the Mannich reaction, is rate controlled. It was not ascertained whether or not more strongly acidic conditions (*e.g.* an acetic acid–acetic anhydride mixture) could alter the course of the reaction.

It should be mentioned that I gave an immediate, deep purple color in the Erlich test with *p*-dimethylaminobenzaldehyde, thus demonstrating that the 2-position was indeed unsubstituted.[6] 4-(1-Methyl-3-indolylethyl)pyridine (III. R= CH_3)[1] also gave a strong positive Erlich test whereas the 2,3-disubstituted analog, II, obtained by the pyridylethylation of 2-methylindole in boiling acetic acid, gave a negative test. On this basis, recent reports that 1,3-disubstituted indoles do not give the Erlich test[3a,7] require re-evaluation. Certainly, there would seem to be no *a priori* reason why a 1,3-disubstituted indole should not form an Erlich dye having the structure A. Inas-

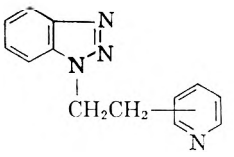


A

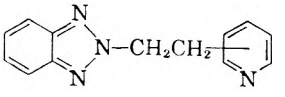
much as there also seems to be no reason to doubt the structures assigned by the earlier workers to the compounds tested (ind-*N*-methyltryptophan[7] and its 1,3-reversed isomer[3a]), the negative tests may be ascribable to features peculiar to the substituents themselves. That, for example, cationic groups close to the indole nucleus are capable of inhibiting the reaction is suggested by the observation that gramine gives a negative test.

Benzotriazole offers an intriguing and closely related problem pertaining to the direction of substitution. It has been shown that alkylation of benzotriazole under alkaline conditions in alcohol solution yields both the 1- and 2-substituted benzotriazole derivatives.[8] The isomeric products have been found to be readily distinguishable on the basis of their ultraviolet absorption spectra in alcohol solution.[8b,c] The 1-substituted derivative is generally formed in somewhat larger amounts.[8a,b] Although one cannot base too much on simple yield data, the ratio of 1- to 2-isomer appears to vary directly with the reactivity of the alkylating agent; *e.g.*, based on the *per cent* yields reported by Krollpfeiffer, *et al.*, pertinent ratios are as follows: for benzyl chloride, 2.8; for methyl iodide, 1.7; for ethyl bromide, 1.1. Wiley and co-workers[9] have extensively studied the base catalyzed addition of benzotriazole and benz-substituted benzotriazoles to α,β-unsaturated carbonyl systems (acrylic acid, acrylonitrile, benzalacetophenone, *etc.*). In the absence of solvent, these conjugated systems were reported to react exclusively at the 1-position of benzotriazole itself,[9a] although presumably for steric reasons, just as exclusively at the 2-position of 4,7-disubstituted (chlorine, bromine) benzotriazoles.[9b,c]

In light of the foregoing it is particularly striking that pyridylethylation of the (unsubstituted) benzotriazole in alcohol solution with a few drops of a quaternary ammonium methoxide as base catalyst provided a mixture of both the 1- and 2-substituted products in which, on the basis of isolated *per cent* yields, the 2-isomer predominated. Thus, with 4-vinylpyridine the ratio of the amounts of 1-substituted (IV) to 2-substituted (V) benzotriazole derivative isolated was 0.65; with 2-vinylpyridine the corresponding ratio of VI to VII was 0.55. The isomeric products were conveniently



IV. 4-Pyridyl



V. 4-Pyridyl

VI. 2-Pyridyl

VII. 2-Pyridyl

separated by taking advantage of the circumstance that the 2-substituted benzotriazoles were quite soluble and the 1-substituted practically insoluble in petroleum ether (b.p. 60–70°). This accords with the reported greater solubility of the 2-isomers in nonpolar solvents.[8] An examination of the ultraviolet absorption spectra provided a firm basis for the structural assignments, IV and VI, showing the two maxima at *ca.* 255 and 280 mμ which are diagnostic for 1-substitution and V and VII the broad, single maximum at *ca.* 275 mμ characteristic of 2-substituted benzotriazoles[8b,c] (*cf.* Table I). It is apparent from Table I that absorption by the pyridine nucleus does not prevent identification of the isomers.

Since both the alkylation and conjugate addition reactions are effected under alkaline conditions, it seems reasonable to implicate the benzotriazole anion in the rate determining step. If this be so, note should be taken of the fact that in the anion the nitrogen atoms in the 1- and 3-positions are indistinguishable. Therefore, on a purely statistical

(6) See F. Feigl, *Spot Tests*, Vol. II, 4th English Edition, Elsevier, Amsterdam, 1954, pp. 198–199; M. Strell, A. Zocher, and E. Kopp, *Chem. Ber.*, **90**, 1798 (1957) and references cited therein.

(7) J. Giral and J. Laguna, *Ciencia* (*Mex.*), **10**, 83 (1950) [*Chem. Abstr.*, **44**, 10605 (1950)].

(8)(a) F. Krollpfeiffer, A. Rosenberg, and C. Mühlhausen, *Ann.*, **515**, 124 (1935); (b) F. Krollpfeiffer, H. Pötz, and A. Rosenberg, *Ber.*, **71**, 596 (1938); (c) H. Specker and H. Gawrosch, *Ber.*, **75**, 1338 (1942).

(9)(a) R. H. Wiley, N. R. Smith, D. M. Johnson, and J. Moffat, *J. Am. Chem. Soc.*, **76**, 4933 (1954); (b) R. H. Wiley, K. F. Hussung, and J. Moffat, *J. Am. Chem. Soc.*, **77**, 5105 (1955); (c) R. H. Wiley and K. F. Hussung, *J. Am. Chem. Soc.*, **79**, 4395 (1957).

TABLE I

ULTRAVIOLET ABSORPTION OF BENZOTRIAZOLE DERIVATIVES[a]

Compound	λ_{max}, mμ	log ε
IV.HCl	257	3.93
	280	3.65
V.HCl	278	4.04
VI.HCl	260	4.00
	280 (shoulder)	3.68
VII.HCl	278	4.09
1-Methylbenzotriazole[b]	255	3.81
	283	3.68
2-Methylbenzotriazole[b]	275	3.90
Pyridine.HCl	255	3.72

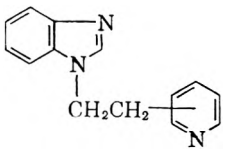
[a] Spectra determined on the hydrochloride salts in 95% ethanol using a Beckman Model DU spectrophotometer. [b] This data from Specker and Gawrosch[8c]; solvent: methanol.

basis one would expect the ratio of 1- to 2-substituted product to be 2. This suggests that alkylation with methyl iodide and ethyl bromide (but not benzyl chloride) as well as pyridylethylation occurs more readily at the 2- than at the 1-position.

In attempting to analyse these results it should be noted that the ultraviolet absorption spectrum of benzotriazole closely resembles that of a 1-substituted derivative whereas the spectrum of the benzotriazole anion just as closely resembles that of a 2-substituted isomer.[8b,c] It might then be inferred that the 1-substituted products are more stable than the 2, but that the electronic charge in the benzotriazole anion resides largely on the 2-nitrogen. On this basis the relative yields obtained in the irreversible (under the conditions) alkylation reactions[8a,b] seem at variance with the illuminating studies made by Kornblum, *et al.*[10] pertaining to the alkylation of ambident anions since these studies would lead to the prediction that the more an alkyl halide tended to react by an S_N1-like process the more it should effect 2-substitution. On the other hand, the reversible conjugate additions studied here and by Wiley and associates[9] have given results which at least are in accord with theory in that certainly under alkaline conditions the systems studied by the earlier workers would be more reactive than the vinylpyridines and would therefore be expected to yield a greater proportion of the more stable, 1-substituted product.[11] It is apparent, in any case, that the energetics of 1- *vs.* 2-substitution are closely balanced and that only slight changes in the nature of the reagents and, no doubt, conditions can markedly alter the course of the reaction.

The structure of the quite remarkably stable 2-substituted benzotriazoles has been the object of much study.[8,12] Their properties (ultraviolet and infrared[13] spectra, weak basicity, high solubility in nonpolar solvents and low melting point) can best be described in terms of a resonance hybrid, of which, in the absence of evidence to the contrary, the conventional quinoid canonical form (*cf.* V) is adopted here.

Reaction of benzimidazole with 2- or 4-vinylpyridine in the presence of base afforded in each case a single isolable product. Inasmuch as the alkylation and base catalyzed cyanoethylation of benzimidazole straightforwardly yield *N*-substituted derivatives,[14] there seems no reason to question formulation of the pyridylethylated products as VIII and IX. It is worth noting that although the anions



VIII. 4-Pyridyl
IX. 2-Pyridyl

of benzotriazole and of indazole[15] can be alkylated at the 2- as well as the 1-position, the anions of indole and of benzimidazole give no evidence of 2-substitution. Without doubt this is a reflection of the relative abilities of carbon and nitrogen to bear a negative charge and/or to act as nucleophilic reagents.

Structure-activity relationships. Many of these compounds display central depressant properties. The most striking, semiquantitatively measurable, pharmacological finding with the 4-(3-indolylethyl)pyridines is that these compounds, tested in mice, strongly inhibit amphetamine-stimulated motor activity at doses which have little or no effect on normal motor activity.[2] Comparison of the efficacies of close relatives has revealed some intriguingly specific structural requirements for this selectivity of biological action. This discussion will, therefore, be confined to a comparison of results obtained in these mouse tests.

The 4-(1-substituted 3-indolylethyl)pyridines (III, R = CH_3,[1] C_2H_5, $C_6H_5CH_2$[1]; R′ = H) are all about equally effective on stimulated and ineffective on normal activity. It would therefore appear that lipophilic balance, at least within this range, is not a determining factor. On the other

(10) N. Kornblum, R. A. Smiley, R. K. Blackwood, and D. C. Iffland, *J. Am. Chem. Soc.*, **77**, 6269 (1955) and preceding papers.

(11) The conditions (no solvent) used by Wiley, *et al.* would also favor product control.

(12)(a) K. v. Auwers, *Ber.*, **71**, 604 (1938); (b) see also D. D. M. Casoni, A. Mangini, R. Passerini, and C. Zauli, *Gazz. chim. ital.*, **88**, 977 (1958) [*Chem. Abstr.*, **53**, 18945 (1959)].

(13) Sadtler Laboratories, Philadelphia, Pa.

(14)(a) I. G. Farbenind. A. G., British Patent **457,621** (1936) [*Chem. Abstr.*, **31**, 3068 (1937)]; (b) see E. S. Schipper and A. R. Day in Elderfield, *Heterocyclic Compounds*, Vol. V, John Wiley and Sons, Inc., New York, 1957, p. 269.

(15) For references see R. C. Elderfield, *Heterocyclic Compounds*, Vol. V, John Wiley and Sons, Inc., New York, 1957, pp. 187–9.

hand, molecular geometry has a marked influence in that rearrangement of the indole substituents as in I and II sharply reduces the selectivity of the depressant action. 4-Skatylpyridine (X) is essentially without effect. In the indole series then, the biological properties under discussion seem to be distinctively provided by a III-type structure.

The considerably more polar benzimidazole derivatives (VIII, IX) are only weakly depressant on motor activity. The benzotriazole derivatives, of intermediate polarity, show intermediate inhibitory abilities. In direct contrast to the indole series, however, in the benzotriazole group it is the 2-pyridyl isomers (VI, VII) that display the selective antagonism to stimulated activity, the 4-pyridyl isomers (IV, V) being weaker and less discriminating in action. It apparently makes no difference, insofar as these biological properties are concerned, whether the benzotriazole nucleus is substituted at the 1- or 2-position. Of all the close analogs of III, the most potent depressants are 2- and 4-(3-indenylethyl)pyridine.[1] Both indene derivatives, however, are more general in their action, being almost as effective against normal as against stimulated activity. The inertness of 2-(1-naphthylethyl)pyridine[16] taken with the earlier indicated specificity of the 1,3-substituted indole structure makes it tempting to speculate as to the possible involvement of the unsaturated 5-membered ring in eliciting the depressant effects. In particular, the indolyl and indenyl derivatives could enter into reaction with oxidative enzyme systems.

EXPERIMENTAL[17]

The pyridylethylation of indoles. These were effected essentially as previously described for the preparation of corresponding derivatives.[1]

A. *4-(2-Methyl-3-indolylethyl)pyridine* (II). 2-Methylindole was treated with 4-vinylpyridine in boiling glacial acetic acid to give a 54% yield of II, m.p. 153–154° after recrystallization from isopropyl alcohol.

Anal. Calcd. for $C_{16}H_{16}N_2$:N (basic), 5.92. Found: N (basic), 5.77.

The *hydrochloride salt* showed m.p. 242–243° after recrystallization from ethanol-methanol.

Anal. Calcd. for $C_{16}H_{17}ClN_2$: C, 70.46; H, 6.28; Cl, 13.00. Found: C, 69.90; H, 6.27; Cl (ionic), 12.97.

B. *4-(1-Ethyl-3-indolylethyl)pyridine* (III). The reaction of 1-ethylindole [b.p. 82–85° (0.7 mm.), n_D^{26} 1.5889][18] with 4-vinylpyridine in boiling glacial acetic acid afforded III, m.p. 47–50° after recrystallization from isopropyl alcohol.

Anal. Calcd. for $C_{17}H_{18}N_2$: N (basic), 5.59. Found: N (basic), 5.66.

The *hydrochloride salt* formed pale yellow crystals, m.p. 167–169°, from isopropyl alcohol–ether.

Anal. Calcd. for $C_{17}H_{19}ClN_2$: C, 71.18; H, 6.67; Cl, 12.36. Found: C, 71.26; H, 6.36; Cl (ionic), 11.99.

C. *4-(3-Methyl-1-indolylethyl)pyridine* (I). 1. *With base catalysis.* A mixture of 13.1 g. (0.1 mole) of skatole, 22.0 g. (0.21 mole) of freshly distilled 4-vinylpyridine, 0.5 g. of copper sulfate, and 50 ml. of ethanol containing 0.5 g. of sodium was heated in a sealed tube at 150° (oil-bath) for 10 hr. The cooled reaction mixture, diluted with toluene and filtered, was extracted with dilute hydrochloric acid. The acid solution was made basic and extracted with ether. Treatment of the ice-cold, dried ether solution with ethereal hydrogen chloride afforded a yellow precipitate which was recrystallized three times from isopropyl alcohol and once from ethanol to yield 9.0 g. (38%) of the *hydrochloride salt* of I in the form of yellow plates, m.p. 211–212°.

Anal. Calcd. for $C_{16}H_{17}ClN_2$: C, 70.46; H, 6.28; Cl, 13.00. Found: C, 70.57; H, 6.18; Cl (ionic), 13.04.

Decomposition of the hydrochloride salt of I gave the base as an oil which could not be crystallized.

The salt gave a positive color test with an acid solution of *p*-dimethylaminobenzaldehyde, indicating that the indole nucleus was not substituted at the α position. 4-(1-Methyl-3-indolylethyl)pyridine[1] also gave a strong positive test. In comparison II gave a negative test.

2. *In acetic acid.* To a solution of 12.0 g. (0.09 mole) of skatole in 100 ml. of boiling glacial acetic acid was added, dropwise with stirring, 11.5 g. (0.11 mole) of freshly distilled 4-vinylpyridine containing 0.5 g. of hydroquinone. Heating under reflux was continued for 32 hr. Removal of the solvent *in vacuo* left a dark, tarry residue which was extracted with dilute hydrochloric acid. The acid solution was made alkaline and the precipitate exhaustively extracted with ether (considerable ether- and chloroform-insoluble, polymeric material remained). After a repetition of the acid-base extraction process, the dried ether solution was treated with ethereal hydrogen chloride in the cold. The resultant precipitate was repeatedly recrystallized from isopropyl alcohol to give 2.3 g. of material melting at 200–205°. Further recrystallization afforded I *hydrochloride*, m.p. 206–209°; a mixture with the product obtained under basic conditions showed m.p. 208–210°. The mother liquors from these recrystallizations afforded material which melted over a wide range and apparently was contaminated by vinylpyridine polymer which could not be removed.

Anal. Found: Cl (ionic), 13.04.

The pyridylethylation of benzotriazole. A. *With 4-vinylpyridine.* To a boiling solution of 40.0 g. (0.33 mole) of benzotriazole in 100 ml. of isopropyl alcohol containing 10 drops of a 40% methanolic solution of benzyltrimethylammonium methoxide was added, dropwise, 31.5 g. (0.3 mole) of undistilled 4-vinylpyridine. After being heated for 30 hr. at reflux the reaction solution was diluted with water and the precipitated oil was dissolved in ether. The ether extract was extracted with 5% hydrochloric acid, the acid extract made alkaline and extracted with ether. Drying and removal of the ether provided a residue which was extracted with hot petroleum ether (b.p. 60–70°). Upon cooling the solution deposited crystals which were twice recrystallized (with charcoal) from petroleum ether to yield 17.0 g. (25%) of colorless flakes, m.p. 92–95°. This is presumed to be *4-(2-benzotriazolylethyl)pyridine* (V).

Anal. Calcd. for $C_{13}H_{12}N_4$: N (basic), 6.25. Found: N (basic), 6.68.

V *hydrochloride* formed colorless needles from isopropyl alcohol, m.p. 197–200°.

Anal. Calcd. for $C_{13}H_{13}ClN_4$: C, 59.88; H, 5.03; Cl, 13.60. Found: C, 60.13; H, 4.74; Cl (ionic), 13.56.

The residual material which had not dissolved in petroleum ether was crystallized from benzene–petroleum ether (with charcoal) to give 11.0 g. (16% yield) of colorless crystals,

(16) A. P. Gray, W. L. Archer, E. E. Spinner, and C. J. Cavallito, *J. Am. Chem. Soc.*, **79**, 3805 (1957).

(17) Microanalyses were performed by the Clark Microanalytical Laboratories, Urbana, Ill., and by the Micro-Tech Laboratories, Skokie, Ill. Melting points are corrected for stem exposure. Basic nitrogens were determined by acetous-perchloric titration; ionic halogens by potentiometric titration with silver nitrate.

(18) Prepared by the alkylation of indole with ethyl iodide using sodamide in liquid ammonia (*cf.* ref.[1]). K. Kawasaki, *Ann. Rept. Shionogi Research Lab.*, **5**, 57 (1955), *Chem. Abstr.*, 50, 16748 (1956), gives b.p. 107–108° (7 mm.).

m.p. 100–102°. This is considered to be *4-(1-benzotriazolylethyl)pyridine* (IV). A mixture of IV and V melted at 85–93°.

Anal. Calcd. for $C_{13}H_{12}N_4$: N (basic), 6.25. Found: N (basic), 6.16.

IV *hydrochloride*, recrystallized from isopropyl alcohol, formed colorless needles, m.p. 200–202°. A mixture melting point of the hydrochloride salts of IV and V was depressed to 190–197°.

Anal. Calcd. for $C_{13}H_{13}ClN_4$: C, 59.88; H, 5.03; Cl, 13.60. Found: C, 59.91; H, 5.01; Cl (ionic), 13.50.

B. *With 2-vinylpyridine.* Under essentially the same conditions 40.0 g. of benzotriazole was allowed to react with 31.5 g. of 2-vinylpyridine. As before the initial work-up afforded an oil residue which was extracted with hot petroleum ether. Removal of the solvent *in vacuo* and distillation of the residue gave 18.1 g. (27%) of a colorless oil, b.p. 150–155° (0.6 mm.), crystallized on standing. Recrystallization from petroleum ether yielded 15.4 g., m.p. 59–62°, apparently *2-(2-benzotriazolylethyl)pyridine* (VII).

Anal. Calcd. for $C_{13}H_{12}N_4$: N (basic), 6.25. Found: N (basic), 6.27.

VII *hydrochloride*, recrystallized from isopropyl alcohol–ether, formed colorless plates, m.p. 183–185°.

Anal. Calcd. for $C_{13}H_{13}ClN_4$: C, 59.88; H, 5.03; Cl, 13.60. Found: C, 60.20; H, 5.00; Cl (ionic), 13.59.

Distillation of the residual, insoluble oil yielded 10.2 g. (15%) of (presumably) *2-(1-benzotriazoylethyl)pyridine* (VI) as a thick, colorless oil, b.p. 150–158° (0.4 mm.), which could not be crystallized.

Anal. Calcd. for $C_{13}H_{12}N_4$: N (basic), 6.25. Found: N (basic), 6.30.

VI *hydrochloride* formed colorless crystals, m.p. 161–163°, from isopropyl alcohol–ether. A mixture melting point of the hydrochloride salts of VI and VII was depressed to 148–153°.

Anal. Calcd. for $C_{13}H_{13}ClN_4$: C, 59.88; H, 5.03; Cl, 13.60. Found: C, 59.90; H, 5.00; Cl (ionic), 13.67.

The pyridylethylation of benzimidazole. A. *4-(1-Benzimidazolylethyl)pyridine* (VIII). To 23.6 g. (0.23 mole) of freshly distilled 4-vinylpyridine and 23.6 g. (0.2 mole) of benzimidazole dissolved in 200 ml. of isopropyl alcohol was added 5 ml. of Triton A-20. The solution was heated at reflux for 20 hr. and evaporated to dryness *in vacuo*. Hydrogen chloride gas was bubbled into a solution of the residue in ethanol-ether and the resultant white precipitate was recrystallized from ethanol-ether to yield 19.7 g. (33%) of VIII *dihydrochloride*, m.p. 208–211°.

Anal. Calcd. for $C_{14}H_{15}Cl_2N_3$: C, 56.76; H, 5.10; Cl, 23.94. Found: C, 56.84; H, 5.05; Cl (ionic), 23.56.

An aqueous solution of the dihydrochloride salt was made weakly basic and exhaustively extracted with chloroform. Drying and removal of the chloroform gave VIII as a green oil residue which crystallized on standing, m.p. 97–98°.

Anal. Calcd. for $C_{14}H_{13}N_3$: N (basic), 12.56. Found: N (basic), 12.25.

B. *2-(1-Benzimidazolylethyl)pyridine* (IX). A mixture of 17.7 g. (0.15 mole) of benzimidazole, 17.9 g. (0.17 mole) of 2-vinylpyridine and a few drops of a 40% methanol solution of benzyltrimethylammonium methoxide was heated in an oil-bath. After being gradually raised, the temperature of the bath was maintained at 180° for a period of 3 hr. The reaction mixture was allowed to cool and the resultant thick oil dissolved in hot benzene. The cooled benzene solution deposited 5.6 g. (32%) of recovered benzimidazole, m.p. and mixture m.p. 168–170°. Concentration of the mother liquor left a residue which was extracted with anhydrous ether. Acidification of the ether solution with ethereal hydrogen chloride and recrystallization of the precipitate from ethanol–ethyl acetate (with charcoal) afforded 10.1 g. (23% yield) of IX *dihydrochloride*, m.p. 205–207°.

Anal. Calcd. for $C_{14}H_{15}Cl_2N_3$: C, 56.76; H, 5.10; Cl, 23.94. Found: C, 56.85; H, 5.12; Cl (ionic), 23.30.

4-Skatylpyridine (X). A previous paper described the reductive alkylation of indole with pyridinecarboxaldehydes in glacial acetic acid to give the corresponding skatylpiperidines.[19] 4-Skatylpyridine was prepared by the same process except that a palladium instead of a platinum catalyst was used to make it possible to stop the reduction before hydrogenation of the pyridine ring occurred.[20]

To an ice-cold solution of 23.5 g. (0.22 mole) of 4-pyridinecarboxaldehyde in 200 ml. of glacial acetic acid was added 23.4 g. (0.2 mole) of indole. The resultant orange solution was hydrogenated over 5 g. of 10% palladium on charcoal in an Adams-Parr apparatus at 50 p.s.i. and room temperature. One equivalent of hydrogen was absorbed in 5 hr., by which time the rate of uptake had become very slow. The filtered solution was diluted with about 1 l. of water and extracted with ether. Drying and removal of the ether and recrystallization of the residue (with charcoal) from aqueous methanol yielded 14.8 g. (46% based on indole) of 4-(3,3'-diindolylmethyl)pyridine as light yellow crystals, m.p. 152–155°.[1,19]

The aqueous layer was made alkaline with solid potassium carbonate and extracted with chloroform. Drying and removal of the solvent left a dark residue which was taken up in hot benzene. The cooled benzene solution was decanted from a thick, black oil which had separated, and evaporated to dryness *in vacuo*. The residue was crystallized from aqueous methanol to give, after the removal of initial dark, oily precipitates and treatment with charcoal, 1.7 g. of X, m.p. 108–110°.

Anal. Calcd. for $C_{14}H_{12}N_2$: N (basic), 6.73. Found: N (basic), 6.81.

The *hydrochloride salt* of X, recrystallized from isopropyl alcohol–ether, melted at 194–196°.

Anal. Calcd. for $C_{14}H_{13}ClN_2$: C, 68.71; H, 5.35; Cl, 14.49. Found: C, 68.83, H, 5.46; Cl (ionic), 14.36.

4-Skatylpyridine hydrochloride (in 95% ethanol) showed absorption in the ultraviolet typical of an additive combination of the indole and pyridine chromophores: λ_{max} 223 mμ (log ϵ 4.34); λ_{max} 259 mμ (log ϵ 3.79); λ_{max} 280 mμ (log ϵ 3.81).

Acknowledgment. The authors are grateful to Dr. T. B. O'Dell and associates for unpublished biological data discussed herein, and to Mr. D. F. Cortright and Miss M. Unroe for the determinations of ionic halogens, basic nitrogens, and ultraviolet spectra.

DECATUR, ILL.

(19) A. P. Gray, *J. Org. Chem.*, **23**, 1453 (1958).

(20) This constitutes a one step synthesis of 4-skatylpyridine, albeit in low yield. Although this compound has apparently not been previously reported, 2-skatylpyridine has been obtained from a multi-step synthesis by G. R. Clemo and J. C. Seaton, *J. Chem. Soc.*, 2582 (1954).

[CONTRIBUTION FROM NITROGEN DIVISION, ALLIED CHEMICAL CORP.]

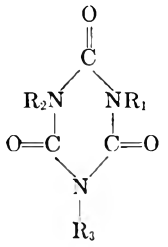
Isocyanurates. I. Some Condensation Reactions of Cyanuric Acid[1]

THOMAS C. FRAZIER, EDWIN D. LITTLE, AND BILLY E. LLOYD[2]

Received March 28, 1960

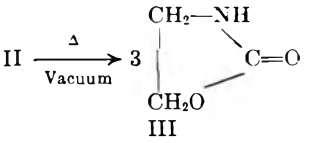
New cyanuric acid derivatives in which side chains contain functional groups have been synthesized. Specific condensations of cyanuric acid have been obtained with ethylene oxide, allyl chloride, ethyl chloroacetate, and acrylonitrile, respectively. All resulting compounds have been shown to exist in the isocyanurate form.

Three general methods are useful for the preparation of isocyanurates (derivatives of *s*-triazine-2,4,6-[1H, 3H, 5H]trione): thermal rearrangement of cyanurates,[3] trimerization of certain alkyl or aryl isocyanates,[4] and condensation of alkyl halides with certain salts of cyanuric acid.[5] Little has been done using the cyanuric acid nucleus as a site for condensation reactions where side chains containing functional groups are formed. We have found that a variety of isocyanurates can be formed under alkaline conditions.



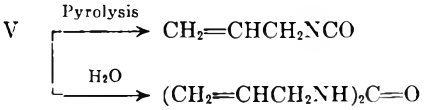
I. R_1, R_2, R_3 = —H
II. R_1, R_2, R_3 = —CH_2CH_2OH
IV. R_1 = —H; R_2, R_3 = —$CH_2CH{=}CH_2$
V. R_1, R_2, R_3 = —$CH_2CH{=}CH_2$
VI. R_1, R_2, R_3 = —$CH_2COOC_2H_5$
VII. R_1 = —H; R_2, R_3 = —CH_2CH_2CN
VIII. R_1, R_2, R_3 = —CH_2CH_2CN
IX. R_1 = —H; R_2, R_3 = —CH_2CH_2COOH
X. R_1, R_2, R_3 = —CH_2CH_2COOH
XI. R_1, R_2, R_3 = —$CH_2CH_2COOC_2H_5$
XII. R_1 = —H; R_2, R_3 = —$CH_2CH_2CH_2NH_2$
XIII. R_1, R_2 = —H; R_3 = —$CH_2CH_2CH_2NH_2$

Ethylene oxide and cyanuric acid (I) in dimethylformamide containing sodium hydroxide catalyst reacted in a 3:1 molar ratio to form tris(2-hydroxyethyl) isocyanurate (II). The isomeric tris(2-hydroxyethyl) cyanurate has been reported[6] from the transesterification of trimethyl cyanurate and ethylene glycol. The iso structure was assigned to our product on the bases of infrared peaks in the carbonyl region, hydrolysis of II to ethanolamine and vacuum pyrolysis of II to 2-oxazolidone (III). The transformation of II to



III, possibly through the hydroxyethyl isocyanate intermediate, offers a convenient synthetic route to III not involving phosgene.

Triallyl isocyanurate (V) has been prepared from the reaction of allyl chloride and potassium cyanate under pressure.[7] We have found that allyl chloride reacts easily with an aqueous solution of cyanuric acid maintained at *p*H 10–10.5 and catalyzed by a small amount of cuprous ion. Both diallyl isocyanurate (IV) and V were isolated from the reaction mixture. The assignment of the iso structure to the products was made on the basis of a comparison with an authentic sample of triallyl cyanurate,[8] which did not show infrared absorption in the carbonyl region shown by our compound. A vacuum pyrolysis of V, containing caustic, gave a small amount of allyl isocyanate. This conversion is similar to the formation of III from II. The identity of the allyl isocyanate was established by its conversion to allylurea and *N*-allyl-*N'*-phenylurea. *N*,*N'*-diallylurea was also isolated from the pyrolysis residue. A similar reaction has been observed with triethyl isocyanurate. The latter compound forms ethyl isocyanate and *N*,*N'*-diethylurea under stringent conditions.[9]



The synthesis of tris(2-carbethoxymethyl) isocyanurate (VI) from potassium cyanate and ethyl chloracetate has been reported.[10] Our attempts to repeat this work failed. Subsequently, it was found VI could be prepared in a 60% yield by heating trisodium cyanurate and ethyl chloroacetate at 150–200° for several hours. An attempt to prepare

(1) Presented before the Division of Organic Chemistry at the Southeastern Regional meeting of the American Chemical Society, Richmond, Va., November 5–7, 1959.

(2) Present address: W. R. Grace and Company, Memphis, Tenn.

(3) E. Bilmann and J. Bjerrum, *Ber.*, **50**, 506 (1917); A. Hofmann, *Ber.*, **19**, 2061 (1886).

(4) F. Gal, *Compt. rend.*, **61**, 527 (1865); A. Hofmann, *Ber.*, **18**, 765 (1885).

(5) A. Hofmann, *Ber.*, **18**, 2796 (1885); J. Ponomarew, *Ber.*, **18**, 3271 (1885); E. Fisher, *Ber.*, **30**, 2616 (1897).

(6) J. Dudley, *et al.*, *J. Am. Chem. Soc.* **73**, 2999 (1951).

(7) D. Kaiser and D. Holm-Hansen, U. S. Patent **2,536,849** (1951).

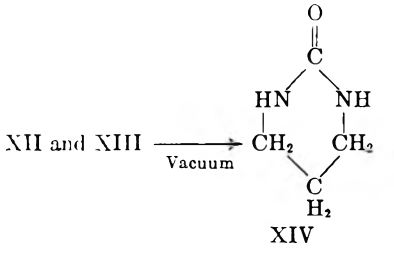
(8) Sample obtained from Monomer-Polymer, Inc.

(9) M. Nencki, *Ber.*, **9**, 1008 (1876).

(10) Ger. Patent **812,312** (1949).

this material under conditions described for triallyl isocyanurate did not yield VI. This can be explained by the rapid hydrolysis of VI to urea derivatives.

Tris(2-cyanoethyl) isocyanurate (VIII) and bis(2-cyanoethyl) isocyanurate (VII) can be prepared by allowing acrylonitrile and I to react in dimethylformamide containing a quaternary ammonium base catalyst. These new nitriles are readily hydrolyzed by aqueous mineral acid to the corresponding carboxylic acids. The triscarboxylic acid (X) is easily esterified to XI. Catalytic pressure hydrogenation of VIII in ammonia resulted in the loss of one or two of the cyanoethyl groups to give bis(3-aminopropyl) isocyanurate (XII) and mono(3-aminopropyl) isocyanurate (XIII). The ease of decyanoethylation of VIII was shown by its transformation to VII in liquid ammonia at 80°. Tetrahydropyrimidinone-2 (XIV) was isolated



XIV

from a vacuum distillation of mixtures obtained in the above hydrogenations. The latter reaction once again illustrates the apparent ease with which certain alkyl isocyanurates form alkyl isocyanates.

EXPERIMENTAL[11]

Cyanuric acid (I). A three kilogram-sample of urea was melted in a three-l. round bottom flask and immersed in a molten lead bath heated to above 300°. A vigorous evolution of ammonia began and continued for about 1 hr. During this time the flask contents were at about 225°; at the end of the period the contents of the flask had solidified. The pot temperature was maintained at about 250° for an additional hour. The flask was removed from the bath, allowed to cool, and then broken to recover the solid product. The crude product (1900 g.) was ground and refluxed for 2 hr. with 6*N* nitric acid using 3.5 g. of pyrolyzate per 100 ml. of acid. On cooling this solution, long needle-like crystals precipitated, were filtered, washed with water and dried, to give 1600 g. of product (yield 75%). Recrystallizing this material from water gave I of at least 99% purity.

Anal. Calcd. for $C_3H_3N_3O_3$: C, 27.90; H, 2.33; N, 32.56. Neut. equiv., 129.0. Found: C, 28.00; H, 2.57; N, 32.58. Neut. equiv., 128.6.

Tris(2-hydroxyethyl) isocyanurate (II). To 2000 ml. of dimethylformamide in a three-necked flask equipped with submerged gas inlet, stirrer, thermometer, and Dry Ice cooled condenser was added 175 g. I and 3 g. sodium hydroxide. The reaction mixture was heated to 130° and 175 g. gaseous ethylene oxide fed in at a rate to maintain the temperature at 135–140°. On completion of the oxide addition the insoluble sodium cyanurate was removed by filtration and the excess solvent evaporated at reduced pressure. The solid crude product remaining was recrystallized from methanol to give 275 g. of II, m.p. 134–136°.

Anal. Calcd. for $C_9H_{15}N_3O_6$: C, 41.38; H, 6.0; N, 16.09. Found: C, 41.40; H, 5.9; N, 16.08.

Hydrolysis of II in strong sodium hydroxide gave 3 moles of carbon dioxide and ethanolamine. The latter was identified by its index of refraction, boiling point, and infrared spectra. Infrared scan of II in potassium bromide showed absorption at 5.93 μ for the carbonyl group.

Conversion of tri-(2-hydroxyethyl) isocyanurate (II) *to oxazolidone* (III). The vacuum pyrolysis of II (127 g.) was effected by slowly heating to 180° while maintaining the pressure at 1–2 mm. III distilled as a liquid at 130–140° and quickly solidified in the receiver to give 114 g. of product (yield 90%), m.p. 85–87°. The product was further purified by crystallization from chloroform and melted 89–90° (lit.,[12] m.p. 88–90°).

Triallyl isocyanurate (V). To a three-necked flask fitted with addition funnel, stirrer, Dry Ice-acetone cooled reflux condenser, and thermometer was added 65 g. I, 60 g. sodium hydroxide, and 800 ml. water. The solution was heated to 50° and 0.5 g. cuprous chloride catalyst was added. Allyl chloride (250 g.) was introduced dropwise during a 15 min. interval and heating was continued for 15 min. Sufficient 50% sodium hydroxide was added as needed to maintain the *p*H at 10–10.5 throughout the run. The crude product was removed by benzene extraction, washed with water, dried and distilled to remove the benzene solvent. Residual crude V weighed 107.6 g. (yield 86%), b.p. 100–110°/0.2–0.5 mm., m.p. 19–22°, n_D^{30} 1.5110.

Anal. Calcd. for $C_{12}H_{15}N_3O_3$: C, 57.84; H, 6.06; N, 16.86. Found: C, 57.85; H, 6.40; N, 16.86.

Diallyl isocyanurate (IV). The aqueous residue from triallyl isocyanurate synthesis was acidified to *p*H 1–2 with sulfuric acid. The diallyl isocyanurate (IV) was collected by filtration; yield 12.4 g. (11.9%), m.p. 143–145°.

Anal. Calcd. for $C_9H_{11}N_3O_3$: C, 51.65; H, 5.27; N, 20.10. Found: C, 51.87; H, 5.39; N, 19.90.

Tris(carbethoxymethyl) isocyanurate (VI). Trisodium cyanurate (65.0 g.) and ethyl chloroacetate (122.5 g.) were placed in a 320 cc. stainless steel autoclave and heated at 190–195° for 6 hr. The contents were washed from the cooled autoclave with ethanol and filtered to remove the unchanged sodium cyanurate. The filtrate was distilled under vacuum to remove ethanol and excess ethyl chloroacetate leaving 78.0 g. of crude product (yield 60%), b.p. 200–240°, 0.4–1.0 mm. Redistilling this product gave a fraction boiling at 210–220°/0.45 mm. This liquid crystallized on standing, m.p. 71–78° after recrystallization from ethanol.

Anal. Calcd. for $C_{15}H_{21}N_3O_9$: C, 46.51; H, 5.4; N, 10.85. Found: C, 46.65; H, 5.89; N, 10.72.

Attempted saponification of VI in 100 ml. of 5% sodium hydroxide at reflux resulted in ring rupture with the formation of *N,N*,-dicarbethoxymethyl urea, m.p. 148–150° (from ethanol). An authentic sample prepared by the reaction of ethyl glycinate and phosgene[13] failed to depress the melting point of the solid hydrolysis product.

Cyanoethyl isocyanurates. A slurry of I (43 g.) in 250 ml. dimethylformamide containing 12 ml. of "Triton B" (trimethylbenzyl ammonium hydroxide, 38% in water) was prepared. Acrylonitrile (53 g.) was added dropwise over a period of 1 hr. The slurry was refluxed at 120–130° for 2.5 hr. A clear solution formed which on cooling gave 31.8 g. (yield 33%) of tris(2-cyanoethyl) isocyanurate (VIII), m.p. 220–230°; recrystallized from dimethylformamide, m.p. 228–230°.

Anal. Calcd. for $C_{12}H_{12}N_6O_3$: C, 50.00; H, 4.17; N, 29.18. Found: C, 50.01; H, 4.26; N, 29.10.

Evaporation of the dimethylformamide solution from the synthesis of VIII above at reduced pressure gave 56.4 g. (yield 67%) of bis(2-cyanoethyl) isocyanurate (VII),

(11) Temperatures and melting points reported are uncorrected.

(12) S. Frankel and M. Cornelius, *Ber.*, **51**, 1654 (1918).

(13) E. Fisher, *Ber.*, **34**, 440 (1901).

m.p. 190–210°; recrystallized from ethanol, m.p. 216–218°.

Anal. Calcd. for $C_9H_9N_3O_3$: C, 46.00; H, 3.83; N, 29.80. Found: C, 46.13; H, 3.68; N, 30.02.

A mixture of VIII (15 g.) and 150 cc. concd. hydrochloric acid heated at reflux for 4 hr. gave 17.9 g. (yield 99%) of tris(2-carboxyethyl) isocyanurate (X), m.p. 226–230°; recrystallization from water, m.p. 228–229°.

Anal. Calcd. for $C_{12}H_{15}N_3O_9$: C, 41.75; H, 4.35; N, 12.17. Neut. equiv., 115.0. Found: C, 41.87; H, 4.39; N, 12.10. Neut. equiv., 115.2.

Hydrolysis of VII (7.9 g.) as described above gave 9.0 g. (yield 99%) of bis(2-carboxyethyl) isocyanurate (IX), m.p. 287–289° after recrystallization from water.

Anal. Calcd. for $C_9H_{11}N_3O_7$: C, 39.57, H, 4.03; N, 15.38. Neut. equiv., 136.5 and 91.0. Found: C, 39.69; H, 3.91; N, 15.25. Neut. equiv., 135.7 and 91.5.

Tris(2-carboxyethyl) isocyanurate (X) (34.5 g.) refluxed with 200 ml. of 5*N* absolute ethanolic hydrogen chloride for 2 hr. gave 40.0 g. (yield 93%) of tris(2-carbethoxyethyl) isocyanurate (XI), m.p. 50–52° after recrystallization from ethanol.

Anal. Calcd. for $C_{18}H_{27}N_3O_9$: C, 50.35; H, 6.33; N, 9.80. Found: C, 50.16; H, 6.33; N, 9.78.

Hydrogenation of tris(2-cyanoethyl) isocyanurate (VIII). A stainless steel autoclave containing 50.0 g. of VIII, 17.1 g. Raney nickel and 61.3 g. anhydrous ammonia was pressurized to 1400 p.s.i.g. with hydrogen and heated to 80–82° for 5 hr. Additional hydrogen was added as the reaction proceeded until theoretical uptake was realized.

The autoclave was cooled, vented, and the product washed from the bomb with absolute ethanol and filtered from the catalyst. Evaporation of the alcohol solution gave a sirupy mass practically free of ammonia. Extraction of the sirupy mass with ethanol gave 23.9 g. of bis(3-aminopropyl) isocyanurate (XII), m.p. 212–215°; crystallized from water and then from *N*-methylpyrrolidone, m.p. 205–207°.

Anal. Calcd.: Mol. wt., 243. Neut. equiv., 121.5 and 243. Found: Mol. wt. by freezing point depression of water: 236. Neut. equiv., 126 and 252.

Reaction with diluric acid gave a didiluratate salt.

Anal. Calcd. for $C_{17}H_{23}N_{11}O_{13}$: C, 34.62; H, 3.90; N, 26.15. Found: C, 34.64; H, 3.77; N, 25.93.

A mixture of 43.0 g. of VIII, 100 ml. of ethanol, 15.6 g. of wet W-2 Raney nickel and 18.1 g. of ammonia was placed in a 320 ml. autoclave and heated to 155–160° for 3 hr. at 2000 p.s.i.g. hydrogen pressure. The autoclave was cooled, vented, and the contents washed out with ethanol. The catalyst was filtered and the solution concentrated to give 15.0 g. mono(3-aminopropyl) isocyanurate (XIII).

Anal. Calcd. for $C_6H_{10}N_4O_3$: C, 38.75; H, 5.38; N, 30.10. Neut. equiv., 186. Found: C, 39.05; H, 5.64; N, 30.08; Neut. equiv., 187.

Attempted isolation of the above amines *via* vacuum distillation gave appreciable quantities of tetrahydropyrimidinone-2 (XIV), m.p. 263–265° (lit.,[14] m.p. 263–265°). The identity of the pyrimidone-2 was established by hydrobromic acid hydrolysis to 1,3-diaminopropane and comparison of the dihydrochloride and the picrate salts of the latter with authentic materials. The known and the unknown salts gave identical infrared spectra.

Conversion of tris(2-cyanoethyl) isocyanurate (VIII) *to bis(2(cyanoethyl) isocyanurate* (VII). Heating VIII (50 g.) and 70 g. of anhydrous ammonia in a 320-ml. autoclave for 4 hr. at 80° gave 39.1 g. of VII (yield 96%), m.p. 216–218°. A mixed melting point with an authentic sample of bis(2-cyanoethyl) isocyanurate gave no depression. Infrared spectra of the compounds were identical.

HOPEWELL, VA.

(14) E. Fisher and H. Koch, *Ann* **232**, 224 (1886).

[CONTRIBUTION FROM THE DEPARTMENT OF BIOLOGICAL SCIENCES, STANFORD RESEARCH INSTITUTE]

Potential Anticancer Agents.[1] XXXIX. An Alternative Synthesis of 9-(2′,3′-Anhydro-β-D-ribofuranosyl)adenine

ALLEN BENITEZ, OSBORNE P. CREWS, JR., LEON GOODMAN, AND B. R. BAKER

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A seven-step synthesis of 9-(2′,3′-anhydro-β-D-ribofuranosyl)adenine (VIII) from 9-(β-D-xylofuranosyl)adenine (I) was accomplished. The direct coupling route to VIII using 2-*O*-acetyl-5-*O*-benzoyl-3-*O*-(*p*-tolylsulfonyl)-D-xylofuranosyl chloride (XIb) was explored but proved less satisfactory than the use of the 5-*O*-methoxycarbonyl analog (XIa) of XIb.

In a previous paper[2] from these laboratories, the synthesis of the anhydronucleoside (VIII) from 1,2-di-*O*-acetyl-5-*O*-methoxycarbonyl-3-*O*-tosyl-D-xylofuranose (X) was described. The over-all yield of this versatile intermediate (VIII) from X was only 8.9% with essentially all of the low yield being attributable to difficulties in the coupling reaction between the chlorosugar (XI) and chloromercuri-6-benzamidopurine. It was felt that better over-all yields of X might be obtainable by carrying out the necessary transformations on a suitable and more readily accessible preformed nucleoside. The coupling reaction between 2,3,5-tri-*O*-benzoyl-D-xylofuranosyl bromide and chloromercuri-6-benzamidopurine has been reported to give approximately 45% of 9-(β-D-xylofuranosyl)adenine (I)[3] and this nucleoside (I) appeared to be a suitable starting material for an alternative synthesis of VIII.

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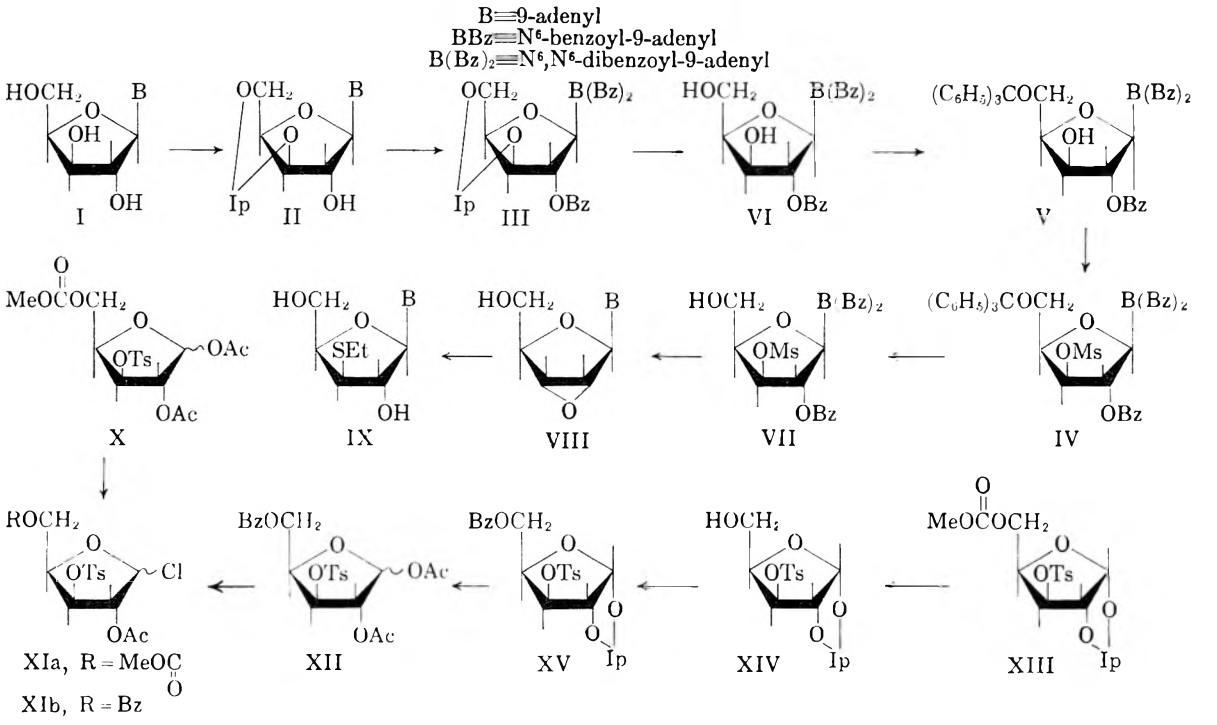
(2) C. D. Anderson, L. Goodman, and B. R. Baker, *J. Am. Chem. Soc.*, **81**, 3967 (1959).

(3) B. R. Baker and K. Hewson, *J. Org. Chem.*, **22**, 966 (1957).



The conversion of I to the 3′,5′-*O*-isopropylidene derivative (II)[3] in 68% yield was accomplished by reaction with acetone at room temperature using a large quantity of ethanesulfonic acid as a catalyst. Reaction of II with a large excess of benzoyl chloride in pyridine for three to five days gave a 66% yield of a crystalline compound whose analysis showed that three benzoyl groups had been introduced and whose infrared spectrum showed no —NH absorption; its structure seems to be best represented as the N^6,N^6-dibenzoyladenine derivative (III). Cleavage of the *O*-isopropylidene group from III with 70% aqueous acetic acid at 50°[4] gave a good yield of crude VI. A partial purification of VI was carried out by partitioning the product between the layers of a benzene-methanol-water mixture. The major fraction (74% calculated as VI), isolated from the benzene-rich layer, appeared from the infrared spectrum to be mainly the N^6,N^6-dibenzoyl compound (VI), although efforts to obtain it in analytically pure form were unsuccessful; it was the material used for the remainder of the synthetic sequence to VIII. The material isolated from the water-rich phase appeared to be mostly the N^6-monobenzoyl compound, corresponding to VI, and was probably a useful precursor of VIII although it was not used. The crude dihydroxy nucleoside (VI) was tritylated at 50–55° to form V and the reaction mixture was directly treated with excess methanesulfonyl chloride to form the mesylate (IV). The crude tritylated mesylate (IV) was detritylated by the procedure of Schaub, Weiss, and Baker[4] using 80% aqueous acetic acid at 80° for twenty-five minutes and the crude mesylate, benzoate (VII), was converted with sodium methoxide to the anhydronucleoside (VIII) by the procedure of Anderson, *et al.*,[2] in an over-all yield of 28% based on the acetonide (II).

As was described previously,[2] the procedure of Baker and Hewson[5] was used to precipitate the picrate of VIII, as a means of separating VIII from nonbasic materials. Regeneration of the picrate of VIII was studied using Dowex 2 (CO_3), Dowex 2 (OAc), and Dowex 2 (Cl); using a standardized and comparable procedure with each resin, the recovery of VIII was best with the acetate form of the resin, somewhat less with the chloride form, and poorest with the carbonate form. The same order of resin regeneration efficiency was found in the recovery of adenosine from adenosine picrate. Adsorptive losses on the resins are responsible for the lowered yields with the more basic resins.[5]

The over-all yield of VIII from 2,3,5-tri-*O*-benzoyl bromide was 6–8%, comparable with that from the direct coupling reaction with XIa.

In order to study the effect of the blocking group at the 5-position of the sugar on the coupling reaction with chloromercuri-6-benzamidopurine, 1,2-*O*-isopropylidene-5-*O*-methoxycarbonyl-3-*O*-tosyl-D-xylofuranose (XIII)[6] was cleaved with a catalytic quantity of sodium methoxide in methanol to the 5-hydroxy sugar (XIV), which was directly benzoylated to give the crystalline 5-*O*-benzoyl compound

(4) R. E. Schaub, M. J. Weiss, and B. R. Baker, *J. Am. Chem. Soc.*, 80, 4692 (1958).

(5) B. R. Baker and K. Hewson, *J. Org. Chem.*, 22, 959 (1957).

(6) C. D. Anderson, L. Goodman, and B. R. Baker, *J. Am. Chem. Soc.*, 80, 5247 (1958).

(XV). Acetolysis of XV to the diacetate (XII) and cleavage of the diacetate (XII) to give the chloro sugar (XIb) were carried out as described for the 5-*O*-methoxycarbonyl compound.[6] The coupling reaction of XIb with chloromercuri-6-benzamidopurine, however, gave a somewhat poorer crude yield of VIII than did the reaction of XIa, making it clear that the low yield of VIII from XIa could not be attributed solely to the 5-*O*-methoxycarbonyl blocking group.

A further investigation of the coupling reaction between XIa and chloromercuri-6-benzamidopurine on a large scale has shown that certain modifications of the procedure lead to a large improvement in the reaction, as shown by the nearly threefold increase in yield of the 3′-ethylthionucleoside (IX) isolated by using the crude anhydronucleoside (VIII) from the coupling reaction. These modifications are outlined in the Experimental.

EXPERIMENTAL[7]

9-(3′,5′-O-Isopropylidene-β-D-xylofuranosyl)adenine (II). To a well stirred mixture of 18.9 g. (70.6 mmoles) of 9-(β-D-xylofuranosyl)adenine (I)[3] and 530 ml. of dry acetone was added 29.0 ml. (*ca.* 0.35 mole) of ethanesulfonic acid. After being stirred for 7 hr. at room temperature, the mixture was poured into a cold stirred solution of 45 g. (0.53 mole) of sodium bicarbonate in 200 ml. of water. The resulting solution was stirred at room temperature for 2 hr. and was evaporated to dryness *in vacuo* (finally at 2 mm. and 50°). The thoroughly powdered residue was extracted with 700 ml. of chloroform for 22 hr. using a Soxhlet extractor. The extract was evaporated *in vacuo* to leave 14.85 g. (68%) of crystalline solid, m.p. 206.0–207.5°, suitable for use in the next step. Further crystallization of the product from methanol gave material, m.p. 212.5–214.0° (lit.[3] m.p. 204–207°); it was chromatographically homogeneous in solvent A with R_{Ad} 1.74.

These experimental modifications give a considerably higher yield than previously reported.[3]

N^6,N^6-Dibenzoyl-9-(2′-O-benzoyl-3′,5′-O-isopropylidene-β-D-xylofuranosyl)adenine (III). A solution of 4.00 g. (13.0 mmoles) of the acetonide (II) in 50 ml. of reagent pyridine was prepared by gentle heating. The solution was cooled in an ice bath and 11.0 g. (78.0 mmoles) of benzoyl chloride was added dropwise and with stirring over a period of 30 min. The reaction mixture was stored at room temperature for 96 hr. protected from moisture, then was poured into 70 ml. of cold water. The aqueous mixture was extracted with five 30-ml. portions of chloroform; the combined extracts were washed with two 60-ml. portions of saturated aqueous sodium bicarbonate solution and with one 100-ml. portion of water, then were dried over magnesium sulfate. After filtration, the filtrate was evporated to dryness *in vacuo* and re-evaporated *in vacuo* after the addition of 50 ml. of toluene. The final residue weighed 10.02 g. and was extracted with ten 50-ml. portions of boiling petroleum ether (b.p. 64–69°) decanting the hot solvent each time, to leave 7.94 g. of crystalline solid, m.p. 144–185°. The material was recrystallized from 60 ml. of benzene to give 6.34 g. of the benzene solvate, m.p. 125–140°. This solvate was then heated with 100 ml. of boiling petroleum ether (b.p. 64–69°) and gave, on cooling, 5.36 g. (66%) of crystalline solid, m.p. 195–196°, which was identical with the analytical sample described below.

A portion (0.407 g.) of the product was recrystallized from 10 ml. of benzene and it slowly deposited 0.399 g. of crystalline solid that was still solvated after drying at 2 mm. and 100° for 17 hr., m.p. 164.5–165.5°.

Anal. Calcd. for $C_{34}H_{29}N_5O_7 \cdot 0.75C_6H_6$: C, 67.7; H, 4.94. Found: C, 67.3; H, 5.04.

A portion (0.184 g.) of the benzene-recrystallized material was boiled with 20 ml. of petroleum ether (b.p. 64–69°). Filtration of the mixture gave 0.151 g. of solid, m.p. 194–196°; $\lambda_{max(\mu)}^{KBr}$ 5.78 (ester C=O), 5.90 (amide C=O), 11.77 (strong band related to isopropylidene group), 13.96 ($C_6H_5CO_2$), 14.30 [$(C_6H_5CO)_2N$]; there was no OH or NH absorption near 3.0 μ. The compound traveled as a single spot on paper in solvents C and A with R_{Ad} 1.56 and 3.14, respectively.

Anal. Calcd. for $C_{34}H_{29}N_5O_7$: C, 65.9; H, 4.72; N, 11.3. Found: C, 65.8; H, 4.86; N, 11.4, 11.6.

The above material could be recrystallized from ethyl acetate to give a material, m.p. 136–140°, which was evidently another crystal form.

Anal. Found: C, 65.5; H, 5.01; N, 11.3.

N^6,N^6-Dibenzoyl-9-(2′-O-benzoyl-β-D-xylofuranosyl)adenine (VI). A solution of 5.36 g. (8.65 mmoles) of the benzoylated purine (III) in 75 ml. of 70% aqueous acetic acid was stirred at 50° for 4.75 hr., whereupon complete solution was effected. Stirring and heating (50°) was continued for 3.25 hr. more and the solution was allowed to stand 15 hr. at room temperature before being evaporated to dryness *in vacuo* at 35°. The residue weighed 5.58 g. and was triturated with three 50-ml. portions of boiling petroleum ether (b.p. 65–69°) and again evaporated to dryness *in vacuo* at 30°. The residue (5.47 g.) was partitioned using a mixture of 160 ml. of benzene, 96 ml. of methanol, and 64 ml. of water. The upper benzene-rich phase, on evaporation *in vacuo*, gave 3.71 g. (74% calculated as VI) of white solid, m.p. 90–120°; $\lambda_{max(\mu)}^{Nujol}$ 3.02 (OH), 5.80 (ester C=O), 14.00 ($C_6H_5CO_2$), 14.32–14.50 [$(C_6H_5CO)_2N$]. There was no isopropylidene absorption near 11.8 μ; the lack of amide C=O near 5.9 μ remains unexplained. On paper chromatography in solvents C and A, the material showed major spots with R_{AD} 1.65 and 3.20, respectively, which were not easily distinguished from starting material III; there were additional trace spots in each of these solvent systems. The material could be recrystallized from benzene or from water but the resulting solids had broad melting ranges and analytical values that did not fit any reasonable structure.

The water-rich phase was evaporated *in vacuo*, leaving 1.54 g. (32% calculated as the N^6-monobenzoyl purine corresponding to VI) of solid, m.p. 100–118°; $\lambda_{max(\mu)}^{Nujol}$ 3.02 (OH), 5.80 (ester C=O), 5.95 (amide C=O), 14.02 ($C_6H_5CO_2$); there was no isopropylidene absorption near 11.8 μ. On paper chromatography, the material showed three spots in solvent C with R_{Ad} 1.38, 1.54, and 1.64, and two spots in solvent A with R_{Ad} 2.74 and 3.18.

N^6,N^6-Dibenzoyl-9-(2′-O-benzoyl-3′-O-methanesulfonyl-5′-O-trityl-β-D-xylofuranosyl)adenine (IV). A solution of 3.71 g. (*ca.* 7.8 mmoles) of the dihydroxy compound (VI) (material prepared as above and processed through partition in the benzene-methanol-water system) in 7 ml. of reagent pyridine was combined with a solution of 2.39 g. (8.57 mmoles)

(7) Boiling points and melting points are uncorrected; the latter were obtained with the Fisher-Johns apparatus. Paper chromatograms were run by the descending technique on Whatman No. 1 paper in the following solvent systems: A, water-saturated *n*-butyl alcohol[8]; B, 5% disodium hydrogen phosphate[9] (without the usual organic phase); C, benzene-water-methanol (2:1:6).[10] Adenine was used as a standard (spot locations are expressed as R_{Ad} units with adenine at 1.00) and spots were detected by visual examination under ultraviolet light.

(8) J. G. Buchanan, C. A. Dekker, and A. G. Long, *J. Chem. Soc.*, 3162 (1950).

(9) C. E. Carter, *J. Am. Chem. Soc.*, **72**, 1466 (1950).

(10) T. Wieland and W. Kracht, *Angew. Chem.*, **69**, 172 (1957).

of triphenylchloromethane in 10 ml. of pyridine and the resulting solution was stirred for 72 hr. at 50–54° with exclusion of moisture. Methanesulfonyl chloride (1.34 g., 11.7 mmoles) was then added and the mixture was stirred for an additional 16 hr. at the same temperature. The reaction mixture was diluted with 60 ml. of chloroform followed by 100 ml. of water. Solid sodium bicarbonate was added to the vigorously stirred mixture until the aqueous phase was just basic to litmus paper. The chloroform phase was separated, dried over magnesium sulfate, filtered, and the filtrate evaporated *in vacuo* at 30°. The residue was dissolved in 30 ml. of toluene and the evaporation repeated to leave 6.17 g. of a foam, m.p. 80–100°; $\lambda_{max(\mu)}^{Nujol}$ 5.78–5.90 (ester and amide C=O), 8.48 (—OSO_2—), 13.09 (mono substituted benzene), 14.10–14.25 (C_6H_5C=O). Paper chromatography in solvents C and A showed main spots with R_{Ad} 1.64 and 3.50, respectively, not easily distinguishable from the starting material (VI).

N^6,N^6-Dibenzoyl-9-(2′-O-benzoyl-3′-O-methanesulfonyl-β-D-xylofuranosyl)adenine (VII). A mixture of 6.17 g. of the crude 5′-*O*-trityl compound (IV) and 100 ml. of 80% aqueous acetic acid was heated at 80° for 25 min. (complete solution resulted in 5 to 6 min.). The reaction mixture was evaporated *in vacuo* at 30° and the residue was dissolved in 30 ml. of absolute ethanol and re-evaporated *in vacuo*. The evaporation with absolute ethanol was repeated twice more to remove actic acid. The final residue was triturated with six 50-ml. portions of hot (90°) petroleum ether (b.p. 64–69°) and one 40-ml. portion of boiling ether to leave 3.56 g. of residue, m.p. 105–125°, which was used directly for the preparation of the anhydronucleoside (VIII).

A portion (0.100 g.) of the residue was dissolved in 10 ml. of benzene, the solution was filtered to remove some insoluble solid, and the filtrate was diluted with 40 ml. of petroleum ether (b.p. 64–69°) and cooled. The precipitated solid (0.051 g.) was collected; $\lambda_{max(\mu)}^{Nujol}$ 2.99 (OH, NH), 5.78–5.90 (ester and amide C=O), 8.45 (—OSO_2—), 14.03 (C_6H_5C=O); there was no monosubstituted benzene absorption (due to trityl group) near 13.0 μ.

Anal. Calcd. for $C_{25}H_{23}N_5O_8S.C_6H_6$: S, 5.08. Found: S, 4.08, 4.03.

9-(2′,3′-Anhydro-β-D-ribofuranosyl)adenine (VIII). To a cold (0°), filtered solution of 3.52 g. (*ca* 6.4 mmoles) of crude VII in 175 ml. of methanol was added a cold solution of 0.345 g. (6.38 mmoles) of sodium methoxide in 15 ml. of methanol. The reaction mixture was stored at 3° for 6 days protected from moisture, then was filtered and the filtrate adjusted to *p*H 7 with glacial acetic acid. The solution was evaporated *in vacuo* at 30° and the residue was partitioned between 200 ml. of water and 100 ml. of chloroform. The aqueous layer was evaporated to dryness *in vacuo* at 35° to leave 2.00 g. of residue which was shown by paper chromatography in solvents A and B to contain VIII. The residue (2.00 g.) was dissolved in 100 ml. of water and to this solution was added a warm (30°) solution of 2.56 g. (9.5 mmoles) of picric acid in 120 ml. of water. The solution containing the precipitated picrate was maintained at 3° for 18 hr., filtered, and the picrate washed with 10 ml. of cold water. The damp picrate was suspended in 125 ml. of water and damp Dowex 2 (OAc) was added portionwise to the stirred suspension until the supernatent liquid had become essentially colorless. Stirring was continued for 6 hr. and the resin was removed by filtration and washed with three 20-ml. portions of water. The combined filtrate plus washings were decolorized with Norit A, filtered with the aid of Celite, and the filtrate evaporated to dryness *in vacuo* (30° and 1 mm.) to leave 0.82 g. (28% over-all yield from the acetonide II) of solid that decomposed gradually on heating[11] and that had $[\alpha]_D^{26}$ −18.3° (0.6% in 20% aqueous pyridine). The infrared spectrum of the material agreed well with that of VIII prepared previously[2] and paper chromatography in solvents A and B showed main spots with the proper R_{Ad}[2] but with several trace spots as contaminants. The solid was recrystallized twice from absolute ethanol (150 ml./g.) to give finally 0.16 g. of solid which darkened near 185° but showed no definite melting point, $[\alpha]_D^{26}$ −16.0° (0.6% in 20% pyridine), $[\alpha]_D^{30}$ −32.8° (0.53% in water). Its infrared spectrum was identical with that previously reported[2] and on paper chromatography in solvents A and B, it moved as a single spot with R_{Ad} 0.81 and 1.32, respectively.

In a study of the regeneration of the picrate of VIII with several types of Dowex 2 resin, a damp picrate (1.67 g.) from crude VIII prepared as above was divided into three equal portions which were regenerated with Dowex 2 (OAc), Dowex 2 (Cl), and Dowex 2 (CO_3). The acetate resin (2.21 g.) gave 0.122 g. of good nucleoside (VIII), the chloride resin (1.40 g.) gave 0.110 g. of VIII, and the carbonate resin (1.24 g.) gave 0.104 g. of VIII. A similar study of the regeneration of adenosine from its picrate showed that Dowex 2 (OAc) gave a 94% recovery, Dowex 2 (Cl) a 90% recovery, and Dowex 2 (CO_3) a 77% recovery of adenosine.

1,2-O-Isopropylidene-3-O-(p-tolylsulfonyl)-D-xylofuranose (XIV). To a solution of 10.0 g. (24.9 mmoles) of the 5-*O*-carbomethoxy compound (XIII)[6] in 300 ml. of cold (0°) methanol was added 0.134 g. (2.48 mmoles) of sodium methoxide dissolved in 5 ml. of methanol. The reaction mixture was allowed to stand for 16 hr. at room temperature in a stoppered flask and was then evaporated to dryness *in vacuo* at 30°. To the residue was added 50 ml. of chloroform and 50 ml. of water. The mixture was adjusted to *p*H 7 with glacial acetic acid and the chloroform layer was separated. The aqueous phase was extracted with two more 50-ml. portions of chloroform, then the combined chloroform extracts were dried over magnesium sulfate and filtered. The filtrate was evaporated *in vacuo* at 30°, leaving 8.96 g. (105%) of product; $\lambda_{max(\mu)}^{film}$ 2.81 (OH), 7.25, 8.37, 8.48 (—OSO_2—), 11.74 (isopropylidene), 12.23 (*p*-disubstituted benzene); there was no C=O absorption in the 5.5–6.0 μ region.

5-O-Benzoyl-1,2-O-isopropylidene-3-O-(p-tolylsulfonyl)-D-xylofuranose (XV). To a cold (0°) stirred solution of 1.0 g. (2.9 mmoles) of the 5-hydroxy compound (XIV) in 10 ml. of reagent pyridine was added, dropwise, 0.61 g. (4.34 mmoles) of benzoyl chloride. The stoppered reaction mixture was allowed to stand at room temperature for 17 hr., then 0.1 ml. of water was added to the solution followed by stirring for 30 min. The mixture was diluted with 25 ml. of chloroform and the resulting solution was washed with two 25-ml. portions of water, three 25-ml. portions of 1*M* aqueous sodium bicarbonate solution, and one 25-ml. portion of water. After drying over magnesium sulfate, the solution was filtered and the filtrate evaporated *in vacuo*, leaving 1.15 g. (89%) of crystalline product. The solid was recrystallized from 120 ml. of petroleum ether (b.p. 64–69°), yielding 0.88 g. (68%) of product, m.p. 94.5–95.5°. Another similar recrystallization gave the analytical sample, m.p. 96.0–96.5°, $[\alpha]_D^{38}$ −63° (1% in chloroform); $\lambda_{max(\mu)}^{Nujol}$ 5.78 (ester C=O), 7.82 (ester C—O—C), 8.39, 8.48 (—OSO_2—), 11.78 (isopropylidene), 12.29 (*p*-disubstituted benzene), 14.12 (C_6H_5C=O).

Anal. Calcd. for $C_{22}H_{24}O_8S$: C, 58.9; H, 5.39; S, 7.15. Found: C, 59.1; H, 5.62; S, 7.03.

1,2-Di-O-acetyl-5-O-benzoyl-3-O-(p-tolylsulfonyl)-D-xylofuranose (XII). Using the procedure described for the 5-*O*-methoxycarbonyl compound (XIII),[6] 7.38 g. (16.5 mmoles)

(11) In reference 2, the melting point of VIII was given as 200–203° dec. and $[\alpha]_D^{25}$ as −3° (0.6% in 20% aqueous pyridine). The melting point behavior of this compound, however, is completely dependent on the rate of heating and only with a very rapid rate can any kind of a melting behavior be observed. With normal heating rates, decomposition begins near 125° and darkening and softening continue up to 300°. When the optical rotation of the analytical sample[2] was redetermined, it was found to be $[\alpha]_D^{26}$ −17.5° (0.4% in 20% aqueous pyridine) and $[\alpha]_D^{26}$ −35.2° (0.33% in water).

of XV was converted to the diacetate (XII) which was recovered as 8.42 g. (104%) of a syrup; $\lambda_{max(\mu)}^{film}$ 5.68 (acetate C=O), 5.78 (benzoate C=O), 7.27, 8.39, 8.49 (—OSO_2—), 7.84 (benzoate C—O—C), 8.07, 8.21 (acetate C—O—C), 12.24 (*p*-disubstituted benzene), 14.00 (C_6H_5C=O).

*2-O-Acetyl-5-O-benzoyl-3-O-(p-tolylsulfonyl)-*D*-xylofuranosyl chloride* (XIb). The above diacetate (XII), 8.42 g., was converted to the chloride (XIb) by the procedure described for the preparation of XIa. A white, solid residue remained which showed none of the 8.07 μ absorption attributed to the C—O—C of the 1-*O*-acetate. The residue was directly coupled with chloromercuri-6-benzamidopurine using the procedure described for the coupling of XIa.[2] The solid product from the coupling and deblocking procedure, after regeneration of the picrate, weighed 0.48 g. and contained the anhydronucleoside (VIII), adenine, and some other purine-containing materials, as shown by paper chromatography in solvents A and B. If the residue had been pure VIII, the yield would have been 10.5% based on the isopropylidene compound (XV).

*9-[3′-Deoxy-3′-(ethylthio)-β-*D*-xylfuranosyl]adenine* (IX).[2] The conversion of 353 g. (0.79 mole) of diacetate (X) to the chloro sugar (XIa) was carried out as described previously.[2] Coupling of the chloro sugar (XIa) with 560 g. (0.785 mole) of 66.7% chloromercuri-6-benzamidopurine mixed with Celite was run for 2.25 hr.; it was found necessary to extract the filter cake with five 900-ml. portions of boiling chloroform to remove all the product. The crude, blocked nucleoside (345 g.) was converted to the anhydronucleoside (VIII) by dissolving it in 1600 ml. of methanol, cooling the solution to 10°, and adding a cold (10°) solution of 35 g. (0.65 mole) of sodium methoxide in 500 ml. of methanol. The resulting, stoppered solution, after standing at room temperature 14–15 hr., was adjusted to *p*H 7.4 with glacial acetic acid, then evaporated *in vacuo* at 55°, leaving 311 g. of crude VIII. A solution of the residue in 600 ml. of methanol was heated under reflux for 20 hr. with a methanolic sodium ethyl mercaptide solution (prepared from 227 g. (4.2 moles) of sodium methoxide, 340 ml. (4.6 moles) of ethanethiol, and 900 ml. of methanol) with exclusion of moisture. The solution was cooled to room temperature and adjusted to *p*H 8 with glacial acetic acid while cooling the mixture with an ice bath and maintaining the temperature below 45°. After evaporating the solution *in vacuo* at 50°, the residue was dissolved in 1500 ml. of water and continuously extracted with chloroform for 3.5 days to give 54.2 g. of crude IX. Recrystallization was effected by dissolving the material in 1500 ml. of 95% ethanol, evaporating the solution to 700 ml., and chilling to give 43.8 g. of a first crop, m.p. 183–185° (prior melting and resolidification 130–160°), whose infrared spectrum and paper chromatographic behavior were in excellent agreement with the previous analytical sample,[2] and a second crop of 3.1 g., m.p. 180° (with prior melting and resolidification 130–150°). The total product, 46.9 g., constituted a 19% over-all yield from the diacetate (X).

The main changes in the procedure from that of reference 2 are: (1) thorough extraction of the Celite residues from the initial coupling reaction with chloroform, (2) shorter reaction time in the deblocking to form VIII (3) neutralization of the reaction mixture from the reaction of VIII with sodium ethyl mercaptide before evaporation.

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MENLO PARK, CALIF.

[CONTRIBUTION FROM THE DEPARTMENT OF BIOLOGICAL SCIENCES, STANFORD RESEARCH INSTITUTE]

Potential Anticancer Agents.[1] XLIV. Some Derivatives of Uracil-5- and -6-carboxylic Acid

LEONARD O. ROSS, LEON GOODMAN, AND B. R. BAKER

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The reaction of the butyl esters of uracil-5- and 6-carboxylic acid with hydrazine, butylamine, and with 2-aminoethanol gave the expected amides. The hydrazide of uracil-6-carboxylic acid was converted with nitrous acid to uracil-6-carboxazide.

In a continuation of interest in derivatives of uracil as potential anticancer agents,[2,3] attention was focused on some transformations of uracil-5-carboxylic acid and orotic acid (uracil-6-carboxylic acid). The latter compound is a key intermediate in the *de novo* synthesis of pyrimidine ribonucleotides and deoxyribonucleotides[4] and, as such, represents an interesting area for the synthesis of possible antimetabolites.

The principal objective in these studies was to prepare a number of new amides from the uracil-5- and 6-carboxylic acids. One of the common routes to amides, *via* an acid chloride, was not feasible because of the unavailability of the acid chlorides of the two uracil acids. A few attempts in this work to prepare these acid chlorides were unsuccessful, probably because of the insolubility of the acids; no mention of the two acid chlorides appears in the literature. Accordingly, the preparation of the amides *via* the esters of uracil-5-carboxylic acid and orotic acid was investigated.

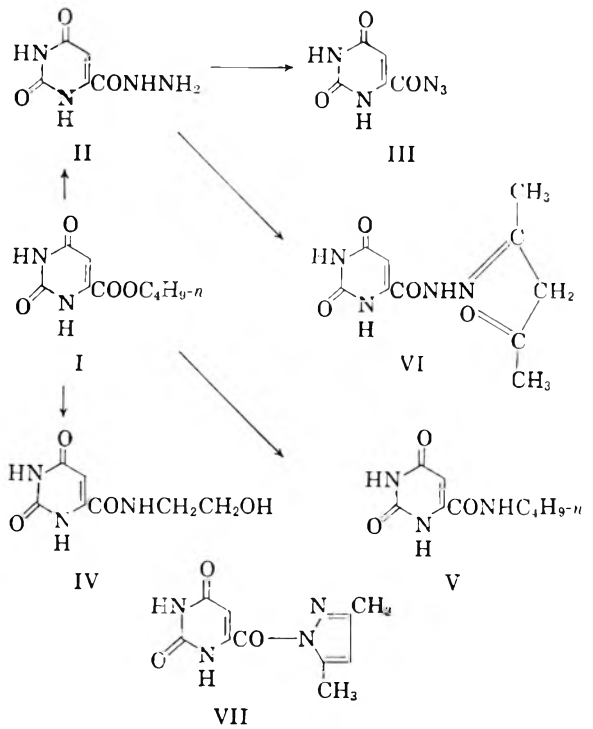
(1) This work was carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Public Health Service, Contract No. SA-43-ph-1892. The opinions expressed in this paper are those of the authors and are not necessarily those of the Cancer Chemotherapy National Service Center. For the preceding paper in this series, *cf.* W. A. Skinner, A. P. Martinez, H. F. Gram, L. Goodman, and B. R. Baker, *J. Org. Chem.*, in press.

(2) A. Benitez, L. O. Ross, L. Goodman, and B. R. Baker, *J. Am. Chem. Soc.*, in press, paper XXXVI of this series.

(3) W. A. Skinner, M. G. M. Schaelstraete, and B. R. Baker, *J. Org. Chem.*, **25**, 149 (1960), paper XXVIII of this series.

(4) J. N. Davidson, *The Biochemistry of the Nucleic Acids*, Methuen & Co., Ltd., London, 1957, p. 161.

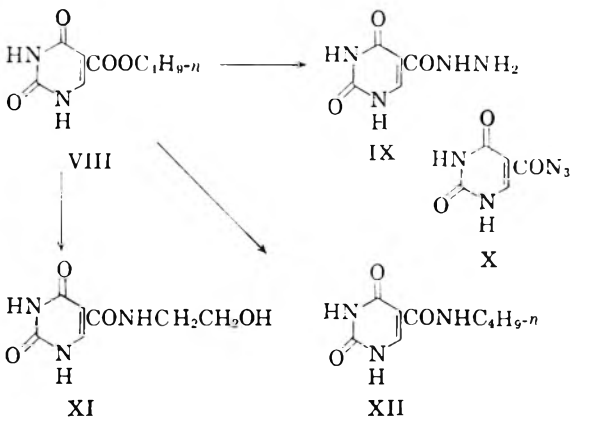
The *n*-butyl ester (I) of orotic acid, chosen in order to enhance the solubility of the orotic acid derivative in organic solvents, was prepared in good yield by the reaction of the acid with *n*-butyl alcohol in the presence of concentrated sulfuric acid. A mixture of the ester (I) and excess *n*-butylamine in refluxing ethanol gave a fair yield of the *n*-butylamide (V) and the reaction of I with excess 2-aminoethanol in ethanolic solution, carried out in a sealed bomb at 100°, gave a good yield of the 2-hydroxyethylamide (IV).



The infrared spectra of the two crystalline amides IV and V, run in Nujol mulls, showed no similarities in the 2.9–7.0 μ region but the ultraviolet spectra of the two compounds were very similar and in general agreement with that of the *n*-butylester (I). It seems clear that the two amides show markedly different interactions in the crystal state but show structural similarity in solution. A number of attempts were made to convert IV to the interesting 2-chloroethylamide of orotic acid by the use of thionyl chloride. There was a definite introduction of chlorine into IV but no pure product could be isolated from the reaction.

The *n*-butyl ester (I) with hydrazine hydrate in methanol gave an excellent yield of the carboxyhydrazide (II). In turn, the hydrazide (II), in cold dilute hydrochloric acid with a slight excess of sodium nitrite, gave a fair yield of the carboxyazide (III) which was readily identified by the strong azide infrared absorption at 4.59 μ. The carboxyhydrazide (II) was allowed to react with 1,3-pentanedione in an effort to prepare the orotylpyrazole (VII). Acyl pyrazoles have been prepared similarly by Ried and Schleimer[5] and have been used as acylating agents. In the reaction of 1,3-pentanedione with II, however, the reaction seemed to stop at the simple hydrazone (VI) stage. The crystalline product had a correct analysis for VI (although this would not preclude a monohydrate of VII). When attempts were made to make a derivative of the free carbonyl group in VI with phenylhydrazine or *p*-nitrophenylhydrazine, the hydrazide (II) was regenerated, a strong indication that the pyrazole ring had not formed. In the experiments of Ried and Schleimer,[5] reaction of an amine with an acylpyrazole led to displacement at the carbonyl carbon to yield a amide and the free pyrazole; a similar course of reaction between VII and phenylhydrazine would have given the phenylhydrazide of orotic acid as the product rather than II, which was actually isolated and would be the expected product from VI by hydrolysis.

In the uracil-5-carboxylic acid series, the *n*-butyl ester (VIII) was formed under similar conditions to those used in the preparation of I. There was somewhat more difficulty than in the orotic acid series in the conversion of VIII to the



2-hydroxyethylamide (XI) and to the *n*-butylamide (XII), both preparations requiring the use of considerably higher temperatures in a sealed bomb. The 5-carboxyhydrazide (XI) was readily prepared in high yield from the ester (VII). Attempts to convert IX to the azide X gave very capricious results. In a few cases a strong azide band was present in the infrared spectrum of the product but in most of the attempts there was no evidence for the formation of X. Attempts to convert IX to a pyrazole by reaction with 1,3-pentanedione gave intractable products.

It was noteworthy in a comparison of ultraviolet spectra of the 5-substituted- and 6-substituted uracils that the 5-substituted derivative absorbed at a shorter wave length and with greater intensity at all three *p*H conditions employed than did the corresponding 6-substituted derivative.

(5) W. Reid and B. Schleimer, *Ann.*, **619**, 43 (1958).

This same relationship is true in a comparison of the ultraviolet spectra of uracil-5-carboxylic acid[6] and orotic acid.[7]

EXPERIMENTAL[8]

n-Butyl orotate (I). A suspension of 2.0 g. (12.8 mmoles) of orotic acid in a mixture of 200 ml. of *n*-butyl alcohol and 2.0 ml. of concd. sulfuric acid was heated under reflux for 6 hr. The solution was filtered to remove 0.30 g. of orotic acid and the filtrate was concentrated *in vacuo* to about 40 ml. and chilled. Water (50 ml.) was added to the chilled concentrate causing the precipitation of 1.90 g. (82% based on utilized orotic acid) of crystalline product, m.p. 178–180°. Recrystallization of the solid from 50 ml. of water gave 1.80 g. (78%) of the analytical sample, m.p. 182–184°; $\lambda^{KBr}_{max(\mu)}$ 3.23 (NH); 5.78 and 6.00 (uracil C=O); 5.87 (ester C=O); 6.14, 6.70 and 7.15 (pyrimidine ring); 7.93 (ester C—O—C); $\lambda^{pH\ 1}_{max(m\mu)}$ 286 (ε 5800); $\lambda^{pH\ 7}_{max(m\mu)}$ 280 (ε 7500); $\lambda^{pH\ 13}_{max(m\mu)}$ 284 (ε 7300). The product moved as a single spot on paper in solvent A with R_{Ad} 1.41.

Anal. Calcd. for $C_9H_{12}N_2O_4$: C, 50.9; H, 5.70; N, 13.2. Found: C, 50.7; H, 5.72; N, 13.1.

Orotyl hydrazide (II). A stirred mixture of 5.0 g. (23.5 mmoles) of *n*-butyl orotate (I), 9.20 g. (0.185 mole) of hydrazine hydrate, and 50 ml. of reagent methanol was heated on the steam bath for 20 min. under gentle reflux, then chilled. The precipitated material (3.0 g., 75%) was removed by filtration and from the evaporated filtrate a second crop (0.80 g.) of the same material was recovered, giving a total crude yield of 95% of product which failed to melt at 300°. The material was recrystallized from 145 ml. of water with the aid of Norit to give 2.63 g. (66%) of product, m.p. >300°, $\lambda^{KBr}_{max(\mu)}$ 3.08 and 3.18 (NH and NH_2); 5.85–6.32 (uracil C=O, amide C=O, NH_2 and pyrimidine); 6.75 (pyrimidine ring); $\lambda^{pH\ 1}_{max(m\mu)}$ 282 (ε 6000); $\lambda^{pH\ 7}_{max(m\mu)}$ 305 (broad, ε 5500); $\lambda^{pH\ 7}_{max(m\mu)}$ 295 (ε 8600). On paper chromatography in solvent C and D, the compound moved as a single spot with R_{Ad} 1.10 and 1.55, respectively.

Anal. Calcd. for $C_5H_6N_4O_3.H_2O$: C, 31.9; H, 4.28; N, 29.7. Found: C, 32.0; H, 4.36; N, 29.5.

Orotyl azide (III). A cold (7–10°) suspension of 1.0 g. (5.9 mmoles) of the hydrazide (II) in a mixture of 5.0 ml. of 6*M* hydrochloric acid in 100 ml. of water was vigorously stirred while a solution of 0.44 g. (6.4 mmoles) of sodium nitrite in 5 ml. of water was added dropwise over a 10-min. period. The suspension was stirred 10 min. more at 7–10° and was filtered. The solid residue was washed with three 20-ml. portions of cold water and was dried to give 0.60 g. (56%) of product; this compound gave no definite melting point, but gradually decomposed, with the decomposition most noticeable at 180–190°; $\lambda^{KBr}_{max(\mu)}$ 2.90 and 3.15 (NH); 4.49 and 4.59 (N_3); 5.8–6.0 (uracil C=O); 6.13 and 6.68 (pyrimidine ring); no satisfactory paper chromatographic solvent system was found for this compound.

Anal. Calcd. for $C_5H_5N_5O_3.1/2\ H_2O$: C, 31.6; H, 2.12; N, 36.8. Found: C, 32.0; H, 2.58; N, 37.4.

N-(2-Hydroxyethyl)orotamide (IV). A mixture of 1.0 g. (4.71 mmoles) of the ester (I), 1.0 g. (16.3 mmoles) of 2-aminoethanol, and 20 ml. of absolute ethanol was heated in a stainless steel bomb at 100° for 14 hr. After cooling to room temperature, the contents of the bomb were transferred and evaporated *in vacuo*. The solid residue was slurried with 20 ml. of reagent methanol and the suspension filtered to give 0.80 g. (85%) of solid product, m.p. 272–274° dec. The solid was dissolved in 10 ml. of water, the solution treated with Norit and filtered. Hot methanol (20 ml.) was added to the filtrate and, on chilling, 0.60 g. (64%) of product was obtained, m.p. 278–280°; $\lambda^{Nujol}_{max(\mu)}$ 2.98 and 6.57 (NH), 6.00 (uracil C=O); 6.10 (amide C=O); 9.41 (C—OH); surprisingly, there was no OH absorption near 3.0 μ; $\lambda^{pH\ 1}_{max(m\mu)}$ 280 (ε 6500); $\lambda^{pH\ 7}_{max(m\mu)}$ 280–295 (ε 4900); $\lambda^{pH\ 13}_{max(m\mu)}$ 312 (ε 6600). On paper chromatography in solvent A the compound moved as a single spot with R_{Ad} 0.70.

Anal. Calcd. for $C_7H_9N_3O_4$: C, 42.2; H, 4.55; N, 21.0. Found: C, 42.2; H, 4.71; N, 21.0.

N-Butyl orotamide (V). A stirred mixture of 4.50 g. (2.12 mmoles) of the ester (I), 4.25 g. (58.8 mmoles) of *n*-butylamine, and 50 ml. of absolute ethanol was heated under reflux for 7 hr. and evaporated *in vacuo* to a semi-solid slurry. Water (25 ml.) was added and the mixture was warmed until complete solution was attained. The hot solution was treated with Norit and filtered. The chilled filtrate deposited 2.0 g. (45%) of crystalline solid, m.p. 275–276°. The solid was recrystallized from 25 ml. of water to give 1.80 g. (41%) of product with unchanged melting point: $\lambda^{Nujol}_{max(\mu)}$ 3.04 and 6.43 (NH), 5.74 (uracil C=O), 6.00 (uracil C=O and amide C=O), 6.12 (pyrimidine ring); $\lambda^{pH\ 1}_{max(m\mu)}$ 279 (ε 6400); $\lambda^{pH\ 7}_{max(m\mu)}$ 307 (ε 4900); $\lambda^{pH\ 13}_{max(m\mu)}$ 311 (ε 6400). On paper chromatography in solvent A the product moved as a single spot with R_{Ad} 1.50.

Anal. Calcd. for $C_9H_{13}N_3O_3$: C, 51.1; H, 6.20; N, 19.8. Found: C, 51.5; H, 6.58; N, 20.2.

Mono-6-uracilylhydrazone of 1,3-pentanedione (VI). A stirred mixture of 0.50 g. (2.95 mmoles) of the hydrazide (II), 0.30 g. (3.00 mmoles) of 1,3-pentanedione, and 35 ml. of *N,N*-dimethylformamide was heated at 80° for 3 hr. The solvent was evaporated *in vacuo* at 80–90°, benzene (20 ml.) was added to the residue, and the evaporation was repeated, leaving 0.30 g. of solid, m.p. 184–188° dec. The solid was extracted with 10 ml. of boiling absolute ethanol, the mixture was filtered, and the filtrate was chilled to give a small amount of crystalline product, m.p. 228–230° dec.; $\lambda^{Nujol}_{max(\mu)}$ 2.97 and 3.07 (NH), 5.82 and 5.98 (uracil C=O), 6.10 and 6.85 (pyrimidine ring); $\lambda^{pH\ 1}_{max(m\mu)}$ 273 (ε 8800); $\lambda^{pH\ 7}_{max(m\mu)}$ 276 (ε 7900); $\lambda^{pH\ 13}_{max(m\mu)}$ 242 (shoulder, ε 8700), 285 (ε 6100). On paper chromatography in solvent D the compound moved as a single spot with R_{Ad} 1.90.

Anal. Calcd. for $C_{10}H_{12}N_4O_4$: C, 47.6; H, 4.76; N, 22.2. Found: C, 47.3; H, 4.70; N, 21.6.

Subsequent preparations using 1.00 of the hydrazide II and recrystallizing the crude residue from hot water gave a 51% yield of material, m.p. 225–228° dec., whose infrared spectrum was identical with that of the analytical sample.

When the hydrazone (VI), dissolved in aqueous ethanol containing a few drops of glacial acetic acid, was heated on the steam bath for 10 min. with an excess of either phenylhydrazine or *p*-nitrophenylhydrazine and the solution chilled, the solid product obtained in good yield was the hydrazide (II), m.p. >300° and identical with authentic II in infrared spectrum and paper chromatographic behavior.

5-Carbo-n-butoxyuracil (VIII). A stirred suspension of 1.0 g. (2.8 mmoles) of uracil-5-carboxylic acid, 50 ml. of *n*-butyl alcohol, and 0.30 ml. of concd. sulfuric acid in an apparatus equipped with a water separator was heated

(6) M. M. Stimson, *J. Am. Chem. Soc.*, **71**, 1470 (1949).

(7) H. Vanderhaege, *Bull. soc. chem. Belg.*, **62**, 611 (1953).

(8) Boiling points and melting points are uncorrected; the latter were obtained with the Fisher-Johns apparatus. Paper chromatography was done by the descending technique on Whatman No. 1 paper and the spots were detected by visual examination under ultraviolet light. Adenine was used as a standard and the spots were located relative to R_{Ad} 1.00. The solvent systems used were A,[9] *n*-butanol–acetic acid–water (5:2:3); B,[10] *i*-propanol–2*M* hydrochloric acid (65:35); C,[11] ammonium sulfate–*i*-propanol–water (2:28:70); D,[12] 2-methoxyethanol–water (9/1).

(9) D. M. Brown, A. Todd, and S. Varadarajan, *J. Chem. Soc.*, 2388 (1956).

(10) G. R. Wyatt, *Biochem. J.*, **48**, 584 (1951).

(11) A variant of a system used by R. Markham and J. D. Smith, *Biochem. J.*, **49**, 401 (1951).

(12) A. E. Bender, *Biochem. J.*, **48**, XV (1951) (Proc. Biochemical Society).

under reflux for 3 hr., resulting in complete solution. The chilled mixture gave 1.0 g. (74%) of crude product, m.p. 230–234°. The solid was recrystallized from 40 ml. of hot methanol to give 0.60 g. (44%) of product, m.p. 237–239°; $\lambda_{max(\mu)}^{KBr}$ 3.11 (NH); 5.70–5.80 (uracil and ester C=O), 6.60 (NH and pyrimidine ring); 6.13, and 6.99 (pyrimidine ring), 8.15 (ester C—O—C); $\lambda_{max(m\mu)}^{pH\ 1}$ 270 (ε 13300); $\lambda_{max(m\mu)}^{pH\ 7}$ 272 (ε 11900); $\lambda_{max(m\mu)}^{pH\ 13}$ 239 (ε 13700), 291 (ε 17900). On paper chromatography in solvent A, the product moved as a single spot with R_{Ad} 1.57.

Anal. Calcd. for $C_9H_{12}N_2O_4$: C, 50.9; H, 5.70; N, 13.2. Found: C, 51.1; H, 5.79; N, 13.0.

Uracil-5-carboxyhydrazide (IX). A stirred suspension of 0.50 g. (2.36 mmoles) of the ester (VIII) in 5 ml. of hydrazine hydrate was heated under reflux for 15 min. and the resulting solution cooled to room temperature. Methanol (10 ml.) was added to the solution and, on chilling, 0.30 g. (75%) of product, m.p. >300°, was obtained. The solid was recrystallized from 40 ml. of water with the aid of Norit to give 0.20 g. (50%) of product, m.p. >300°; $\lambda_{max(\mu)}^{Nujol}$ 3.09 and 6.30 (NH_2), 3.25 and 3.30 (NH), 5.65 and 5.78 (uracil C=O), 5.99 (amide C=O), 6.65 (NH and pyrimidine ring), 6.09 and 6.92 (pyrimidine ring); $\lambda_{max(m\mu)}^{pH\ 1}$ 219 (ε 12800), 273 (ε 12000); $\lambda_{max(m\mu)}^{pH\ 7}$ 223 (ε 8500), 278 (ε 10800); $\lambda_{max(m\mu)}^{pH\ 13}$ 244 (broad ε 10200), 292 (ε 16800). On paper in solvent B the product moved as a single spot with R_{Ad} 0.43.

Anal. Calcd. for $C_5H_6N_4O_3$: C, 35.2; H, 3.52; N, 32.8. Found: C, 35.3; H, 3.74; N, 32.8.

N-(2-Hydroxyethyl)uracil-5-carboxamide (XI). A mixture of 1.0 g. (4.7 mmoles) of 5-carbo-*n*-butoxyuracil (VIII), 0.86 g. (14.2 mmoles) of 2-aminoethanol, and 15 ml. of absolute ethanol was heated in a stainless steel bomb at 150–155° for 15 hr. The bomb was cooled and the contents were evaporated to dryness *in vacuo* at 50–60°. Water (6 ml.) was added to the residual sirup and the solution was adjusted to *p*H 1 with 6*M* hydrochloric acid. On chilling, the solution deposited 0.45 g. (48%) of product, m.p. 244–246°. This was recrystallized from 30 ml. of hot water to yield 0.25 g. (26%) of material, m.p. 284–285°; $\lambda_{max(\mu)}^{Nujol}$ 2.98, 3.09, 3.19, 3.31 (NH, OH), 5.81 and 5.90 (uracil and amide C=O), 6.25 (pyrimidine ring), 9.38 (C—OH); $\lambda_{max(m\mu)}^{pH\ 1}$ 221 (ε 13100), 272 (ε 12700); $\lambda_{max(m\mu)}^{pH\ 7}$ 221 (ε 13100), 273 (ε 12000); $\lambda_{max(m\mu)}^{pH\ 13}$ 244 (ε 11000), 290 (ε 17000). On paper chromatography in solvent A the product moved as a single spot with R_{Ad} 0.83.

Anal. Calcd. for $C_7H_9N_3O_4$: C, 42.2; H, 4.55; N, 21.0. Found: C, 42.3; H, 4.77; N, 20.7.

N-(n-butyl)uracil-5-carboxamide (XII). A mixture of 0.50 g. (2.36 mmoles) of ester (VIII) and 2.0 g. (27 mmoles) of *n*-butylamine was heated in a stainless steel bomb at 170° for 15 hr. The bomb was cooled and the contents were evaporated to dryness *in vacuo* at 70–80°. Water (20 ml.) was added to the semi-crystalline residue and the mixture was adjusted to *p*H 1 with 6*M* hydrochloric acid, causing the precipitation of a solid, 0.35 g. (73%), m.p. 290–293°. The solid was recrystallized from 50 ml. of hot water to yield 0.30 g. (63%) of the analytical sample, m.p. 290–291°; $\lambda_{max(\mu)}^{Nujol}$ 3.06 and 3.22 (NH), 5.78 and 5.89 (uracil C=O), 6.19 (pyrimidine ring); surprisingly, there was no amide carbonyl band near 6.0 μ; $\lambda_{max(m\mu)}^{pH\ 1}$ 222 (ε 12600), 272 (ε 12200); $\lambda_{max(m\mu)}^{pH\ 7}$ 222 (ε 13000), 273 (ε 12600); $\lambda_{max(m\mu)}^{pH\ 13}$ 243 (ε 12000), 290 (ε 17600). On paper chromatography in solvent A the product moved as a single spot with R_{Ad} 1.45.

Anal. Calcd. for $C_9H_{13}N_3O_3$: C, 51.1; H, 6.19; N, 19.9. Found: C, 51.3; H, 6.21; N, 19.9.

Acknowledgment. The authors are indebted to Dr. P. Lim for interpretation of the infrared spectra and to his staff for the paper chromatographic results. They also wish to thank Mr. O. P. Crews, Jr., and his group for the large-scale preparation of certain intermediates.

MENLO PARK, CALIF.

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, CIBA PHARMACEUTICAL PRODUCTS, INC.]

Guanidines with Antihypertensive Activity

ROBERT P. MULL, MARY E. EGBERT, AND MARY R. DAPERO

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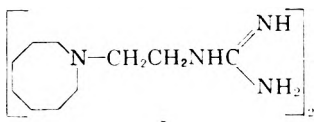
[2-(Octahydro-1-azocinyl)ethyl]guanidine sulfate was found to have protracted antihypertensive properties with the capacity to block sympathetic efferent transmission, presumably at the nerve terminals. Alterations of the ring, side chain, and terminal grouping were investigated and the relationship of these modifications to activity ascertained.

The observation that hexahydro-1-azepinylpropionamidoxime[1] possessed protracted antihypertensive activity with an unusual mechanism of action has prompted a wider search for large-membered heterocyclic compounds which might display similar unique pharmacological properties. Previous communications[2] on this study disclosed that [2-(octahydro-1-azocinyl)ethyl]guanidine sulfate (I) markedly lowered the arterial pressure of unanesthetized renal and neurogenic dogs and



I

blocked sympathetic efferent transmission, presumably at the nerve terminals. The protracted

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antihypertensive properties of this compound were corroborated in man when it was submitted for clinical trial.

From the variety of guanidine compounds investigated, some conclusions regarding structure and activity could be drawn. With reference to ring size, it was found that whereas the pyrrolidyl and piperidyl compounds exhibited moderate pharmacological properties, a significant increase in antihypertensive activity occurred when the hexahydroazepinyl moiety was present. The eight-membered ring derivative, [2-(octahydro-1-azocinyl)ethyl]guanidine sulfate, possessed maximum activity. Further increase in ring size was accompanied by diminution of activity. These findings are similar to those in the amidoxime series except that maximum activity, in that instance, was associated with the hexahydroazepine ring system. A variety of other ring systems, *e.g.*, the thiazepinyl, morpholinyl, phenothiazinyl, and pyridyl, were used in place of the octahydroazocinyl moiety, but only the pyridyl had noteworthy activity; the dialkylaminoalkyl guanidines were inactive.

Side chain variations disclosed that for optimal activity the ethyl side chain was essential. Alteration of the chain produced less active compounds, frequently with more pronounced pharmacological side effects. These findings, too, are similar to those noted with the amidoximes except that peak activity in that case was noted with the propyl side chain. Replacement of the guanidino portion of the molecule by those functional groups described in the Experimental section gave inactive compounds.

In general, the guanidines were prepared from the appropriate amines and a 2-methylthiopseudourea salt according to the method of Rathke.[3] The amines were obtained by lithium aluminum hydride reduction of the nitriles which in turn were readily synthesized by condensation of an aliphatic or cyclic imine with a halonitrile. The preparation of the larger ring systems has been previously described.[1,4,5] Hexahydro-5-oxo-1,4-thiazepine was prepared from tetrahydro-1-thiopyran-4-one by utilizing the Schmidt reaction for the ring expansion; reduction of this lactam with lithium aluminum hydride gave the desired 1,4-hexahydrothiazepine. All other compounds were prepared by established synthetic methods and are given in the Experimental or tables.

EXPERIMENTAL[6]

Tables I and II list those nitriles and amines not previously reported in the literature. 1-Pyrrolidylacetonitrile,[7] 1-piperidylacetonitrile,[8] hexahydro-1-azepinylacetonitrile,[9] octahydro-1-azocinylacetonitrile,[1b] 2-(1-pyrrolidyl)ethylamine,[10] 2-(1-piperidyl)ethylamine,[10] 2-(hexahydro-1-azepinyl)ethylamine,[9] 2-(2-pyridyl)ethylamine,[11] 2-(4-pyridyl)ethylamine,[12] and 3-(10-phenothiazinyl)propylamine[13] have been previously characterized.

The preparation of [2-(octahydro-1-azocinyl)ethyl]guanidine sulfate is given to illustrate the general method used in preparing the guanidines listed in Table III.

Octahydro-1-azocinylacetonitrile (II). Octahydroazocine[5] (109.2 g.; 0.96 mole) in 280 ml. of benzene was added to a solution of 73 g. (0.96 mole) of chloroacetonitrile in 500 ml. of benzene containing a suspension of 51.5 g. (0.48 mole) of anhydrous sodium carbonate. Vigorous stirring and refluxing was continued for 4 hr. The reaction mixture was then cooled, filtered, concentrated *in vacuo*, and fractionated. See Table I footnote for reference to physical properties of this material.

2-(Octahydro-1-azocinyl)ethylamine (III). While stirring, 127.5 g. (0.83 mole) of octahydro-1-azocinylacetonitrile in 300 ml. of ether was added slowly to 44.5 g. (1.17 mole) of lithium aluminum hydride in 2 l. of ether. The solution was then refluxed for 3 hr. and stirred at room temperature overnight. The solution was cooled and decomposed by carefully adding 40 ml. of water, 50 ml. of 20% sodium hydroxide, and 125 ml. of water to the solution. After filtration and concentration of the ether solution, the residual oil was fractionated. See Table II footnote for reference to physical properties of this material.

[2-(Octahydro-1-azocinyl)ethyl]guanidine sulfate (I). 2-Methylthiopseudourea sulfate (86 g.; 0.31 mole) was added to 98 g. (0.62 mole) of 2-(octahydro-1-azocinyl)ethylamine dissolved in 300 ml. of water and the mixture refluxed for 8 hr. Vigorous evolution of methyl mercaptan took place and solid separated. After cooling, the solid was removed by filtration and recrystallized from ethanol-water. See Table III, footnote c, for reference to physical properties of this material.

1-(Octahydro-1-azocinyl)-1-phenyl-2-propanone. A solution of 36.2 g. (0.17 mole) of 1-bromo-1-phenyl-2-propanone[14] in 100 ml. of benzene was slowly added to a stirring mixture of 38 g. (0.34 mole) of octahydroazocine in 125 ml. of benzene. After refluxing for 3 hr. the solution was stirred an additional 21 hr. at room temperature. After filtration and concentration *in vacuo*, the residual oil was fractionated to give a yellow oil, b.p. 115–128° (0.4 mm.), yield 12.4 g. (30%), n_D^{28} 1.5312.

Anal. Calcd. for $C_{16}H_{23}NO$: C, 78.37; H, 9.39; N, 5.71. Found: C, 78.17; H, 9.20; N, 5.91.

The *oxime* was recrystallized from ethanol-water and melted at 85–88°.

Anal. Calcd. for $C_{16}H_{24}N_2O$: C, 73.91; H, 9.30; N, 10.78. Found: C, 73.30; H, 9.16; N, 11.29.

1-Methyl-2-(octahydro-1-azocinyl)-2-phenethylamine. 1-Octahydro-1-azocinyl)-1-phenyl-2-propanone oxime (13.38 g.; 0.05 mole) in 100 ml. of ether was added to a refluxing solution of 4.35 g. (0.114 mole) of lithium aluminum hydride in 150 ml. of ether. The solution was refluxed for an additional 3 hr. and decomposed by successive additions of 10 ml. of water, 12 ml. of 20% sodium hydroxide and 30 ml.

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TABLE I

PHYSICAL PROPERTIES OF THE NITRILES R—$(CH_2)_m$CN

R	m	Yield, %	B.P.	mm.	n_D^t	t	Molecular Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Octahydro-1-azocinyl[a]	1	87	114–118	14	1.4720	24	$C_9H_{16}N_2$	71.11	71.17	10.61	10.62	18.43	18.36
Octahydro-1-azocinyl	3	71	140–144	15	1.4751	28	$C_{11}H_{20}N_2$	73.39	73.56	11.20	11.21	15.56	15.26
Octahydro-1-azoninyl	1	83	120–125	13	1.4783	27	$C_{10}H_{18}N_2$	72.35	72.28	10.93	11.13	16.88	16.76
1-Azacycloundecyl	1	63	149–153	15	1.4849	25	$C_{12}H_{22}N_2$	74.29	74.32	11.43	11.44	14.44	14.32
Hexahydro-1,4-thiazepin-4-yl	1	56	148–150	13	1.5268	24	$C_7H_{12}N_2S$	53.89	53.93	7.75	7.77	17.95	17.90

[a] Designated as compound II under Experimental.

TABLE II

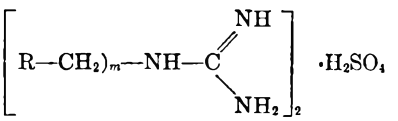
PHYSICAL PROPERTIES OF THE AMINES R—$(CH_2)_m$$NH_2$

R	m	Yield, %	B.P.	mm.	n_D^t	t	Molecular Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Octahydro-1-azocinyl[a]	2	89	108–111	14	1.4830	22	$C_9H_{20}N_2$	69.29	69.26	12.92	12.92	17.96	17.89
Octahydro-1-azocinyl	3	70	94–98	0.4	1.4858	25	$C_{10}H_{22}N_2$	70.65	70.98	13.04	13.70	16.48	16.88
Octahydro-1-azocinyl	4	74	70–77	0.35	1.4818	28	$C_{11}H_{24}N_2$	71.80	71.97	13.15	12.97	15.23	15.24
Octahydro-1-azoninyl	2	76	64–68	0.7	1.4859	26	$C_{10}H_{22}N_2$	70.65	70.88	13.04	12.93	16.48	16.61
1-Azacycloundecyl	2	70	87–90	0.3	1.4880	28	$C_{12}H_{26}N_2$	72.79	72.94	13.24	13.11	14.15	14.11
Hexahydro-1,4-thiazepin-4-yl	2	33	120–122	13	1.5293	24	$C_7H_{16}N_2S$	52.54	52.86	10.08	10.33	17.51	17.46

[a] Designated as Compound III under Experimental.

TABLE III

PHYSICAL PROPERTIES OF THE GUANIDINES



R	m	Yield, %	M.P.,[a] dec.	Molecular Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1-Pyrrolidyl	2	80	159–162	$C_{14}H_{34}N_8O_4S$[b]	41.01	40.92	8.36	8.76	27.33	27.05
1-Piperidyl	2	53	204–207	$C_{16}H_{38}N_8O_4S$	43.77	43.37	8.73	8.64	25.53	25.54
Hexahydro-1-azepinyl	2	83	208–215	$C_{18}H_{42}N_8O_4S$	46.29	46.33	9.07	9.16	24.00	24.39
Octahydro-1-azocinyl	2	74	276–281	$C_{20}H_{46}N_8O_4S$[c]	48.55	48.49	9.37	9.51	22.64	22.49
Octahydro-1-azocinyl	3	82	248–252	$C_{22}H_{50}N_8O_4S$	50.52	50.14	9.64	9.74	21.43	20.61
Octahydro-1-azocinyl	4	66	215–235	$C_{24}H_{56}N_8O_6S$[d]	50.66	50.69	9.92	9.73	19.69	19.40
Octahydro-1-azoninyl	2	70	272–275	$C_{22}H_{50}N_8O_4S$	50.52	50.86	9.64	9.70	21.43	20.88
1-Azacycloundecyl	2	70	260–273	$C_{26}H_{58}N_8O_4S$	53.93	54.08	10.10	10.10	19.35	19.25
Hexahydro-1,4-thiazepin-4-yl	2	63	207–214	$C_{16}H_{38}N_8O_4S_2$	38.20	37.59	7.62	7.60	22.28	21.94
4-Morpholinyl	2	41	177–189	$C_{14}H_{34}N_8O_6S$	38.04	38.12	7.75	7.77	25.35	24.41
10-Phenothiazinyl	3	52	127–130	$C_{32}H_{38}N_8O_4S_3$	55.30	54.95	5.51	5.70	16.12	15.73
2-Pyridyl	2	48	147–150	$C_{16}H_{26}N_8O_4S$	45.11	45.50	6.15	6.06	26.31	26.49
4-Pyridyl	2	56	256–257	$C_{16}H_{26}N_8O_4S$	45.11	45.36	6.15	6.48	26.31	26.17
Diethylamino	2	66	210–215	$C_{14}H_{38}N_8O_4S$[e]	40.52	40.82	9.23	9.20	27.00	26.95
Di-*n*-butylamino	2	63	120–123	$C_{22}H_{54}N_8O_4S$[f]	50.23	50.39	10.35	10.92	21.30	21.51
Di-*n*-propylamino	2	73	190–205	$C_{18}H_{46}N_8O_4S$[e]	46.00	46.05	9.87	9.96	23.84	23.81

[a] The recrystallizations were from ethanol-water unless otherwise noted. [b] Prepared by permitting the reactants to stand at room temperature for several days after which the product crystallized from the reaction mixture as an analytically pure sample. [c] Designated as Compound I under Experimental. [d] Monohydrate, recrystallized from ethanol. [e] Recrystallized from ethanol-ether. [f] Recrystallized from water.

of water. After filtration, concentration *in vacuo*, and fractionation of the residual oil, 6.5 g. (51%) of product was obtained, b.p. 136–146° (0.6 mm.), n_D^{28} 1.5353.

Anal. Calcd. for $C_{16}H_{26}N_2$: C, 78.11; H, 10.65; N, 11.39. Found: C, 78.52; H, 10.25; N, 10.81.

[1-Methyl-2-(octahydro-1-azocinyl)-2-phenethyl]guanidine sulfate was prepared from 5 g. (0.02 mole) of 1-methyl-2-(octahydro-1-azocinyl)-2-phenethylamine and 2.83 g. (0.01 mole) of 2-methylthiopseudourea sulfate. Recrystallization from ethanol-ether gave 4.1 g. (61%) of crystalline material, m.p. 145–155° dec.

Anal. Calcd. for $C_{34}H_{42}N_8O_4S$: C, 60.49; H, 8.66; N, 16.60. Found: C, 60.40; H, 8.37; N, 16.81.

Hexahydro-5-oxo-1,4-thiazepine. With moderate cooling, 12.7 g. (0.19 mole) of sodium azide was slowly added to 15 g. (0.13 mole) of tetrahydro-1-thiopyran-4-one[15] in 65 ml. of concd. hydrochloric acid. After the addition was completed, stirring was continued for an additional 4 hr. at room temperature. Solid sodium carbonate was then added until the solution was slightly alkaline, sufficient water being added to dissolve salts present. After extraction with chloroform, drying, and concentrating to a low volume, petroleum ether was added to precipitate the product. Recrystallization was from carbon tetrachloride–heptane to give 11.5 g. (63%) of product, m.p. 115–118°.

Anal. Calcd. for C_5H_9NOS: C, 45.84; H, 6.93; N, 10.69; S, 24.48. Found: C, 45.13; H, 6.79; N, 10.10; S, 24.23.

1,4-Hexahydrothiazepine. To a solution of 5.9 g. (0.15 mole) of lithium aluminum hydride in 800 ml. of ether was added, with stirring, 12 g. (0.09 mole) of solid hexahydro-5-oxo-1,4-thiazepine. After refluxing for 24 hr., the mixture was carefully decomposed with 20 ml. of water. After filtration and concentration of the filtrate, the residue was fractionated to give 9.5 g. (88%) of product, b.p. 192–193° n_D^{27} 1.5342.

Anal. Calcd. for $C_5H_{11}NS$: C, 51.32; H, 9.48; N, 11.97; S, 27.41. Found: C, 51.23; H, 8.96; N, 11.22; S, 27.85.

The *hydrochloride salt* was recrystallized from isopropyl alcohol–ether to give material which melted at 210–212°.

Anal. Calcd. for $C_5H_{12}ClNS$: C, 39.25; H, 7.91; N, 9.16; Cl, 23.17. Found: C, 39.08; H, 7.89; N, 9.06; Cl, 23.04.

[2-(Octahydro-1-azocinyl)ethylamino]-2-imidazoline hydroiodide. To 4 g. (0.025 mole) of 2-(octahydro-1-azocinyl)-ethylamine in 10 ml. of water was added 6.26 g. (0.025 mole) of 2-methylthio-2-imidazoline[16] hydroiodide and the mixture warmed on the steam bath until evolution of methyl mercaptan ceased. The oil which separated on cooling was dissolved in ethanol and reprecipitated by addition of ether. This low melting material amounted to 6 g. (67%).

Anal. Calcd. for $C_{12}H_{25}IN_4$: C, 40.91; H, 7.16; N, 15.92. Found: C, 39.66; H, 7.25; N, 15.65.

[2-(Octahydro-1-azocinyl)ethyl]-2-thiopseudourea dihydrochloride. 2-(Octahydro-1-azocinyl)ethylchloride hydrochloride[5] (2 g.; 0.01 mole) was added with stirring to a solution of 0.8 g. (0.01 mole) of thiourea in 26 ml. of ethanol and refluxed for 6 hr. The solid which separated after cooling was recrystallized from ethanol to give 1.6 g. (56%) of material, m.p. 212–215°.

Anal. Calcd. for $C_{10}H_{23}Cl_2N_3S$: C, 41.70; H, 8.05; N, 14.59. Found: C, 41.59; H, 7.96; N, 14.37.

Acknowledgment. The authors wish to express their appreciation to Mr. Louis Dorfman and his associates for the microanalyses.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, LOS ANGELES]

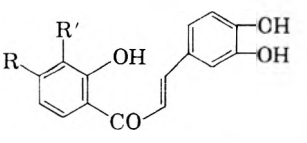
Anthochlor Pigments. XIV. The Pigments of *Viguiera multiflora* (Nutt.) and *Baeria chrysostoma* (F. and M.)

MASAME SHIMOKORIYAMA AND T. A. GEISSMAN

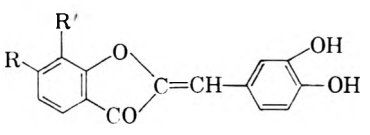
Received March 28, 1960

The flower petals of two composites, neither of which is a member of the subtribe Coreopsidinae, have been found to be pigmented with chalcones and aurones. The presence of these (anthochlor) pigments in plants not in the subtribe of which they have heretofore seemed to be characteristic offers further evidence concerning their biosynthetic relationships. As in earlier examples, a chalcone is accompanied by the structurally corresponding aurone in each instance of its occurrence.

The designation "anthochlor" has been applied to the polyhydroxychalcones and -aurones (2-benzal-3-coumaranones) typified by the widely distributed compounds butein (I) and sulfuretin (V):



I. Butein, R = OH, R′ = H
II. Coreopsin, R = *O*-glucosyl, R′ = H
III. Okanin, R = R′ = OH
IV. Marein, R = *O*-glucosyl, R′ = OH



V. Sulfuretin, R = OH, R′ = H
VI. Sulfurein, R = *O*-glucosyl, R′ = H
VII. Maritimetin, R = R′ = OH
VIII. Maritimein, R = *O*-glucosyl, R′ = OH

Pigments of these classes that contain a resorcinol-derived ring (as in I and II) rather than one derived from phloroglucinol[1] occur in numerous genera of compositae, and most characteristically

in members of the tribe Heliantheae, subtribe Coreopsidinae.[2]

The recognition, by qualitative tests, of the presence of anthochlor pigments in *Viguiera multiflora* Nutt., a member of the Heliantheae but not of the Coreopsidinae, and in *Baeria chrysostoma* F. and M., a member of the tribe Helenieae, was of special interest, as it indicated a chemical relationship between these species that was not forecast by their taxonomic classification. Accordingly, a detailed study of these two species was undertaken with a view to establishing the identity of all of their flavonoid pigments.

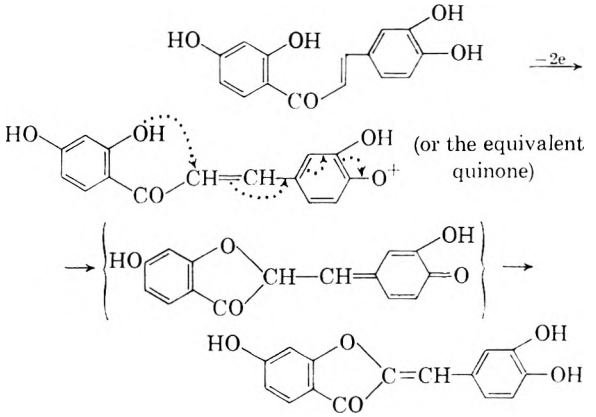
Viguiera multiflora flowers were separated into ray and disc flowers and the former examined in detail. Chromatographic separation of the constituents of an alcoholic extract led to the isolation of coreopsin (II) and quercimeritrin (quercetin 7-glucoside) in crystalline form, and to the identification by spectrometric and chromatographic methods of sulfurein (VI), sulfuretin (V), butein (I), and caffeic and chlorogenic acids. From experience in work with other plants containing chalcone and aurone glycosides, it is probable that the aglucons butein and sulfuretin are hydrolytic artefacts that arose after the flowers were collected.

The whole flower heads of *Baeria chrysostoma* were extracted and the constituents separated by chromatography on paper. The following compounds were isolated in crystalline form: butein, caffeic acid, quercetin, isoquercitrin, coreopsin, okanin (III), and marein (IV). In addition to these, sulfurein, sulfuretin, maretimein (VIII), maritimetin (VII), and chlorogenic acid were identified by spectrometric, chromatographic and chemical procedures.

These findings show that *Viguiera multiflora* and *Baeria chrysostoma* have patterns of pigmentation that are remarkably similar to these previously found in certain *Coreopsis* species. Butein and its 4′-glucoside, coreopsin, have been identified in a number of *Coreopsis* and *Cosmos* species, and constitute what are probably the commonest of the naturally occurring anthochlor pigments.[3–5] The corresponding aurone, sulfuretin, and its 6-glucoside, sulfurein,[6] have been found in *Cosmos sulfureus*,[7] the yellow *Dahlia variabilis*,[8] and in *Coreopsis gigantea* and *C. maritima*.[9] The presence of caffeic and chlorogenic acids is so common in numerous composites as to make their discovery in the present study quite unexceptional. Quercetin 7-glucoside (quercimeritrin) is known to occur in the sunflower, *Helianthus annuus*,[10] but has not previously been found in other genera of the tribe. The flavones that have so far been found to co-occur with anthochlor pigments are luteolin in *Cosmos sulfureus*,[7] its 7-glucoside in *Coreopsis maritima*,[8] and isoquercitrin in *Cosmos sulfureus*.[4]

It is interesting to note that *Baeria chrysostoma* contains nearly the same pigment complex as does *Coreopsis maritima*[9]; the exception is that in *Baeria* isoquercitrin (quercetin 3-glucoside), and in *C. maritima* luteolin 7-glucoside, accompany the chalcones coreopsin and marein and the aurones sulfurein and maritimein.

The presence of the chalcone-aurone pairs coreopsin-sulfurein (in *Viguiera* and *Baeria*) and marein-maritimein (in *Baeria*) emphasizes further the close interrelationship of chalcones and aurones and supports the hypothesis that aurones are directly derived from chalcones by way of an oxidation reaction. The conversion of 3,4-dihydroxychalcones into aurones occurs with ease under ordinary conditions. Butein, when allowed to stand in alcoholic solution slowly changes into sulfuretin, and it has been found experimentally that in air in the presence of alkali the change is rapid.[11] The formulation of this reaction in the following way suggests possible implications in the oxidation of other 3,4-dihydroxylated flavonoid compounds:



(1) It is of interest to note that aurones based upon the phloroglucinol ring have not been found in the Compositae, but are present in such diverse genera as *Oxalis* and *Antirrhinum*; see ref. 2.

(2) T. A. Geissman, J. B. Harborne, and M. K. Seikel, *Les Heterocycles Oxygenes*, Colloques Internat. du Centre National de Recherche Scientifique, Lyon, 1955, pp. 277–285.

(3) T. A. Geissman, *J. Am. Chem. Soc.*, **63**, 656; **63**, 2689 (1941); T. A. Geissman and C. D. Heaton, *J. Am. Chem. Soc.*, **65**, 677; **66**, 486 (1944); M. K. Seikel and T. A. Geissman, *J. Am. Chem. Soc.*, **72**, 5720 (1950).

(4) M. Shimokoriyama and S. Hattori, *J. Am. Chem. Soc.*, **75**, 1900 (1953).

(5) T. A. Geissman and L. Jurd, *J. Am. Chem. Soc.*, **76**, 4475 (1954).

(6) L. Farkas, L. Pallos, and Z. Paál, *Chem. Ber.*, **92**, 2847 (1959).

(7) T. A. Geissman, *J. Am. Chem. Soc.*, **64**, 1704 (1942).

(8) C. G. Nordstrom and T. Swain, *Chem. and Ind.*, 823 (1953); *Arch. Biochem. Biophys.*, **60**, 329 (1956).

(9) T. A. Geissman, J. B. Harborne, and M. K. Seikel, *Arch. Biochem. Biophys.*, **78**, 825 (1956).

(10) C. E. Sando, *J. Biol. Chem.*, **68**, 407 (1926).

(11) J. B. Harborne and T. A. Geissman, unpublished observations in this laboratory.

It is of interest to note that in studies of this reaction in which various model compounds were examined, 4-hydroxyl and 4-hydroxyl-3-methoxylchalcones were not converted into aurones.[11]

The fact that all of the flavonoid compounds known to be present in the *Viguiera* and *Baeria* species examined contain the 3,4-dihydroxyphenyl residue indicates their close biosynthetic relationship. The presence of quercimeritrin in *Viguiera* and of isoquercitrin in *Baeria*, along with the 6-(aurone numbering) and 4'-(chalcone numbering) glycosides of the anthochlor pigments indicates that the processes of glycosylation in the flavone and anthochlor pigments bear no direct connection with each other.

The taxonomic relationships suggested by these findings offer attractive ground for speculation but must be assessed with caution. That anthochlor pigmentation is not a purely accidental feature is shown by the fact that it is highly characteristic of the sub-tribe Coreopsidinae (being found, for example, in *Cosmos*, *Coreopsis*, *Dahlia*, *Bidens*) but is encountered only rarely outside of that group of genera. Qualitative tests in this laboratory have shown that *Viguiera laciniata* and *Baeria macrantha* also contain pigments of this class, an indication that it is the genera *Viguiera* and *Baeria* that are so characterized and not simply the two species *V. multiflora* and *B. Chrysostoma*. That these observations suggest that there is a closer relationship between *Viguiera* and the genera of the Coreopsidinae than between *Viguiera* and other genera of the Heliantheae is a reasonable speculation; but by the same token, *Baeria*, of the tribe Helenieae, should be considered to be more closely related to members of another taxonomic tribe than with those of its own, no other of which has been found to be anthochlor-pigmented.

EXPERIMENTAL

General remarks. The filter paper used for the isolation of the pure compounds described below was Whatman No. 3 paper (19 × 45 cm.) that had been prewashed with butanol: 2N acetic acid (1:1) (BAW); 30% acetic acid (AA); and 50% ethanol, in this order, each for 3 days. In the preparation of solutions for spectrophotometric measurements, Whatman No. 1 paper, prewashed as above, was used, and the final operation was carried out by the half-banding method.[12] All solvents were freshly distilled. For the elution of glycosides and chlorogenic acid, 50% aqueous ethanol was used; for aglycones and caffeic acid, 95% ethanol. In determining shifts in absorption spectra caused by aluminum chloride, 3 drops of 5% ethanolic aluminum chloride were added to the sample and blank solutions (3 ml.) in the spectrophotometer cuvettes. Where identifications were made by chromatographic and spectrometric means, authentic samples were used as standards for comparison.

Viguiera multiflora. Flowers were collected near Gothic, Colorado, in August, 1959. The whole flower heads were dried at once in a current of warm air. The rays were separated, and 8 g. was extracted five times, each with 80 ml. of methanol. The combined extracts were filtered and evaporated under reduced pressure and the aqueous concentrate washed thoroughly with benzene and with petroleum ether (b.p. 20–40°), and then exhaustively extracted with ethyl acetate (20 times). Evaporation of the ethyl acetate solution yielded a residue that was dissolved in 8 ml. of 50% ethanol. A similar extract of the disc florets gave a paper chromatogram that was nearly the same as that of the ray flowers; it was not studied in detail.

To each of four Whatman No. 3 sheets was applied 1 ml. of the stock solution; development with BAW gave five distinct bands. These were eluted and purified by repeated chromatography with BAW and AA.

Bands 1 and 2 contained caffeic acid, butein, and sulfuretin (band 1) and quercetin and chlorogenic acid. These were readily identified by comparison with authentic specimens and by their ultraviolet absorption spectra.

Band 3 gave butein on hydrolysis. When the eluate was evaporated and the residue dissolved in 2 ml. of 30% ethanol, coreopsin crystallized (18 mg.). It melted at 213–214° (reported[10] m.p. 209–211°, 215–216°).

Anal. Calcd. for $C_{21}H_{22}O_{10}\cdot{}^1/_2H_2O$: C, 56.88; H, 5.23. Found: C, 57.15; H, 5.25.

Band 4 contained as its chief component sulfurein, identified by its ultraviolet absorption and chromatographic comparison with authentic material.

Band 5 contained a flavone glycoside. When the eluate was evaporated and dissolved in 1 ml. of 50% ethanol, 3 mg. of the crystalline glycoside separated. Recrystallization from 40% ethanol gave 2 mg. of pure material, m.p. 247–248°. It was identified as quercimeritrin (reported[10] m.p. 247–249°) from the following observations: It showed chromatographic behavior identical with that of authentic quercimeritrin and showed exactly the same color reactions, the bright green-yellow fluorescence (in ultraviolet light) with aluminum chloride being characteristic of flavonols with free 3-hydroxyl groups; it gave quercetin on hydrolysis.

Baeria chrysostoma. Whole flower heads of *B. chrysostoma*, collected in the vicinity of Los Angeles, were dried, ground, and extracted exhaustively with methanol. An ethyl acetate solution was prepared and chromatographed on Whatman No. 3 paper as described for *Viguiera multiflora*. Four distinct bands were developed.

Band 1 was eluted and the eluate evaporated under reduced pressure. A solution of the residue in 3 ml. of 30% ethanol was cooled and soon deposited 16 mg. of crystalline butein. The mother liquor was separated on paper with 30% acetic acid as developing solvent. The two bands that were formed contained caffeic acid (A) and butein plus sulfuretin (B). From the eluate of B was obtained a further 5 mg. of crystalline butein; sulfuretin was identified by chromatographic comparison with authentic material and by its ultraviolet absorption spectrum. The butein, m.p. 213–214°, was analyzed.

Anal. Calcd. for $C_{15}H_{12}O_5\cdot H_2O$: C, 62.06; H, 4.86. Found: C, 62.54; H, 5.17.

Band 2 yielded an eluate that deposited quercetin (11 mg.) on concentration. This was identified by its melting point and chromatographic properties. The mother liquor contained chlorogenic acid.

Band 3 was eluted and the eluate concentrated to 5 ml. and kept at 0°. Crystalline okanin (106 mg.) separated. Recrystallized from 40% ethanol, the okanin melted at 235–240° (reported[13] m.p. 235–240°).

Anal. Calcd. for $C_{15}H_{12}O_6\cdot{}^1/_2H_2O$: C, 60.61; H, 4.41. Found: C, 60.91; H, 4.39.

The mother liquor from the crystalline okanin was further separated by chromatography on paper with 30% acetic acid. Four bands were formed; these contained, respectively, A) chlorogenic acid; B) isoquercitrin, obtained in crystalline

(12) T. A. Geissman, J. B. Harborne, and M. K. Seikel, *J. Am. Chem. Soc.*, 78, 825 (1956).

(13) F. E. King and T. J. King, *J. Chem. Soc.*, 569 (1951).

form (24 mg., m.p. 196–198°, identified by comparison with an authentic specimen; C) coreopsin, obtained in crystalline form (18 mg.), m.p. 213–214°, and sulfurein; and D) additional okanin, from which 50 mg. of crystalline material was isolated, and maritimetin.

Band D, after elution and concentration of the eluate to 5 ml., yielded 309 mg. of marein. This was crystallized as bright orange aggregates from 50% ethanol. When hydrolyzed with 5% hydrochloric acid it gave a mixture of okanin and the isomeric flavano-okanin. The presence of marein in the mother liquors was readily established by paper chromatographic comparison with authentic material and by spectral measurements.

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LOS ANGELES, CALIF.

[CONTRIBUTION FROM THE LABORATORY OF CHEMISTRY OF NATURAL PRODUCTS, NATIONAL HEART INSTITUTE, NATIONAL INSTITUTES OF HEALTH, U. S. PUBLIC HEALTH SERVICE, DEPARTMENT OF HEALTH, EDUCATION AND WELFARE]

Alkaloids of *Ormosia jamaicensis* (Urb.)—Jamaicensine and Jamaidine

H. A. LLOYD AND E. C. HORNING

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Jamaicensine, $C_{14}N_{22}N_2O$, and jamaidine, $C_{15}H_{24}N_2O_2$, have been isolated from seeds of *Ormosia jamaicensis* (Urb.) and *O. panamensis* (Benth.) Jamaicensine closely resembles, but may not be identical with, a new alkaloid angustifoline isolated recently from *Lupinus angustifolius*. Jamaidine is isomeric with hydroxylupanine but not identical with it.

Three isomeric bases of formula $C_{20}H_{33}N_3$ present in seeds of *Ormosia panamensis* (Benth.) and other *Ormosia* species were described in a previous paper.[1] Several additional alkaloids, two of which were oxygen-containing, were also found in seeds of *Ormosia* species which were examined, except for *O. stipitata* (Schery).[2] The oxygen-containing alkaloids have now been isolated and characterized. Seeds of *O. panamensis* and *O. jamaicensis* (Urb.) were used as the source of these compounds. The extraction process was carried out as described previously,[1] in such a way as to yield an ether solution that contained the three major bases (panamine, ormosanine, ormosinine) and a chloroform solution that contained two major components and several minor ones. Chromatography on alumina provided these two components in pure form. They were named jamaicensine and jamaidine.

Jamaicensine (m.p. 80.5–81°) was found to have an empirical formula $C_{14}H_{22}N_2O$ through analysis of the base and a number of derivatives. The hydrochloride and picrate were formed in 1:1 ratio of acid to base, and a determination of the neutral equivalent showed that only one basic group was present. A strongly positive Simon test indicated that this was a secondary amino group. This was confirmed through the preparation of an acetyl and a benzoyl derivative, and through the preparation of *N*-methyljamaicensine. The latter compound gave a negative Simon test. Additional analytical determinations indicated that one active hydrogen atom was present in the alkaloid, and that no C-methyl, *N*-methyl or *O*-methyl groups were present. No absorption was found through the ultraviolet region (above 220 mμ). The infrared absorption spectrum showed a strong carbonyl band at 1625 cm.$^{-1}$; this suggested that the oxygen atom was present in an amide group, possibly of the α-piperidone type. Strong absorption bands at 919 and 998 cm.$^{-1}$ and absorption at 3078 cm.$^{-1}$ in the carbon-hydrogen region suggested that a vinyl group $RCH{=}CH_2$ was present.[3] When the alkaloid was hydrogenated in acetic acid solution with platinum (Adams' catalyst), dihydrojamaicensine was formed. The infrared spectrum of this compound retained the carbonyl (amide) absorption band, but the bands at 3078 and 998 cm.$^{-1}$ were no longer present and only a weak band remained at 919 cm.$^{-1}$. Additional evidence for a terminal methylene group was obtained by oxidation of the alkaloid with a periodate-permanganate mixture; formaldehyde was isolated as the dimedone derivative.

The reduction of the ethylenic double bond and of the carbonyl (amide) group was effected in hydrochloric acid solution with a platinum catalyst. Dihydrodesoxyjamaicensine contained no oxygen and the infrared spectrum showed no evidence of a carbonyl or a terminal methylene group. This reduction method is applicable to lactams of the sparteine family.[4] The sum of evidence suggests that jamaicensine is a tricyclic base containing a lactam group, a secondary amino group, and a side chain with a vinyl group.

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(1) H. A. Lloyd and E. C. Horning, *J. Am. Chem. Soc.*, 80, 1506 (1958).

(2) H. A. Lloyd and E. C. Horning, *J. Org. Chem.*, 23, 1074 (1958).

(3) W. F. Cockburn and L. Marion, *Can. J. Chem.*, 30, 92 (1952); L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, 2nd Edition, John Wiley and Sons, N. Y., 1958, p. 34.

(4) F. Galinovsky and E. Stern, *Ber.* 77, 132 (1944).

Wiewiorowski, Galinovsky, and Bratek[5] recently reported the isolation of a new lupine alkaloid, angustifoline, from *Lupinus angustifolius* and *L. perennis*. This compound was reported to contain both a tertiary amino group and an amide group. The empirical formula of angustifoline is the same as that of jamaicensine, and there is a very close correspondence in the properties of the derivatives of angustifoline and those found for jamaicensine. A comparison of the pertinent data is given in Table 1. The extent of agreement suggests strongly that the two alkaloids may be identical, but the evidence for a secondary amine structure in jamaicensine is unequivocal. The two names should be retained until angustifoline can be reinvestigated.

TABLE I

PROPERTIES OF ANGUSTIFOLINE AND JAMAICENSINE DERIVATIVES

Angustifoline $C_{14}H_{22}N_2O$	Jamaicensine $C_{14}H_{22}N_2O$
M.p. 79–80°	M.p. 80.5–81°
$[\alpha]_D^{20}$ −7.5° (EtOH)	$[\alpha]_D^{25}$ +5.2 (EtOH)
$C_{14}H_{22}N_2O \cdot HCl \cdot H_2O$ m.p. 134–135°	$C_{14}H_{22}N_2O \cdot HCl$ m.p. 96–97°
Monopicrate m.p. 186°	Monopicrate m.p. 182–185°
Dihydroangustifoline	Dihydrojamaicensine
M.p. 82–83°	M.p. 82.5–83.5°
$[\alpha]_D^{20}$ +36.8° (EtOH)	$[\alpha]_D^{23}$ +37.2° (EtOH)
Dihydrodesoxyangustifoline	Dihydrodesoxyjamaicensine
Dipicrate m.p. 207° dec.	Dipicrate m.p. 204–210° dec.

Jamaidine, (m.p. 194.5–195°) was found to have an empirical formula $C_{15}H_{24}N_2O_2$. Analytical determinations indicated that an active hydrogen atom was present, and that C-methyl, *O*-methyl and *N*-methyl groups were absent. The Simon test was negative. A neutral equivalent determination indicated that only one nitrogen atom was present in a basic group. No absorption was found in the ultraviolet region (above 220 mμ). The infrared spectrum contained a strong band at 1625 cm.$^{-1}$ indicative of a carbonyl (amide) group. Bands at 3620 cm.$^{-1}$ and 3425 cm.$^{-1}$ were indicative of an hydroxyl group (nonbonded and bonded). An acetyl derivative was prepared.

Jamaidine was not reduced with a platinum catalyst in ethanol, and *O*-acetyl-jamaidine was not reduced with a platinum catalyst in acetic acid. When jamaidine was hydrogenated in hydrochloric acid solution with a platinum catalyst, the product was a base with an empirical formula $C_{15}H_{26}N_2O$. This substance showed no carbonyl (amide) absorption in the infrared spectrum, but the hydroxyl absorption bands were unchanged.

(5) M. Wiewiorowski, F. Galinovsky, and M. D. Bratek, *Monatsh.*, **88**, 663 (1957).

The structural information suggested that jamaidine was a hydroxylactam, probably of the sparteine or matrine group. The hydroxyl group was removed by Galinovsky's method,[6] and the product (after hydrogenation) had an infrared spectrum identical with that of an authentic specimen of *dl*-lupanine, and the molecular rotation was identical with that of *d*-lupanine. However, jamaidine is not identical with 13-hydroxylupanine, the only known naturally-occurring hydroxylupanine. The melting points, infrared spectra, and perchlorates of the two alkaloids are different and desoxyjamaidine does not correspond to 13-hydroxysparteine, the reduction product of the alkaloid, hydroxylupanine. Additional studies on both alkaloids are in progress.

EXPERIMENTAL[7]

Extraction. Seeds of *Ormosia jamaicensis* (1500 g.), processed in the manner reported in a previous paper,[1] yielded 35 g. of crude material from an ether extract and 8.1 g. of material from a chloroform extract. The two residues were examined by ascending paper chromatography on Whatman #1 paper, in a solvent system of *sec*-butyl alcohol, hydrochloric acid, and water (100:20:36). The ether extract consisted of a mixture of ormosinine, ormosanine, and panamine as described previously,[1] with traces of other bases. The chloroform extract was mostly jamaicensine (*Rf* 0.84) and jamaidine (0.60) and smaller amounts of alkaloids of *Rf* 0.32, 0.40 (ormosinine), 0.52 (panamine), 0.69 (ormosanine), and 0.96.

An extraction of *Ormosia panamensis* seeds gave substantially the same results.

Isolation of jamaicensine and jamaidine. The crude alkaloids of the chloroform extract were dissolved in dry thiophene-free benzene and chromatographed on Merck alumina (400 g.). The separation was followed by paper chromatography in the solvent system described above. Some nonbasic material was eluted with benzene. Elution with benzene–ethyl acetate (3:1) and benzene–ethyl acetate (3:2) gave 1.55 g. of a mixture of alkaloids of *Rf* 0.30, 0.43, 0.54, 0.68, and increasing amounts of jamaicensine (0.84). Elution with benzene–ethyl acetate (2:3) and pure ethyl acetate gave 2.45 g. of a semicrystalline fraction consisting of jamaicensine with traces of other alkaloids. Several recrystallizations from hexane yielded 2.1 g. of jamaicensine, m.p. 78–80°. Continued elution of the column with ethyl acetate and ethyl acetate–chloroform (9:1) gave 1.34 g. of an oily mixture of jamaicensine and jamaidine (*Rf* 0.60). Upon addition of ether to this oil, jamaidine (0.65 g.) crystallized as small needles, m.p. 185–188°. Elution with chloroform gave a brown oil (0.75 g.), a mixture of jamaicensine, jamaidine, and an alkaloid of *Rf* 0.98. Further chromatography of the intermediate fractions yielded small amounts of jamaicensine and jamaidine.

Jamaicensine. The material obtained by column chromatography was sublimed at 60° (0.001 mm.) and recrystallized twice from hexane to give clusters of short needles, m.p. 80.5–81°, $[\alpha]_{589}^{25}$ +5.2°, $[\alpha]_{436}^{26}$ +20.4° (*c* 0.95, ethanol).

Anal. Calcd. for $C_{14}H_{22}N_2O$: C, 71.75; H, 9.46; N, 11.96; neut. equiv., 234.3; active H, 0.43 (one), (C)CH_3, 6.42.

(6) F. Galinovsky and M. Pöhm, *Monats.*, **80**, 864 (1949).

(7) All melting points were observed on a Kofler stage. The optical rotations were taken with a Rudolph photo-electric spectropolarimeter and the infrared spectra were recorded on a Perkin-Elmer Model 21 or a Beckman IR-7 double-beam spectrophotometer. Analyses were performed by Mr. J. F. Alicino, Metuchen, N. J., and Mr. W. Manser, Zurich, Switzerland.

Found: C, 71.54; H, 9.37; N, 11.61; neut. equiv., 238; active H, 0.50; OCH_3, none; (C)CH_3, 1.22; (N)CH_3, none.

Jamaicensine hydrochloride. A solution of jamaicensine in ethanol was made acid to Congo Red by addition of a few drops of concd. hydrochloric acid. The hydrochloride was precipitated by addition of ether and was recrystallized from acetone containing a drop of methanol; it formed fine needles, m.p. 96–98°, $[\alpha]_{589}^{23}$ +15°, $[\alpha]_{436}^{23}$ +39° (*c* 0.92 ethanol).

Anal. Calcd. for $C_{14}H_{22}N_2O \cdot HCl$: C, 62.09; H, 8.56; N, 10.35; Cl, 13.09. Found: C, 61.95; H, 8.58; N, 10.24; Cl, 13.21.

Jamaicensine picrate was prepared by treating the free base in ether with an excess of a saturated ether solution of picric acid. The precipitate was washed with ether and recrystallized twice from ethanol, m.p. 182–185° dec.

Anal. Calcd. for $C_{14}H_{22}N_2O \cdot C_6H_3N_3O_7$: C, 51.83; H, 5.44; N, 15.11. Found: C, 51.90; H, 5.43; N, 15.17.

N-Methyljamaicensine hydriodide was prepared by refluxing the free base in acetone with an excess of methyl iodide. It was recrystallized four times from acetone-ether to give needles, m.p. 196–199°.

Anal. Calcd. for $C_{15}H_{25}N_2OI$: C, 47.88; H, 6.70; N, 7.45; I, 33.73. Found: C, 47.56; H, 6.79; N, 7.46; I, 33.84.

N-Methyljamaicensine. A solution of the hydriodide in water was made strongly basic with sodium hydroxide and extracted exhaustively with chloroform. The chloroform extract yielded a crystalline residue which was sublimed and recrystallized twice from hexane to give iridescent plates, m.p. 90–91°.

Anal. Calcd. for $C_{15}H_{24}N_2O$: C, 72.54; H, 9.74; N, 11.28; neut. equiv., 248.4. Found: C, 72.80; H, 9.72; N, 11.32; Neut. equiv., 246.

N-Benzoyljamaicensine prepared by the Schotten-Baumann method was recrystallized three times from benzene-cyclohexane to give small prisms, m.p. 194.5–195.5°.

Anal. Calcd. for $C_{21}H_{26}N_2O_2$: C, 74.52; H, 7.74; N, 8.28. Found: C, 74.35; H, 7.81; N, 8.28.

N-Acetyljamaicensine. A solution of jamaicensine in acetic anhydride was allowed to stand overnight at room temperature. The excess anhydride was destroyed with water and the solution was neutralized with sodium carbonate and extracted with chloroform. Evaporation of the dried organic extract yielded a colorless sirup which crystallized on trituration with ether. Three recrystallizations from cyclohexane-ether gave thick needles, m.p. 150.5–151.5°.

Anal. Calcd. for $C_{16}H_{24}N_2O_2$: C, 69.53; H, 8.75; N, 10.14. Found: C, 69.59; H, 8.80; N, 10.10.

Dihydrojamaicensine. A solution of 240 mg. of jamaicensine in 15 ml. of glacial acetic acid was added to 15 ml. of acetic acid containing 70 mg. of reduced platinum oxide catalyst, and the mixture was stirred under hydrogen at room temperature and atmospheric pressure. The reduction stopped in 10 min. after 1 equivalent of hydrogen was absorbed. The solution was filtered from the catalyst and evaporated to dryness *in vacuo*. The residue was dissolved in a small amount of water and the solution was made strongly alkaline with sodium hydroxide pellets and extracted with ether and chloroform. The combined extracts, when dried and evaporated, yielded 211 mg. of thick oil which crystallized to a buff-colored product on trituration with a few drops of ether. The material was sublimed at 60° (0.001 mm.) and recrystallized from hexane to give colorless prisms, m.p. 82.5–83.5°, $[\alpha]_{589}^{23}$ +37.2°, $[\alpha]_{436}^{23}$ +90.3° (*c* 1.24, ethanol).

Anal. Calcd. for $C_{14}H_{24}N_2O$: C, 71.14; H, 10.24; N, 11.85; (C)CH_3, 6.36; neut. equiv., 236.3. Found: C, 71.09; H, 10.21; N, 11.75; (C)CH_3, 2.98; neut. equiv., 233.

Dihydrojamaicensine hydrochloride was prepared in ethanol-ether and recrystallized twice from wet acetone to give fine long needles, m.p. 89–90.5°.

Anal. Calcd. for $C_{14}H_{24}N_2O \cdot HCl \cdot H_2O$: C, 57.81; H, 9.36; N, 9.63; Cl, 12.19; (C)CH_3, 5.17. Found: C, 57.66; H, 9.30; N, 9.68; Cl, 12.09; (C)CH_3, 2.93.

Hydrogenation of jamaicensine with platinum in dilute hydrochloric acid. A solution of 238 mg. of jamaicensine in 20 ml. of 1*N* hydrochloric acid was stirred under hydrogen with 250 mg. of reduced platinum oxide catalyst. The reduction stopped in 5 hr. after 3 equivalents of hydrogen were absorbed at room temperature and atmospheric pressure. The catalyst was removed by filtration and the solution was made strongly basic with sodium hydroxide pellets and extracted with chloroform to yield 225 mg. of thick colorless oil.

Dipicrate of dihydrodesoxyjamaicensine. A solution of the oil in ether was treated with an ether solution of picric acid and the precipitate was recrystallized three times from ethanol to give small needles, m.p. 204–210° dec.

Anal. Calcd. for $C_{14}H_{26}N_2 \cdot 2C_6H_3N_3O_7$: C, 45.88; H, 4.74; N, 16.47. Found: C, 45.91; H, 4.63; N, 16.22.

Oxidation of jamaicensine with potassium permanganate–periodic acid. An aqueous solution of periodic acid (30 mg.) was added to a solution of 30 mg. of jamaicensine and a crystal of potassium permanganate in 10% acetic acid. The brown solution was allowed to stand for 10 min. and filtered through charcoal. A solution of 30 mg. of dimedone in 50% aqueous alcohol was added and the mixture was heated for 2 min. (water bath). Upon standing fine long needles separated. The product was recrystallized from aqueous alcohol, and the m.p. and mixed m.p. with an authentic sample of dimedone derivative of formaldehyde was 189–191°.

Jamaidine. Sublimation of the crude product followed by repeated recrystallizations from acetone yielded colorless needles, m.p. 194.5–195°, $[\alpha]_{589}^{23}$ +63.7°, $[\alpha]_{436}^{23}$ +141° (*c* 0.66, ethanol).

Anal. Calcd. for $C_{15}H_{24}N_2O_2$: C, 68.15; H, 9.15; N, 10.60; active H, 0.38 (one); neut. equiv., 264.4. Found: C, 67.91, 68.02; H, 9.30, 9.15; N, 10.78, 10.70; active H, 0.31; neut. equiv., 267; (N)CH_3, none; (C)CH_3, none; OCH_3, none.

Jamaidine perchlorate. This salt was prepared and recrystallized from methanol; it formed small prisms, m.p. 175–177°.

Anal. Calcd. for $C_{15}H_{24}N_2O_2 \cdot HClO_4$: C, 49.38; H, 6.91; N, 7.68; Cl, 9.72; neut. equiv., 364.8. Found: C, 49.42, 49.57; H, 6.81, 6.71; N, 7.59, 7.74; Cl, 9.66, 9.77; neut. equiv., 366.

O-Acetyljamaidine. A solution of jamaidine in acetic anhydride and pyridine was heated for 10 min. (steam bath). The excess anhydride was decomposed with water, and the solution was made strongly basic with sodium hydroxide and extracted with chloroform. The chloroform extract was dried over anhydrous potassium carbonate and concentrated *in vacuo* to give a pale yellow oil which crystallized upon trituration with ether. Two recrystallizations from acetone gave colorless plates, m.p. 170.5–171°. The acetate showed basic properties.

Anal. Calcd. for $C_{17}H_{26}N_2O_3$: C, 66.64; H, 8.55; N, 9.14. Found: C, 66.71; H, 8.52; N, 9.08.

Hydrogenation experiments. A solution of *O*-acetyl jamaidine in acetic acid was stirred for 2 hr. under hydrogen with reduced platinum oxide. No hydrogen was absorbed at room temperature and atmospheric pressure and the base was recovered unchanged. Under similar conditions a solution of jamaidine in ethanol did not absorb hydrogen.

Desoxyjamaidine. A mixture of 136 mg. of jamaidine and 140 mg. of reduced platinum oxide catalyst in 1*N* hydrochloric acid absorbed 2 equivalents of hydrogen in 12 hr., at room temperature and atmospheric pressure. The solution, filtered from the catalyst, was made strongly alkaline and thoroughly extracted with chloroform. The extract was dried and evaporated to yield 124 mg. of colorless crystals, m.p. 174–177°. Two recrystallizations from acetone gave long needles, m.p. 178–179°, $[\alpha]_{589}^{24}$ −25.6°, $[\alpha]_{436}^{24}$ −47.3° (*c* 0.76, ethanol).

Anal. Calcd. for $C_{15}H_{26}N_2O$: C, 71.95; H, 10.47, N, 11 19; neut. equiv. 125.3. Found: C, 72.03; H, 10.37; N, 11.04; neut. equiv., 125.3.

The *dipicrate* of desoxyjamaidine was prepared in ethanol

and recrystallized from ethyl acetate–ethanol, m.p. 122° dec.

Anal. Calcd. for $C_{15}H_{26}N_2O \cdot 2C_6H_3N_3O_7$: C, 45.76; H, 4.55; N, 15.81. Found: C, 46.00; H, 4.84; N, 15.52.

Conversion of jamaidine to d-lupanine. A mixture of 100 mg. of jamaidine and 1 g. of phosphorus pentoxide was heated for 6 hr. at 170–180° under nitrogen. It was then cooled to room temperature and ice water was added to decompose the phosphorus pentoxide. The resulting solution was made strongly basic with potassium hydroxide and extracted with chloroform. The extract was dried, the solvent was evaporated, and the residue was submitted to evaporative distillation in high vacuum (0.01 mm.). A colorless oil (45 mg.) was obtained. The infrared spectrum carbon tetrachloride showed a band at 3021 cm.$^{-1}$ (—CH=CH—) and no hydroxyl absorption. The oil was dissolved in absolute ethanol and hydrogenated at room temperature and atmospheric pressure in the presence of 10% palladium-charcoal catalyst. The solution took up the calculated amount of hydrogen in 5 min. After another 15 min., during which no more hydrogen was absorbed, the catalyst was removed by filtration and the solution was evaporated. Two evaporative distillations of the residue yielded 35 mg. of thick colorless oil, $[\alpha]^{24}_{589}$ +78.5 (c 0.35, ethanol); the reported[8] rotation of *d*-lupanine is $[\alpha]^{20}_{D}$ +79.5. The infrared spectrum of the product was identical with that of an authentic sample of *dl*-lupanine. A picrate, m.p. 180–183° was prepared; the reported[3] melting point of *d*-lupanine picrate is 185°.

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BETHESDA 14, MD.

(8) J. F. Couch, *J. Am. Chem. Soc.*, 59, 1469 (1937).

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE]

Chemistry of the Spiroaminoketal Side Chain of Solasodine and Tomatidine. IV.[1] Chemistry of the Tomatidine Side Chain

YOSHIO SATO, H. GEORGE LATHAM, JR., AND NOBUO IKEKAWA[2]

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Treatment of tomatidine with acetic anhydride yields an acetylated Δ^2-tetrahydropyridylallopregnane and a diacetylamino-5α,20(22)furostene derivative. With a zinc chloride-acetic anhydride-acetic acid solution tomatidine affords a Δ^1-tetrahydropyridylallopregnane derivative. The chemistry of these compounds is discussed.

In the previous papers of this series, solasodine and its derivatives were subjected to a series of reactions which revealed the interesting and interrelated chemistry of the spiroaminoketal system present in these alkaloids. Tomatidine has now been exposed to a similar series of reactions and, as expected, behaves in an analogous manner. The acetic anhydride treatment of tomatidine[3] (I. R = H) yields the crystalline 26-aminodiacetyl-5α-furost-20(22)en-3β-ol acetate (II) and an amorphous component which affords crystalline III. The oxidation and subsequent removal of the 16β-aminodiacetyl ester side chain of II to Δ^{16}-allopregnenolone (VI. R = H) have previously been reported.[3] The oxidative degradation to 3β-acetoxyallopregnenolone (VI. R = Ac) of the 26-aminoacetyl derivative V which is readily obtained from II by chromatography on an alumina column or from the acid catalyzed isomerization of *O,N*-diacetyltomatidine (Ia. R = Ac) has similarly been described.[4] The reversion of V to II can be effected by treatment of V with a solution of acetic anhydride and pyridine.

The above mentioned amorphous residue, obtained from the acetic anhydride treatment of tomatidine, possesses an ultraviolet absorption band at 236 mμ (log ϵ, 3.92) and characteristic infrared absorption bands at 5.78, 5.98, and 6.07 μ. These data are in close agreement with those obtained for the analogous product from solasodine[5] and are consistent for the assignment of an α,β-unsaturated acetylamino function[6,7] to this component. This is supported by the correct elemental analysis[4] (for structure III) as well as by the following transformation. Hydrolysis of the amorphous mass with hydrochloric acid in acetic acid yields the crystalline acetylamino ketone IV as in

(1) For previous papers of this series see *J. Org. Chem.*, 25, 789 (1960).

(2) Visiting Scientist, National Institutes of Health.

(3) Y. Sato, A. Katz, and E. Mosettig, *J. Am. Chem. Soc.*, 74, 538 (1952).

(4) See Part I, Y. Sato, N. Ikekawa, and E. Mosettig, *J. Org. Chem.*, 25, 783 (1960).

(5) See Part II, Y. Sato and N. Ikekawa, *J. Org. Chem.*, 25, 786 (1960).

(6) G. Rosenkrantz, O. Mancera, F. Sondheimer, and C. Djerassi, *J. Org. Chem.*, 21, 520 (1956).

(7) R. Griot and T. Wagner-Jauregg, *Helv. Chim. Acta*, 42, 121, 605 (1959).

the case of the solasodine derivative.[5] The Δ^2-tetrahydropyridines are known for their ease of hydrolysis to acylamino ketones.[8] Finally, the amorphous substance afforded crystalline III when seeded with a crystalline sample of III prepared by treating tomatidine with a solution of zinc chloride, acetic anhydride, and acetic acid mixture and reacting the resultant so-called pseudotomatidine "B" with acetic anhydride in pyridine. Product III thus prepared by this alternate route proved to be identical with III obtained from the amorphous substance.

The site of unsaturation in III is most probably located at the Δ^{22}-position since the NMR spectrum[9,10] indicates vinyl proton absorption. This would fulfill the requirements of a Δ^{22}-structure but not the alternate $\Delta^{20(22)}$-formulation. Endocyclic double bonds are recognized generally to possess greater stability than their exocyclic homologs.[11]

Since pseudotomatidine "B" (VIII) exhibits the same prominent infrared spectra bands (5.76 μ, OAc; 5.99 μ, —C=N—; hydrochloride, 4.0, 4.94, 5.88 μ; perchlorate, 5.90 μ)[12] and undergoes the same reactions as pseudosolasodine "B",[13] it is regarded as its counterpart and accorded the formulation VIII. Treatment of VIII with methyl iodide gives the methiodide IX which with alkali yields the *N*-methyl derivative X.[14] The latter conversion can be reversed by addition of hydrogen iodide. Interestingly IX or X can be converted to *N*-methyltomatidine (XI) by vigorous treatment with alcoholic alkali. Similarly tomatidine (I) is regenerated when an alcoholic solution of VIII is vigorously refluxed with base. Milder saponification yields first the 3-alcohol of VIII. The *N*-acetylated derivative of VIII, (III) has also been found to undergo conversion to tomatidine by prolonged treatment with alcoholic base. The catalytic reduction (platinum oxide, acetic acid) of VIII and the subsequent hydrolysis of the resulting dihydro derivative forms predominantly the higher melting isomer of dihydrotomatidine[15] (XII).

Analogous to *O,N*-diacetylsolasodine,[16] the acid catalyzed isomerization of *O,N*-diacetyltomatidine (Ia) with hydrochloric acid in methanol leads to the formation of 26-acetylamino-22-methoxy-5α-furostan-3β-ol acetate (VII) which can readily be converted to the 26-acetylamino-20(22)furostene derivative V by refluxing with glacial acetic acid. The formation of VII is attributed to the nucleophilic attack of methoxide ion on C-22.[16] In the presence of aqueous acetic acid VII is easily transformed into the corresponding 22-hydroxy compound VIIa.

EXPERIMENTAL[17]

Treatment of tomatidine (I) *with acetic anhydride.*[3,4] A mixture of 500 mg. of tomatidine and 30 ml. of acetic anhydride was refluxed vigorously for 3 hr. The excess reagent was removed *in vacuo* and the oily residue crystallized from methanol-water. The 26-aminodiacetyl derivative II amounted to 230 mg. (35%). The mother liquor was evaporated to dryness and the residue chromatographed on alumina. Fractions eluted with benzene-ether (1:1) consisted principally of *O,N*-diacetyltomatidine (68 mg., 11%). Subsequent elutions with ether yielded 98 mg. (15%) of an amorphous component which displayed the following spectra: $\lambda_{max}^{C_2H_5OH}$ 236 mμ (log ϵ, 3.92); $\lambda_{max}^{CHCl_3}$ 5.78 μ (acetoxy), 5.99, 6.08 μ. When this amorphous substance was dissolved in hexane-ether and seeded with III resulting from the interaction of pseudotomatidine "B" with acetic anhydride and pyridine (see below), 53 mg. of crude crystals (m.p. 148–167°) were obtained. Upon recrystallization from hexane, plates, m.p. 169–172°, $[\alpha]_D^{26}$ +190°, $\lambda_{max}^{C_2H_5OH}$ 236 mμ (log ϵ, 3.88) were secured. It agreed in melting point, mixture melting point, rotation, and infrared spectrum with a sample of III prepared from the acetylation of pseudotomatidine "B" (VIII). The oily mother liquor, after removal of crystalline III, displayed an infrared spectrum similar to III and possessed an ultraviolet absorption maximum at 234 mμ (log ϵ, 3.85) and rotation of +78° ($CHCl_3$).

(8) A. Lipp, *Ann.*, 289, 173 (1896); A. Lipp and E Widnmann, *Ber.*, 38, 2471 (1905).

(9) Peak assignment at 71 c.p.s. (relative to benzene). J. N. Shoolery and M. T. Rogers, *J. Am. Chem. Soc.*, 80, 5121 (1958) give a range of 71 to 78 c.p.s. (corrected from 40 to 60 meg.) for the vinyl protons of a Δ^{22} bond. Spectra were measured in deuterochloroform solution at 0.1*M* concentration on a Varian 60 meg. NMR spectrometer (4300-C) with tetramethylsilane as internal and benzene as external standards. We are deeply indebted to Dr. L. Cohen of this Institute for the measurements and interpretation of the NMR spectra of these compounds.

(10) Proton resonance shift (69 c.p.s.) was also observed for the analogous product obtained from solasodine.[5] Since the reaction of acetic anhydride with solasodine proceeds most likely in the same manner as with tomatidine, the Δ^{22}-position appears as the most tenable one for the corresponding unsaturated tetrahydropyridyl derivative obtained from solasodine. The $\Delta^{20(22)}$ structure proposed for the amorphous product after removal of the Δ^{22} compound seems doubtful since shifts were observed (63 c.p.s., C_6 proton, and 76 c.p.s., C_{23} proton) indicating the presence of Δ^5 and Δ^{22} unsaturation in the molecule. Studies of the remaining amorphous component, after removal of the *N*-acetyl-$\Delta^{22(23)}$-derivative, of both solasodine and tomatidine are being continued.

(11) R. B. Turner and R. H. Garner, *J. Am. Chem. Soc.*, 80, 1424 (1958).

(12) N. J. Leonard and V. W. Gash, *J. Am. Chem. Soc.*, 76, 2781 (1954).

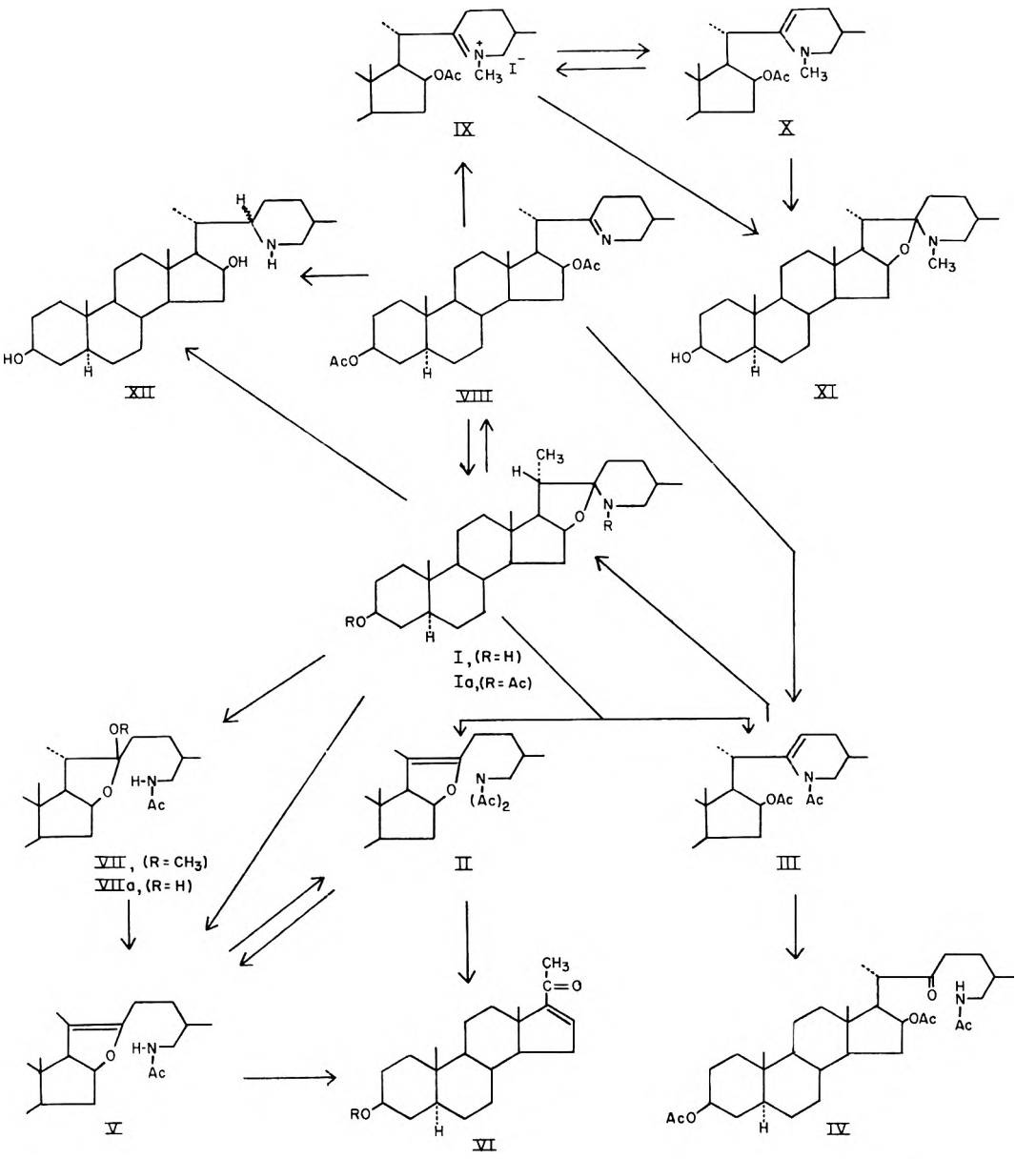
(13) Y. Sato, H. G. Latham, Jr., and E. Mosettig, *J. Org. Chem.*, 22, 1496 (1957).

(14) The double bond in X is probably endocyclic (Δ^{22}) rather than $\Delta^{20(22)}$ as depicted previously[13] for the solasodine analog. Oxidation of X has never yielded any significant amounts of 3β-acetoxy-Δ^{16}-allopregnene-20-one as would be expected of a compound with a $\Delta^{20(22)}$-bond.

(15) Y. Sato and H. G. Latham, Jr., *J. Am. Chem. Soc.*, 78, 3146 (1956).

(16) See Part III, Y. Sato and N. Ikekawa, *J. Org. Chem.*, 25, 789 (1960).

(17) Melting points were taken on the Kofler block and are uncorrected. Microanalyses were performed by the Microanalytical Services Unit of this laboratory under the direction of Mr. Harold G. McCann. The infrared spectra were taken on the Model 21 Perkin-Elmer Infrared Spectrometer by Messrs. H. K. Miller and R. T. Brown of this Laboratory. "Woelm" alumina grade 1 was used as adsorbent for chromatography unless otherwise stated. We thank Dr. E. Becker and Mr. R. B. Bradley for the NMR measurements.



The last fractions of the chromatogram eluted with ether-methanol (0.5%) afforded 214 mg. (35%) of the pseudo derivative V.

Pseudotomatidine "B" (VIII). To 1 g. of tomatidine was added 35 ml. of a zinc chloride solution (prepared by dissolving 8 g. of zinc chloride in a mixture of 70 ml. of acetic anhydride and 30 ml. of glacial acetic acid) and the solution allowed to stand overnight. The reaction mixture was then poured into ice water. After standing for 30 min., ammonium hydroxide was added to the mixture until alkaline. The copious precipitate was crystallized from aqueous methanol to yield 900 mg. of crude crystals which when twice recrystallized from aqueous acetone melted at 132–136°, $[\alpha]_D^{20}$ +6.5° ($CHCl_3$), $\lambda_{max}^{CHCl_3}$ 5.76 μ (OAc); 5.99 μ (—C=N—); hydrochloride, 4.0, 4.94, 5.88 μ; perchlorate, 5.90 μ.

Anal. Calcd. for $C_{31}H_{49}O_4N$: C, 74.51; H, 9.88. Found: C, 74.62; H, 9.80.

3β,16β-Diacetoxy-20-(2'-Δ²'-N-acetyl-5'-methyltetrahydropyridyl)-5α-pregnane (III). A solution of 180 mg. of pseudotomatidine "B" (VIII) in 2 ml. of pyridine and 1.5 ml. of acetic anhydride was allowed to stand overnight at room temperature and poured into ice water. The product which crystallized as plates (180 mg.) from hexane melted at 166–170°. Recrystallization from the same solvent gave a product of m.p. 170–172°, $[\alpha]_D^{20}$ +190° ($CHCl_3$), $\lambda_{max}^{C_2H_5OH}$ 236 mμ (log ϵ, 3.90).

Anal. Calcd. for $C_{33}H_{51}O_5N$: C, 73.16; H, 9.49. Found: C, 73.18; H, 9.66.

Forty milligrams of the above *N*-acetyltetrahydropyridyl derivative III was refluxed with 10 ml. of methanolic potassium hydroxide (10%) for 13 hr. The product which was recrystallized from methanol-water melted at 199–203° and proved to be tomatidine (melting point, mixture melting point, and infrared spectrum).

3β,16β-Diacetoxy-26-acetylaminocholestan-22-one (IV). A solution of 80 mg. of III in 0.6 ml. of 3*N* hydrochloric acid and 3 ml. of acetic acid was allowed to stand for 50 min. at room temperature and poured on ice. After addition of ammonia water to the solution, the product was chromatographed on alumina. The ether-methanol (1%) eluate yielded 44 mg. of crystals (from acetone-hexane) which melted at 126–130°, $\lambda_{max}^{CHCl_3}$ 2.88 μ (N—H), 5.77 μ (OAc and CO), 5.98, 6.57 μ (HN—Ac), $[\alpha]_D^{20}$ +13° ($CHCl_3$). $\lambda_{max}^{C_2H_5OH}$ 287 mμ (log ϵ, 1.91).

Anal. Calcd. for $C_{33}H_{53}O_6N$: C, 70.80; H, 9.54. Found: C, 70.48; H, 9.40.

Hydrolysis of the amorphous substance in the same manner also yields IV.

Methiodide of pseudotomatidine "B" (IX). One hundred milligrams of pseudotomatidine "B" (VIII) with 10 ml. of acetone and 1 ml. of methyl iodide were placed in a sealed reaction flask and allowed to stand at room temperature for 68 hr. Upon concentration and addition of hexane, slightly yellowish granular crystals were obtained (72 mg.). They melted at 252–255°.

Anal. Calcd. for $C_{32}H_{52}O_4NI$: C, 59.90; H, 8.17. Found: C, 60.10; H, 8.09.

When the salt was dissolved in methanol and the solution made basic by dropwise addition of sodium carbonate solution (5%), *N-methylpseudotomatidine* (X) was obtained. Recrystallized from aqueous acetone, the compound crystallized as rods and melted at 151–153°, $\lambda_{max}^{CHCl_3}$ 5.80, 6.08 μ. When a solution of X in ether is treated with an alcoholic solution of hydriodic acid, it reforms the methiodide (IX).

Anal. Calcd. for $C_{32}H_{51}O_4N$: C, 74.81; H, 10.01. Found: C, 75.11; H, 10.19.

N-Methyltomatidine (XI). Sixty milligrams of *N*-methylpseudotomatidine "B" (X) was refluxed for a period of 7 hr. with 14 ml. of methanolic potassium hydroxide (5%), concentrated *in vacuo* and water added to the residue. The precipitate was twice recrystallized from aqueous acetone. It formed plates which melted at 218–220°; its infrared spectrum somewhat resembled tomatidine in the finger print region, $\lambda_{max}^{CHCl_3}$ 2.78, 10.25, 10.43, 11.00, 11.30, 11.45 μ.

Anal. Calcd. for $C_{28}H_{47}O_2N$: C, 78.27; H, 11.03. Found: C, 78.10; H, 10.78.

When the methiodide IX was used in place of X, XI was likewise obtained.

Hydrolysis of pseudotomatidine "B" (VIII). (a). (With 2% methanolic potassium hydroxide). A solution of 400 mg. of pseudotomatidine "B" (VIII) in 40 ml. of methanolic potassium hydroxide (2%) was refluxed for 45 min., concentrated, and water added. The product (330 mg.), m.p. 100–107°, was chromatographed on neutral alumina, and the fraction (189 mg.) eluted with 1% methanol in ether afforded rectangular plates which melted at 157.5–161°, $[\alpha]_D^{20}$ +21° ($CHCl_3$), after recrystallization from aqueous methanol. Its infrared spectrum ($CHCl_3$) displayed bands at 2.78 μ (OH), 5.78 μ (OAc), 5.98 μ (—C=N—). It is the 3-alcohol of VIII.

Anal. Calcd. for $C_{29}H_{47}O_3N$: C, 76.10; H, 10.35. Found: C, 76.26; H, 10.21.

(b). (With 5% methanolic potassium hydroxide). A solution of 90 mg. of VIII in 10 ml. of methanolic potassium hydroxide (5%) was refluxed for 3 hr. The reaction mixture was partially concentrated and water added until precipitation was induced. The substance (70 mg.) crystallized from aqueous methanol and melted at 201–204°. It agreed in melting point, mixture melting point, and infrared spectrum with an authentic sample of tomatidine.

Reduction of VIII. Four hundred milligrams of VIII were dissolved in 7 ml. of glacial acetic acid and reduced over 100 mg. of platinum oxide catalyst under atmospheric pressure. The absorption of gas ceased with the uptake of 1 mole equivalent of hydrogen. After removal of the catalyst by filtration, the filtrate was made alkaline with addition of ammonia water and the copious precipitate subjected to chromatography on alumina after drying. The fractions eluted with benzene and with ether gave 225 mg. of crystalline product which melted at 110–115° when crystallized from ether.

Anal. Calcd. for $C_{31}H_{51}O_4N$: C, 74.21; H, 10.25. Found: C, 73.51; H, 10.26.

Although its elemental analysis was not quite satisfactory, 136 mg. of the above dihydro derivative was subjected to hydrolysis by refluxing with 15 ml. of methanolic potassium hydroxide (5%) solution for 2 hr. The crude product which weighed 112 mg. was chromatographed over alumina. The early fractions (ether-methanol (0.5%) eluate) gave a small amount (18 mg.) of the low melting dihydrotomatidine A while the fractions eluted with 2% and 10% methanol in ether yielded 46 mg. of the high melting dihydrotomatidine B (m.p. 231–234°). The compound was identical in respect to melting point, mixture melting point, and infrared spectrum with an authentic specimen of dihydrotomatidine B,[15] (XII).

Anal. Calcd. for $C_{27}H_{47}O_2N$: C, 77.64; H, 11.34. Found: C, 77.31; H, 11.06.

O,N-Diacetyltomatidine with hydrochloric acid in methanol. A mixture of 250 mg. of *O,N*-diacetyltomatidine (IA), 15 ml. of methanol, and 0.2 ml. of 6*N* hydrochloric acid was allowed to stand for 15 min. at room temperature. The reaction mixture was made alkaline with 0.2 ml. of concd. ammonia water, partially concentrated, and diluted with water. The product was chromatographed over alumina. The ether-methanol (0.5%) eluate gave 185 mg. (73%) of the 22-methoxy compound VII, m.p. 141–144° (acetone), $[\alpha]_D^{20}$ −59° ($CHCl_3$).

Anal. Calcd. for $C_{32}H_{53}O_5N$: C, 72.27; H, 10.05. Found: C, 72.36; H, 10.07.

26-Aminoacetyl-5α-furost-20(22)-en-3β-ol acetate (V). A solution of 48 mg. of the 22-methoxy derivative, VII, in 3 ml. of glacial acetic acid was refluxed for 30 min. After removal of the solvent *in vacuo*, the residue was crystallized from acetone-hexane to yield the pseudo derivative V which melted at 128–131°. It agreed in properties (melting point, infrared spectrum) with an authentic sample of V.

Conversion of V *to* II. Twenty-eight milligrams of the pseudo derivative V was dissolved in a mixture of 0.5 ml. of pyridine and 0.25 ml. of acetic anhydride and refluxed for 1 hr. The excess reagents were removed *in vacuo* and the residue dissolved in ethanol. Water was added to incipient turbidity and the mixture allowed to stand. The compound which formed (20 mg.) was recrystallized from aqueous ethanol and melted at 98–101°. It proved to be identical (melting point and infrared spectrum) with II obtained directly from the acetic anhydride treatment of tomatidine.

26-Acetylamino-22-hydroxy-5α-furostan-3β-ol acetate (VIIa). A solution of the 22-methoxy compound, VII, (80 mg.) in aqueous acetic acid (5 ml. of 80%) was allowed to stand for 2 hr. at room temperature. It was taken up in ether and the ethereal solution washed with water, dilute sodium bicarbonate solution, and again with water. The product recovered from the ethereal extract was chromatographed over alumina. The ether-methanol (2%) eluate afforded 56 mg. of VIIa, m.p. 119–123° (acetone-hexane), $[\alpha]_D^{20}$ −27° ($CHCl_3$).

Anal. Calcd. for $C_{31}H_{51}O_5N$: C, 71.91; H, 9.93. Found: C, 72.15; H, 10.02.

BETHESDA, MD.

[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1]]

Steroidal Sapogenins. LXIV. C-21 Acetoxylation of 12-Keto Steroids[2]

EDWARD S. ROTHMAN, THEODORE PERLSTEIN, AND MONROE E. WALL

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Procedural improvements in C-21 acetoxylation of steroids by iodine and calcium oxide followed by treatment of the resulting 21-iodo steroids with trimethylammonium acetate are described and the method is shown to be applicable to 12-keto steroids.

Ringold and Stork[3] reported a novel and useful procedure for the preparation of 21-acetoxylated steroids from a number of 20-keto pregnanes by reaction with iodine and calcium oxide followed by subsequent reaction of the 21-iodo intermediate with potassium acetate in acetone. In such a way they prepared the 21-acetoxy derivatives of 17α-hydroxyprogesterone, 17α-hydroxy-1,4-pregnadiene-3,20-dione, 11-keto progesterone, and 3α-hydroxypregnane-11,20-dione. More recently Halpern and Djerassi[4] applied similar reactions as the final stage of a cortisone acetate synthesis. We have found the Syntex method to be of great utility. The present paper presents several procedural improvements and in particular describes the extension of this reaction to 12-keto steroids.

It may be recalled that several attempts[5,6,7] to prepare 21-acetoxy-17α-hydroxy-4-pregnene-3,12,-20-trione ("12-keto S") from hecogenin failed when a variety of well known reactions, which ordinarily succeed when the 12-keto group is absent, were unsuccessful. The unfavorable effect of the 12-keto group was particularly demonstrated by the unsuccessful attempt[8] to obtain the 21-acetate derivative of 3β-acetoxy-17α-hydroxy-5-pregnene-12,20-dione by the Julian procedure.[9] Using the presently described method, 12-keto S was prepared by two routes, and the products agreed in physical properties with 12-keto S prepared from desoxycholic acid by Adams, Patel and Petrow.[10]

We followed Ringold and Stork's original procedure from details disclosed in a British patent.[3b] Later Halpern and Djerassi, in a footnote, recommended the use of aged tetrahydrofuran containing peroxides. In our hand the use of these techniques gave variable results and usually iodine uptake was very slow. On the assumption that the reaction was of the free radical type, mainly because of the above mentioned peroxide catalysis, we added small amounts of azobisisobutyronitrile to the reaction mixture as an initiator. Thereafter no further difficulties were encountered, although even with azobisisobutyronitrile induction periods of as long as one hour were sometimes observed.

In a further procedural modification, we used Moreland's excellent trimethylammonium acetate method[11] for replacing the C-21 iodine atom by the acetoxyl group. Moreland's procedure has several advantages over the more widely used potassium acetate method, in particular short reaction time and homogeneity of phase.

The experimental section describes the preparation of the following 21-acetoxy steroids: 21-acetoxy-3β,17α-dihydroxypregnane-20-one, 21-acetoxy-3β,17α-dihydroxy-5-pregnene-20-one, 21-acetoxy-16α,17α-epoxy-5-pregnene-20-one, 21-acetoxy-3β,17α-dihydroxy-5-pregnene-12,20-dione, 21-acetoxy-17α-hydroxy-5-pregnene-3,12,20-trione, and 21-acetoxy-17α-hydroxy-4-pregnene-3,12,20-trione.

By way of general comment it might be mentioned that the acetoxylation procedure gave variable results in the presence of the Δ^4-3-keto grouping. Good yields of 21-acetoxylated product were obtained in 12-keto S preparations, but, on the other hand, conversion of progesterone to 21-acetoxy progesterone consistently gave low yields. In general the maximal yields were obtained with 3β-hydroxy steroids. The iodinations are somewhat exothermic and in larger scale preparations sudden evolution of heat was occasionally observed capable of raising solvents to the boiling point unless a cooling bath was provided.

As a result of the availability of the key intermediate 21-acetoxy-3β,17α-dihydroxy-5-pregnene-12,20-dione, IV, we were able to re-investigate the possibility of preparation of a cortisone analog, VI,

(1) Eastern Utilization Research and Development Division, Agricultural Research Service, United States Department of Agriculture.

(2) Previous paper in this series, Steroidal Sapogenins LXIII, *J. Org. Chem.*, in press.

(3) (a) H. J. Ringold and G. Stork, *J. Am. Chem. Soc.*, 80, 250 (1958). (b) British patent 776,858 to Syntex Corp., June 12, 1957.

(4) O. Halpern and C. Djerassi, *J. Am. Chem. Soc.*, 81, 439 (1959).

(5) W. J. Adams, D. N. Kirk, D. K. Patel, V. Petrow, and I. A. Stuart-Webb, *J. Chem. Soc.*, 2209 (1954).

(6) E. S. Rothman and M. E. Wall, *J. Am. Chem. Soc.*, 78, 1744 (1956).

(7) E. S. Rothman and M. E. Wall, *J. Org. Chem.*, 22, 223 (1957).

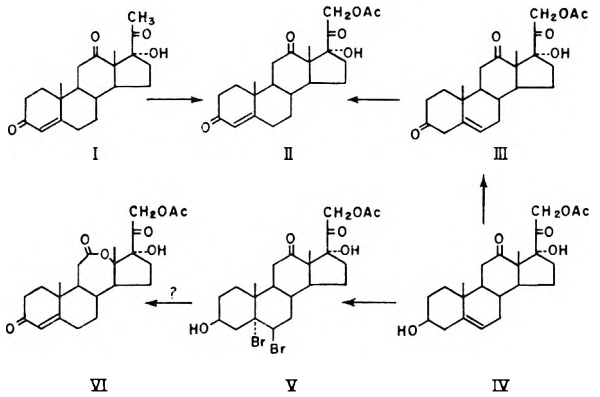
(8) E. S. Rothman and M. E. Wall, *J. Am. Chem. Soc.*, 77, 2229 (1955).

(9) P. L. Julian, E. W. Meyer, W. J. Karpel and I. R. Waller, *J. Am. Chem. Soc.*, 72, 5145 (1950).

(10) W. J. Adams, D. K. Patel, and V. Petrow, *J. Chem. Soc.*, 4688 (1954).

(11) W. T. Moreland, Jr., *J. Org. Chem.*, 21, 820 (1956).

wherein the C-ring is expanded to a 12,13-*seco*-lactone system.[8] The Δ^5 double bond of IV was protected by bromination to give the crystalline product, 21-acetoxy-5α,6β-dibromo-3β,17α-dihydroxyallopregnane-12,20-dione[12] which was submitted to the Baeyer-Villiger reaction conditions.[3] Regeneration of the olefinic bond with sodium iodide gave a product exhibiting the expected lactonic infrared spectrum[13] but the product resisted crystallization.



EXPERIMENTAL[14]

Melting points were determined on the Kofler block but are otherwise not corrected. Rotations were measured in a 2 dm. tube containing 25 mg. of steroid dissolved in 1.5 ml. of chloroform.

21-Acetoxy-3β,17α-dihydroxy-5-pregnene-12,20-dione. Preparation by generalized acetoxylation procedure. A solution of 11.5 g. of 3β,17α-dihydroxy-5-pregnene-12,20-dione, IV, in 85 ml. of tetrahydrofuran and 85 ml. of methanol was treated with 17 g. of powdered calcium oxide and 575 mg. of azobisisobutyronitrile. The mixture was surrounded by a 25° water bath and stirred during addition of 11.4 g. of iodine dissolved in a mixture of 55 ml. of tetrahydrofuran and 35 ml. of methanol. The iodine solution was added rapidly in a dropwise manner to just exceed the rapid decolorization rate. Typically a 5 to 60-min. induction period was observed and thereafter iodine absorption was continuous until an abrupt stop occurred at the indicated 50% excess point.[15] The mixture was then diluted with 450 ml. of methylene chloride and was filtered. The residue was washed on the filter with 200 ml. of methylene chloride and was discarded. The filtrate, diluted with 600 ml. of ether, often became turbid but shaking with as little as 2 ml. of water produced clarification. The organic layer was washed free of excess iodine with 15% aqueous sodium iodide solution, was dried with sodium sulfate, and solvents evaporated under reduced pressure. The 21-iodo residue, without purification, was redissolved in 150 ml. of acetone, mixed with 51.5 ml. of acetic acid and 79 ml. of triethylamine (exothermic reaction), and refluxed for 45 min. After cooling and carefully diluting with 250 ml. of water, the mixture was let stand to deposit crystals of the acetoxylated product in 66% yield, m.p. 185–186°. Recrystallization from ether-hexane and from aqueous ethanol gave the analytical sample, m.p. 187–188°, $[\alpha]_D^{25}$ −13.7°.

Anal. Calcd. for $C_{23}H_{32}O_6$: C, 68.29; H, 7.97. Found: C, 68.43; H, 8.16.

In runs on cruder material it was necessary to extract the reaction mixture with benzene and to chromatograph the crude product. The desired product was rapidly eluted from Florisil with benzene and crystallized in the earliest eluate residues on treatment with ether-hexane.

21-Acetoxy-16α,17α-epoxy-3β-hydroxy-5-pregnen-20-one (VII). Using the above procedure 5 g. of 16α,17α-epoxy-3β-hydroxy-5-pregnen-20-one[16] gave 2.10 g. of the known compound,[17] VII, m.p. 190–192°, previously reported[17] m.p. 190–192°.

21-Acetoxy-3β,17α-dihydroxypregnan-20-one (VIII). In like manner, 2 g. of 3β,17α-dihydroxy pregnan-20-one[18] gave 1 g. of VIII,[18] m.p. 201–205°. The 3-acetate of VIII[18,19] exhibited a double melting point, 90–100°; 153–155°, previously reported, 154–157°[18] and 149–151°.[19]

21-Acetoxy-3β,17α-dihydroxy-5-pregnen-20-one (IX). Similarly, 15.26 g. of 3β,17α-dihydroxy-5-pregnen-20-one[16] gave 10 g. of IX,[20] m.p. 210–212°, previously reported[20] m.p. 211–213°.

21-Acetoxy-17α-hydroxy-4-pregnene-3,12,20-trione (II). A suspension of 300 mg. of 17α-hydroxy-4-pregnen-3,12,20-trione,[6] I, in 2.25 ml. of tetrahydrofuran and 1.5 ml. of methanol was treated with 450 mg. of iodine under the conditions described in the generalized acetoxylation procedure described above. After chromatography on Florisil with 1:1 hexane-benzene 148 mg., m.p. 189–192°, was obtained after crystallization from hexane containing a trace of acetone. The analytical sample of II recrystallized from hexane melted from 190–193°, $[\alpha]_D^{23}$ +109° in reasonably good agreement with the reported values,[10] m.p. 189.5–190.5°, $[\alpha]_D^{20}$ +125°.

Conversion of 3β-acetoxy-5,16-pregnadiene-12,20-dione[7] to 3β,17α-dihydroxy-5-pregnene-dione. The indicated pregnadiene was converted with alkaline hydrogen peroxide as previously described[7] to the 16α,17α-epoxide, the alkalinity of the oxidant concomitantly saponifying the 3-acetate group. Attempts to open the oxirane ring with hydrobromic acid in tetrahydrofuran and in methanol failed[21]; thus 33 g. of the epoxide in 1.32 l. of tetrahydrofuran treated with 45 ml. of 48% hydrobromic acid was recovered unchanged after standing 18 hr. at 25°. In methanolic-aqueous hydrobromic acid, no reaction occurred in 3 days time. However, using precisely the conditions for oxirane opening described for the 11-keto analog,[22] namely anhydrous hydrobromic acid in

(12) The dibromide structure is assigned on the basis that sodium iodide treatment liberated iodine and regenerated the olefinic bond. The dibromide had an optical rotation more negative than the olefin as is the relationship of the 5α,6β-dibromide of cholesterol to cholesterol, whereas the other *trans* dibromide, 5β,6α-, is more dextrorotatory than its olefin precursor, cholesterol (see L. F. and M. Fieser, *Steroids*, Reinhold Publishing Corp., New York, 1959, p. 39).

(13) See Fig. 1 of reference 9 and compare curve D with curve E.

(14) Specification of brand names of materials used does not imply endorsement over similar commercial products.

(15) This point probably has no stoichiometric significance. The rate or amount of iodine uptake seems to be in some way affected by the nature of the surface of the calcium oxide surface. After iodine uptake stopped at about the 50% molar excess point, uptake could be reinduced by addition of a fresh quantity of calcium oxide even though there was already an apparent excess of solid calcium oxide in the system.

(16) P. L. Julian, E. W. Meyer, and I. Ryden, *J. Am. Chem. Soc.*, **72**, 367 (1950).

(17) P. L. Julian, E. W. Meyer, W. J. Karpel, and I. Ryden, *J. Am. Chem. Soc.*, **71**, 3574 (1949); **72**, 5145 (1950).

(18) B. A. Koechlin, T. H. Kritchevsky, and T. F. Gallagher, *J. Am. Chem. Soc.*, **73**, 189 (1951).

(19) R. B. Wagner and J. A. Moore, *J. Am. Chem. Soc.*, **72**, 5301 (1950).

(20) J. Heer and K. Miescher, *Helv. Chim. Acta*, **34**, 359 (1951).

(21) Under similar conditions 16α,17α-epoxy-3β-hydroxy-5-pregnen-20-one gives an excellent yield of bromohydrin.

(22) E. S. Rothman and M. E. Wall, *J. Am. Chem. Soc.*, **81**, 411 (1959), see compound V of that reference.

acetic acid, complete reaction occurred in 25 min. Unlike the 11-ketone case, a substantial amount of 3-acetylation occurred during the reaction. The debromination was carried out as previously described.[7] The mixed 3-alcohol and 3-acetate, 22.2 g. in 1.11 l., of methanol was treated with 22.2 g. of potassium bicarbonate in 222 ml. of water and refluxed in a nitrogen atmosphere for 1 hr. The cooled mixture was diluted with 7 l. of ice-water and after standing overnight was filtered. The 18.9 g. of crystalline product was collected and recrystallized from acetone to give 17.1 g. of diol, m.p. 203–205°, $[\alpha]_D^{25}$ −19.3°.

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.81; H, 8.73. Found: C, 72.83; H, 8.85.

21-Acetoxy-17α-hydroxy-5-pregnene-3,12,20-trione, III. The trioldione monoacetate, IV, 135 mg. dissolved in 25 ml. of acetone (redistilled from potassium permanganate), was cooled to 10° and stirred with 0.10 ml. of an aqueous solution containing 26.7 mg. of chromium trioxide and 0.023 ml. of sulfuric acid.[23] Within 1 min. a gray-green precipitate formed. Stirring was continued an additional 2 min. and the reaction mixture was diluted to 150 ml. with nearly saturated sodium chloride solution. The crystalline precipitate filtered off weighed 130 mg., melted at 155°, and showed no selective ultraviolet absorption maximum and no band at 6 μ in the infrared. The analytical sample was recrystallized from water containing 20% of acetone and finally from hexane, m.p. 172–175°, $[\alpha]_D^{25}$ +8.2°.

Anal. Calcd. for $C_{23}H_{30}O_6$: C, 68.63; H, 7.51. Found: C, 68.30; H, 7.71.

Isomerization of 21-acetoxy-17α-hydroxy-5-pregnene-3,12,20-trione (III) *to the corresponding 4-ene* (II). The 5-ene, III, 600 mg. was stirred and refluxed 2 hr. in 30 ml. of dry acetone with 1.2 g. of potassium acetate. The mixture was cooled, diluted with 60 ml. of water, and concentrated under reduced pressure to 60 ml. final volume. The crystalline precipitate was collected and recrystallized from hexane containing a small proportion of acetone. The product, II, needles melted from 191–193°, $[\alpha]_D^{25}$ +123°, $\lambda_{max}^{CH_2OH}$ 238 mμ, log ε = 4.23, agreed well with the product described above and with the preparation reported by the British group.[10]

21-Acetoxy-5α,6β-dibromo-3β,17α-dihydroxy allopregnane-12,20-dione (V). A solution of 1 g. of 21-acetoxy-3β,17α-dihydroxy-5-pregnene-12,20-dione, α_D −13.7°, in 25 ml. of methylene chloride at 4° was treated with 10.72 ml. of a carbon tetrachloride solution containing a molar equivalent of bromine. The bromine solution was added at a controlled rate during 75 min. time. The mixture was stirred an additional 2 min., solvents were removed *in vacuo* at room temperature and 10 ml. of methanol was added. On stirring, 955 mg. of colorless crystals of V, α_D −28.8°, m.p. 140–141° dec., deposited. A small additional crop separated from the decanted supernatant solution. Some preparations of the dibromide developed coloration on standing due to decomposition. Purer preparations were more stable.

Anal. Calcd. for $C_{23}H_{32}O_6Br_2$: C, 48.95; H, 5.72; Br, 28.32. Found: C, 49.12; H, 5.86; Br, 28.77.

Treatment of the dibromide, V, with perbenzoic acid. The dibromide, V, 1.17 g., dissolved in 7.9 ml. of cold chloroform, was treated with 11 ml. of a solution of perbenzoic acid in the same solvent (1 ml. = 11.52 ml. 0.1*N* sodium thiosulfate) 0.2 ml. of water, and 0.45 ml. of 10% sulfuric acid in acetic acid and was let stand with occasional shaking for 113 hr. in the dark at room temperature. The resulting orange solution was shaken with 100 ml. of ether and 100 ml. of water. Decolorization occurred and the aqueous phase was discarded. The organic layer was washed with aqueous sodium iodide to destroy peroxyacid and was washed cautiously with just enough dilute sodium thiosulfate to decolorize the large excess of liberated iodine, with dilute sodium bicarbonate to remove acids and with saturated sodium chloride solution. Solvents were evaporated under reduced pressure. The residue, dissolved in 25 ml. of acetone, was stirred with 2 g. of potassium iodide and refluxed for 1 hr. After dilution with water, extraction with ether, and removal of liberated iodine by treatment with dilute sodium thiosulfate, the isolated steroid was chromatographed on Florisil.[14] Elution with methylene chloride gave unchanged starting material identified by its infrared spectrum. Further elution with 1:1 methylene chloride gave an intermediate cut rich in unreacted starting material. Elution with 4% methanol in methylene chloride gave 250 mg. of a material yielding an amorphous powder on treatment with ether and having a single broad carbonyl infrared absorption band from 5.7 to 5.8 μ with a weak shoulder at 5.91 μ (in methylene chloride solution). The carbonyl area resembled that of the similarly obtained known 5α—C ring lactonoid corticoid.[13] The substance gave a strong tetrazolium color reaction.

PHILADELPHIA 18, PA.

(23) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, 21, 1547 (1956).

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN CO.]

Microbiological Transformations of Steroids. XVI. Multiple Oxidation of the Steroid Nucleus[1]

A. R. HANZE, O. K. SEBEK, AND H. C. MURRAY

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Two cases of microbial hydroxylation with accompanying oxidation of a pre-existing 11β-hydroxyl group are reported. *Cunninghamella blakesleeana* [A.T.C.C. 8688a (+)] and *Helicostylum piriforme* (A.T.C.C. 8992) were found to convert 11β,21-dihydroxypregna-4,17(20)-dien-3-one (I) to 9α,21-dihydroxypregna-4,17(20)-diene-3,11-dione (II). *Rhizopus arrhizus* (A.T.C.C. 11145) was found to convert the same substrate to 6β,21-dihydroxypregna-4,17(20)-diene-3,11-dione (V). Proof of structures of the two products consisted in their conversion to the known 9α-hydroxy- and 6β-hydroxycortisone acetates, respectively.

DISCUSSION

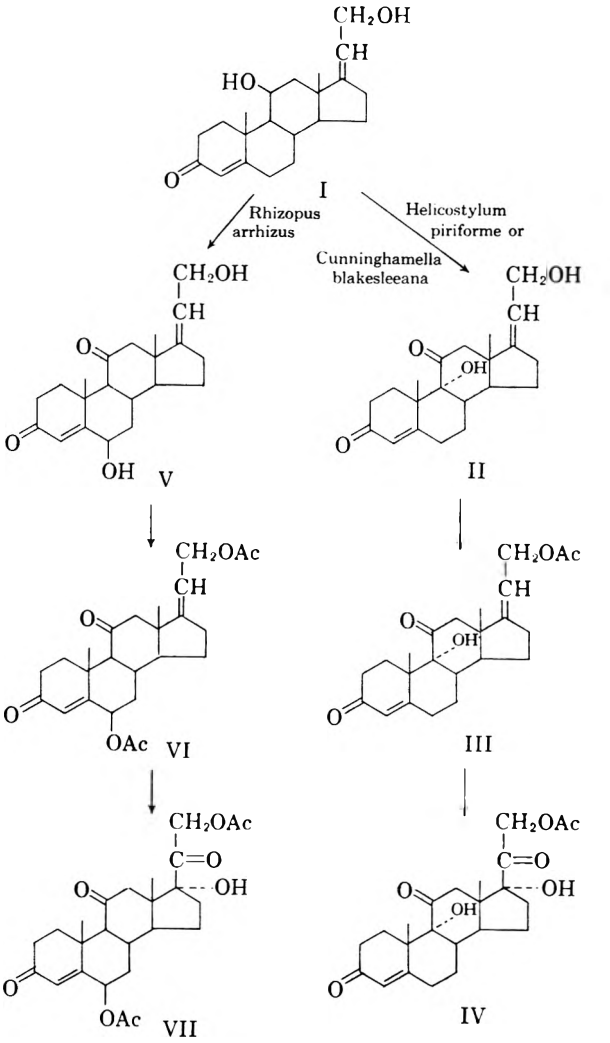
In our continuing investigation of the microbial transformation of steroids, we became interested in determining the positions susceptible to attack by various microorganisms in a steroid containing both a conjugated and an isolated

(1) Paper XV of this series, *J. Am. Chem. Soc.*, 80, 3382 (1958).

double bond. The substrate used for these studies was 11β,21-dihydroxypregna-4,17(20)-diene-3-one (I)[2] (hereafter called dienediol), chosen because the 11 position is blocked, thus decreasing the number of possible products.

Both *Cunninghamella blakesleeana* [A.T.C.C. 8688a (+)] and *Helicostylum piriforme* Bain (A.T.C.C. 8992) have been shown to perform 14-hydroxylation.[1] When the dienediol (I) was incubated with either of these organisms one major product was formed. Although other products were also formed to some degree in both fermentations, the *Helicostylum* gave a much cleaner transformation than did the *Cunninghamella*. The major product, purified by chromatography and recrystallization, differed from the substrate by the presence of an added carbonyl group, shown by the infrared spectrum and elemental analysis. Acetylation produced a monoacetate (III) whose infrared spectrum showed the presence of a free hydroxyl, an ester, and a 1:1 ratio of α,β-saturated ketone to α,β-unsaturated ketone. On the basis of the above data it was hypothesized that oxidation of the 11β-hydroxyl group as well as hydroxylation at C-14 had occurred during the fermentation. The final proof of structure consisted in treatment of the acetate (III) in *t*-butyl alcohol–pyridine with phenyl iodosoacetate in the presence of catalytic amounts of osmium tetroxide[2] to convert the 17-(20)-double bond to a 17α-hydroxy-20-ketone. The supposition that the compound was hydroxylated cortisone acetate was borne out by elemental analysis, infrared and ultraviolet spectra, positive Tollens' test, and papergram mobilities. However, the properties of the compound did not agree with those of the expected 14α-hydroxy cortisone acetate[3] but were identical with those of 9α-hydroxy cortisone acetate (IV) prepared by the oxidation of 9α-hydroxyhydrocortisone acetate,[4] obtained *via* the 9,11-oxide.

The introduction of a hydroxyl group into a steroid molecule with accompanying oxidation of a pre-existing hydroxyl had previously been noted in the case of testosterone. Incubation of this steroid with *Fusarium sp.*[5] resulted in the introduction of a hydroxyl into the 15α-position with concurrent oxidation of the 17β-hydroxyl to a ketone to give 15α-hydroxyandrost-4-ene-3,17-dione. No case, however, has been reported on the oxidation of a 11β-hydroxy steroid to an 11-ketosteroid by a microorganism. The microbial oxidation[6] of Reichstein's Compound S (11-desoxy-



17α-hydroxycorticosterone) with *Cunninghamella blakesleeana* is known to produce both hydrocortisone and cortisone; however, no evidence has been presented to show whether cortisone is a primary or secondary product of the fermentation. We have now shown in shake flask studies the conversion of hydrocortisone to cortisone with this organism, thus establishing the possible route to cortisone in the above fermentation as one involving oxidation of the newly formed 11β-hydroxyl group. The introduction of a hydroxy group into the 9 (or 8) position of a steroid by a microorganism has been reported by several groups.[7] The present

(2) J. A. Hogg, P. F. Beal, A. H. Nathan, F. H. Lincoln, W. P. Schneider, B. J. Magerlein, A. R. Hanze, and R. W. Jackson, *J. Am. Chem. Soc.*, **77**, 4436 (1956).

(3) E. J. Agnello, B. L. Bloom, and G. D. Laubach, *J. Am. Chem. Soc.*, **77**, 4684 (1955).

(4) J. Fried and E. F. Sabo, *J. Am. Chem. Soc.*, **79**, 1130 (1957).

(5) P. D. Meister, H. C. Murray, R. C. Meeks, A. Weintraub, S. H. Eppstein, L. M. Reineke, H. M. Leigh Osborn, and D. H. Peterson, unpublished data.

(6) F. R. Hanson, L. M. Mann, E. D. Nielson, H. V. Anderson, M. P. Brunner, J. R. Karnemaat, D. R. Colingsworth, and W. J. Haines, *J. Am. Chem. Soc.*, **75**, 5369 (1953).

(7a) D. Stone, M. Hayano, R. I. Dorfman, O. Hechter, C. R. Robinson, and C. Djerassi, *J. Am. Chem. Soc.*, **77**, 3926 (1955); (b) J. Fried, R. W. Thoma, D. Perlman, J. E. Herz, and A. Bowman, *Recent Progr. in Hormone Research*, **11**, 157 (1955), Academic Press, Inc., New York, N. Y.; (c) A. Schubert, D. Onken, R. Siebert, and K. Heller, *Helv. Chim. Acta*, **91**, 2549 (1958); (d) G. Rosenkranz, O. Mancera, and F. Sondheimer, *J. Am. Chem. Soc.*, **76**, 2227 (1957);(e.)R. M. Dodson and R. D. Muir, *J. Am. Chem. Soc.*, **80**, 6148 (1958).

example, however, represents, to our knowledge, the first example of the introduction of a hydroxyl group into a steroid molecule with accompanying oxidation of a pre-existing 11β-hydroxyl to an 11-ketone.

Microbial oxidation of the dienediol (I) with *Rhizopus arrhizus* Fischer (A.T.C.C. 11145) also yielded a compound in which a hydroxyl was introduced with concurrent oxidation of the pre-existing hydroxyl group. The product was identified as 6β,21-dihydroxypregna-4,17(20)-diene-3,11-dione (V) on the basis of the following evidence. The compound exhibited infrared absorption bands at 3500 cm.$^{-1}$, 3410 cm.$^{-1}$, 1697 cm.$^{-1}$, 1667 cm.$^{-1}$, and 1617 cm.$^{-1}$. An examination of the spectrum indicated that the compound contained hydroxyl and a 1:1 ratio of α,β-saturated to α,β-unsaturated ketone. The ultraviolet spectrum showed a maximum at 233 mμ with ε 13,850, which is in agreement with that reported for other 6β-hydroxylated steroids.[8] The compound on acetylation formed a diacetate (VI) as evidenced by analysis and infrared spectrum. Final proof consisted in the conversion of the diacetate (VI) to the known 6β-hydroxycortisone diacetate[9] by reaction with phenyl iodosoacetate in the presence of osmium tetroxide.[2]

Hydroxylation of steroids at carbon atom 6 is one of the most common reactions of the fungi and has been reported to occur with numerous genera of the order of Mucorales. The microorganism of the present study, *Rhizopus arrhizus*, converts[10] progesterone to 6β,11α-dihydroxyprogesteron. The conversion of the dienediol (I) to 6β,21-dihydroxypregna-4,17(20)-diene-3,11-dione (V) could thus be represented as a 6β,11α-dihydroxylation to give the 6β-hydroxy-11-ketone.

EXPERIMENTAL[11]

9α,21-Dihydroxypregna-4,17(20)-diene-3,11-dione (II). A fermenter containing 100 l. of a sterile medium at *p*H 4.9, made from commercial dextrose (10 g./l.) and corn steep (20 g./l.), was inoculated with 5.0 l. of vegetative growth of *Helicostylum piriforme* Bain (A.T.C.C. 8992). After 24 hr. of vigorous agitation and aeration at a rate of 20 l. per min. at 28°, 20.0 g. of 11β,21-dihydroxypregna-4,17(20)-diene-3-one (I) was added in 500 ml. of acetone, and the fermentation continued for 48 hr. under the same conditions. Extraction of the conversion products with methylene chloride and work-up as described previously[10] yielded *ca.* 42.0 g. of a semicrystalline residue. Paper chromatography, using the PTF system[12] indicated the presence of a new compound with increased polarity.

The semicrystalline residue was redissolved in *ca.* 1000 ml. of dry methylene chloride and chromatographed on 2000 g. of Florisil,[13] taking six 2-l. fractions of the following solvent mixtures: 18%, 20%, 25%, and 50% acetone in petroleum ether (b.p. 62–72°). Fractions 9–21 were combined, dissolved in hot acetone, treated with Darco G-60 (2 g.), filtered, and the filtrate concentrated until copious crystallization took place. The mixture was cooled in a refrigerator for 2–3 hr., and filtered to give 10.33 g. of II melting at 217–219°. Additional crops of 1.62 g. (m.p. 216–218°) and 360 mg. (m.p. 211.5–214°) were obtained upon further concentration of the initial filtrate, making the over-all yield 12.31 g. (59.0%). Recrystallization from acetone gave material melting at 219.5–221°, $[\alpha]_D$ +173° (*c* 1.022, dioxane); $\lambda_{max}^{alc.}$ 238.5 mμ (15,725); λ_{max}^{Nujol} 3440, 3220, 1697, 1635, and 1603 cm.$^{-1}$

Anal. Calcd. for $C_{21}H_{28}O_4$ (344.43): C, 73.22; H, 8.19. Found: C, 73.32; H, 8.30.

9α,21-Dihydroxypregna-4,17(20)-diene-3,11-dione 21-acetate (III). To a solution of 5.0 g. of 9α,21-dihydroxypregna-4,17(20)-diene-3,11-dione (II) in 15 ml. of dry pyridine at 20° was added 15 ml. of acetic anhydride. After 17 hr. at room temperature the solution was poured into 450 ml. of ice-water mixture. The crystalline product which separated was filtered, washed well with water, and dried; yield 5.53 g. (99.0%), m.p. 172.5–177°. The crystals were dissolved in 70 ml. of hot acetone, the solution clarified and concentrated on a steam bath until crystallization began. The mixture was cooled in a refrigerator and filtered to give 3.83 g. of III, m.p. 188.5–190°, $[\alpha]_D$ +160° (*c* 0.65, acetone), $\lambda_{max}^{alc.}$ 239 mμ (15,750); λ_{max}^{Nujol} 3390, 1725, 1700, 1652, 1623, 1240, and 1224 cm.$^{-1}$

Anal. Calcd. for $C_{23}H_{30}O_5$ (386.47): C, 71.48; H, 7.82. Found: C, 71.42; H, 8.19.

9α-Hydroxycortisone acetate (IV). To an ice-cold solution of 387 mg. (1 mmole) of 9α,21-dihydroxypregna-4,17(20)-diene-3,11-dione 21-acetate (III) in 18.5 ml. of *t*-butyl alcohol containing 0.93 ml. of pyridine and 0.185 ml. of water was added 370 mg. of *N*-methylmorpholine oxide, 800 mg. of phenyl iodosoacetate, and 4.0 mg. of osmium tetroxide. The slurry was stirred at 0–5° for 2 days at which time the reaction mixture was clear. Magnesol[14] (600 mg.) and a solution of 150 mg. of sodium sulfite in 10 ml. of water were added, and the mixture stirred for 15 min. at room temperature. The mixture was filtered and the filtrate concentrated to opalescence under reduced pressure. The solution was cleared by careful addition of *t*-butyl alcohol and stirred at room temperature for 1 hr. The crystals which formed were filtered and washed with *t*-butyl alcohol–water (1:4) and finally water, and dried; yield 245 mg. (58.5%), m.p. 233–236°.[15] Recrystallization from acetone–petroleum ether (b.p. 62–72°) gave 185 mg., m.p. 237–239°, $[\alpha]_D$ +227° (*c* 0.48, $CHCl_3$), $\lambda_{max}^{alc.}$ 239 mμ (15,900), reported[4] m.p. 237–239°, $[\alpha]_D^{23}$ +211° (*c* 0.51, $CHCl_3$), $\lambda_{max}^{alc.}$ 238 mμ (16,500). The compound has an infrared spectrum identical with that of a sample of 9α-hydroxycortisone acetate prepared by the oxidation of 9α-hydroxyhydrocortisone acetate, obtained *via* the 9,11-oxide,[4] with sodium dichromate in acetic acid by W. P. Schneider of these laboratories with λ_{max}^{Nujol} 3400, 1748, 1732, 1710, 1660, 1620, and 1239 cm.$^{-1}$

6β,21-Dihydroxypregna-4,17(20)-diene-3,11-dione (V). 11β,21-Dihydroxypregna-4,17(20)-diene-3-one (I—2.5 g.) was fermented with *Rhizopus arrhizus* (A.T.C.C. 11145)

(8) P. T. Herzig and M. Ehrenstein, *J. Org. Chem.*, **16**, 1050 (1951).

(9) S. Burstein and R. I. Dorfman, *J. Biol. Chem.*, **213**, 581 (1955).

(10) D. H. Peterson, H. C. Murray, S. H. Eppstein, L. M. Reineke, A. Weintraub, P. D. Meister, and H. M. Leigh, *J. Am. Chem. Soc.*, **74**, 5933 (1952).

(11) All melting points were taken in open capillaries and are not corrected for stem exposure. The fermentation procedures using *Cunninghamella blakesleeana* and *Rhizopus arrhizus* were identical to that given for *Helicostylum piriforme*.

(12) A. Zaffaroni, R. B. Burton, and E. H. Keutman, *J. Biol. Chem.*, **193**, 749 (1951).

(13) A synthetic magnesium silicate manufactured by the Floridin Co., Warren, Pa.

(14) Magnesium silicate formerly manufactured by Westvaco-Chlor-Alkali Division, Food, Machinery and Chemical Corp., New York.

(15) A polymorphic modification melted at 212–214°.

in the same manner as that given for the *Helicostylum* fermentation above. The semicrystalline residue obtained upon evaporation of the extraction solvent showed by papergram[12] one major product which was more polar than I and differed in mobility from that produced by the *Helicostylum*. The residue was triturated with acetone and filtered to give 610 mg. of crystals. These were dissolved in 65 ml. of hot acetone, filtered through a bed of Magnesol,[14] and concentrated to crystallization; yield of V, 360 mg., m.p. 252–254°, $[\alpha]_D^{23}$ +107° (*c* 0.86, dioxane), $\lambda_{max}^{alc.}$ 233 mμ (13,850), λ_{max}^{Nujol} 3500, 3410, 1697, 1667, and 1617 cm.$^{-1}$

Anal. Calcd. for $C_{21}H_{28}O_4$ (344.43): C, 73.22; H, 8.19. Found: C, 73.53; H, 8.47.

The mother liquors were combined, concentrated to remove the acetone, and chromatographed on 300 g. of Florisil,[13] taking five 200-ml. fractions of each of the following solvents: methylene chloride, 12%, 20%, 30%, and 50% acetone in petroleum ether (b.p. 62–72°). Fractions 17–21 (1.21 g.) were combined and crystallized from acetone to give 500 mg. of V, melting at 243–247°. Recrystallization of this material from acetone gave 400 mg. with m.p. 246–250°.

6β,21-Dihydroxypregna-4,17(20)-diene-3,11-dione diacetate (VI). A solution of 400 mg. of V in 1 ml. of pyridine and 1 ml. of acetic anhydride was allowed to react overnight at room temperature. Addition of ice and water caused crystallization. The mixture was filtered and the solid dried, yield 440 mg., m.p. 129–135°. Recrystallization from ethyl acetate (1 ml.) and petroleum ether (b.p. 62–72°) (2 ml.) gave 270 mg., m.p. 136–138.5°, $[\alpha]_D$ +66° (*c* 0.72, dioxane), $\lambda_{max}^{alc.}$ 231 mμ (13,250), λ_{max}^{Nujol} 1732, 1700, 1676, 1617, 1250, and 1230 cm.$^{-1}$

Anal. Calcd. for $C_{25}H_{32}O_6$: C, 70.07; H, 7.53. Found: C, 69.70; H, 7.90.

6β-Hydroxycortisone 6,21-diacetate (VII). 6β,21-Dihydroxypregna-4,17(20)-diene-3,11-dione diacetate (580 mg.) was oxidized with phenyliodosoacetate in the presence of osmium tetroxide to yield 400 mg. of 6β-hydroxycortisone 6,21-diacetate by a procedure identical with that given above for the preparation of 9α-hydroxycortisone acetate. Recrystallization from acetone–petroleum ether (b.p. 62–72°) gave 260 mg., m.p. 236–238.5° (reported[12] 225–233°), $[\alpha]_D^{23}$ +124° (*c* 0.33, dioxane), λ_{max}^{Nujol} 3540, 1735, 1712, 1697, 1675, 1620, and 1240 cm.$^{-1}$ The ultraviolet spectrum in sulfuric acid agrees with that given by Burstein and Dorfman.[9] A sample obtained by chromic acid oxidation of 6β-hydroxyhydrocortisone 6,21-diacetate, prepared *via* the 5,6-oxide by G. B. Spero of these laboratories, melted at 231–232°, $[\alpha]_D^{23}$ +127° (dioxane) and was identical with our sample by infrared and paper chromatographic analysis.

Acknowledgment. The authors are indebted to A. Koning for technical assistance; to L. M. Reineke and group for papergram analysis; to Dr. J. L. Johnson, J. E. Stafford, and Mrs. G. S. Fonken for infrared and ultraviolet absorption studies; and to W. A. Struck and associates for analytical data.

KALAMAZOO, MICH.

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF HOWARD UNIVERSITY]

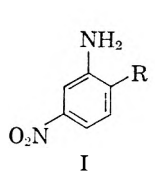
Ultraviolet Spectroscopic Studies of Some Sweet and Nonsweet Isomeric *m*-Nitroanilines[1]

LLOYD N. FERGUSON AND LILLIAN GREEN CHILDERS[2]

Received March 7, 1960

The ultraviolet spectra of some 2- and 4-substituted 5-nitroanilines and of their respective disubstituted constituent compounds have been measured in 95% alcohol. Their absorption bands have been classified and discussed in terms of electronic transitions within the molecules. Certain solvent and salt effects are also reported. Taste-structure relationships which possibly might be drawn from the spectra are pointed out.

It has been observed[3] that many 2-substituted 5-nitroanilines (I) are intensely sweet, whereas the isomeric 4-substituted-5-nitroanilines (II) are bitter or tasteless.



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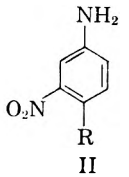


II

Relative sweetness[4]
(Sucrose = 1)

R	I	II
$-OCH_3$	167	Tasteless
$-CH_3$	298	Tasteless
-Br	715	Tasteless

This striking difference in taste of isomeric pairs has aroused our interest in their physicochemical properties and the present paper reports some of their spectroscopic properties. There is even a noticeable difference in the color of the isomers. All of the compounds are yellow to red but the sweet isomer of each couple is lighter than the nonsweet member.

Two types of spectroscopic studies were made in this investigation. The first was to measure the complete ultraviolet spectra down to 210 mμ. It was hoped, through an interpretation of the spectra, to learn if there is any significant difference in electronic interactions of the substituents in the

(1) Number V in a program of physicochemical studies of the sense of taste; No. IV, *J. Org. Chem.*, 25, 1220 (1960).

(2) Taken from the M.S. thesis of L.G.C., Howard University, 1959.

(3) J. J. Blanksma and P. W. M. van der Weyden, *Rec. trav. chim.*, 59, 629 (1940); 65, 329 (1946); *cf.* P. E. Verkade, *et al.*, *Rec. trav. chim.*, 68, 639 (1949) and earlier papers in this series.

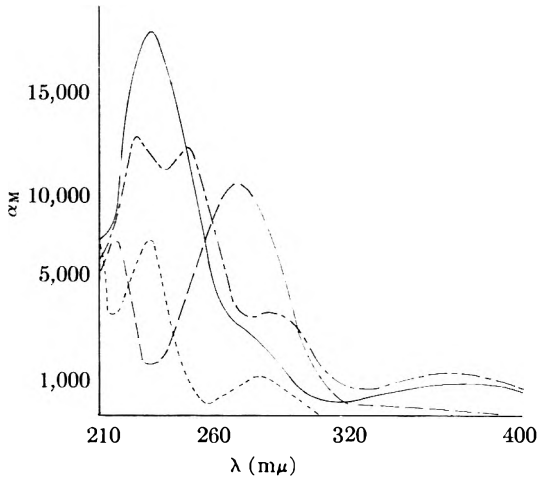


Fig. 1. Absorption spectra of 2-methyl-5-nitroaniline (— — —) and its disubstituted constituents all in alcohol: *o*-toluidine (———), *p*-nitrotoluene (– – – –), and *m*-nitroaniline (———)

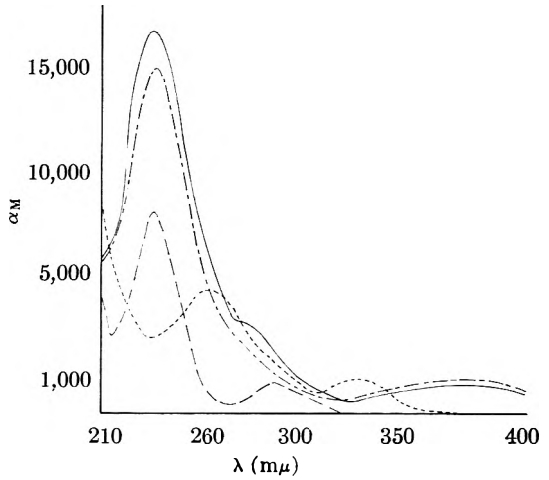


Fig. 2. Absorption spectra of 4-methyl-3-nitroaniline (— — —) and its disubstituted constituents all in alcohol: *p*-toluidine (– – – –), *o*-nitrotoluene (———), and *m*-nitroaniline (———)

sweet and nonsweet isomers. The second type of spectroscopic study involved measuring the absorbancy of the compounds at a wave length of maximum absorption in the presence of various cations. The objective here was to detect any differential behavior of the sweet and tasteless isomers towards cations which are important in biological systems.

EXPERIMENTAL

Sources of compounds. With the exception of 4-carboxy-3-nitroaniline, all of the substituted *m*-nitroanilines were available from other phases of the major investigation.[4] The other organic compounds were obtained from commercial sources. The solid compounds were recrystallized to constant melting points which agreed with those reported in the literature. The liquid compounds were redistilled under reduced pressure and used soon thereafter. The

(4) *Cf.* A. R. Lawrence and L. N. Ferguson, *Nature*, **183**, 1469 (1959).

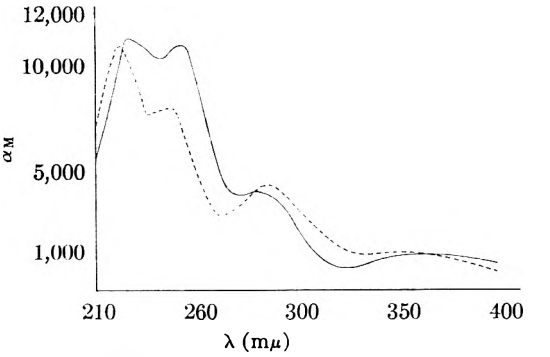


Fig. 3. Absorption spectrum of 2-methyl-5-nitroaniline in alcohol (———) and in water (———)

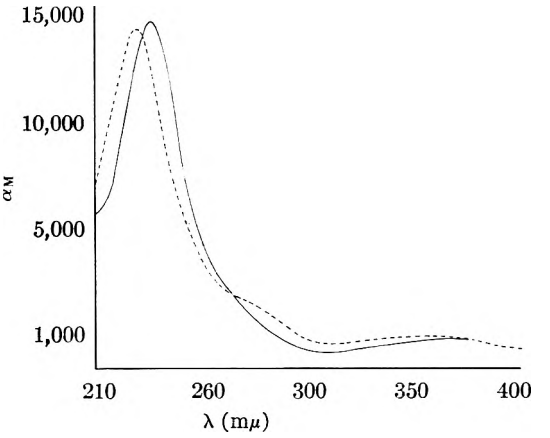


Fig. 4. Absorption spectrum of 4-methyl-3-nitroaniline in alcohol (———) and in water (· · · · · ·)

inorganic salts were the purest commercial grades available and used as purchased.

4-Carboxy-3-nitroaniline.[5] This compound was prepared by nitrating *p*-toluidine in concd. sulfuric acid at −15° to −10° to yield 4-methyl-3-nitroaniline. The latter compound was acetylated with acetic anhydride in benzene, m.p. 142–143° (lit.,[6] m.p. 144°). The acetanilide was oxidized with aqueous potassium permanganate in the presence of magnesium sulfate and the product hydrolyzed in 6*N* hydrochloric acid on a steam bath. The reaction mixture was brought to *p*H 6 with ammonia and evaporated to dryness. The residue was extracted with hot alcohol and the alcohol solution evaporated to dryness. This residue was then washed with water and recrystallized twice from alcohol, m.p. 239–240° (lit.[1] m.p. 239.5° corr.).

Spectral measurements. All measurements were made on a Beckmann Model DU spectrophotometer in 1-cm. matched, fused-silica cells. The solute concentrations were adjusted to give absorbancy readings between 0.2 and 0.8. Measurements were made in distilled water, aqueous solutions of sodium chloride, potassium chloride, magnesium chloride, and manganous chloride, or in 95% ethanol, and in all cases the respective solvent was used as a blank.

DISCUSSION AND RESULTS

Doub and Vandenbelt[8] found for a particular class of trisubstituted compounds (III), in which only

(5) Reported to have a very sweet taste by Bogert and Kropff.[7]

(6) K. Brand and H. Zöller, *Ber.*, **40**, 3324 (1907).

(7) M. T. Bogert and A. H. Kropff, *J. Am. Chem. Soc.*, **31**, 847 (1909).

TABLE I

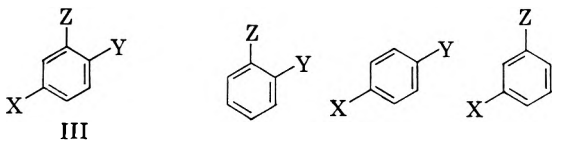
SPECTRAL CHARACTERISTICS OF THE SWEET *m*-NITROANILINES AND THEIR DISUBSTITUTED CONSTITUENTS[a]

(Wave Lengths in mμ)

Compound	Secondary Band		First Primary Band		Second Primary Band		Third Primary Band	
	λ_m	ϵ	λ_m	ϵ	λ_m	ϵ	λ_m	ϵ
2-CH_3-5-NO_2-Aniline[8]	370	1,800	288	4,660	250[b]	11,900	227	12,460
	(354)	(1,860)	(292)	(4,970)	(245)	(8,730)	(222)	(11,420)
m-Nitroaniline[11c]	370	1,358	275[b]	4,000	235	17,200)		
	(358)[9]	(1,450)[9]	(280)[9]	(4,800)[9]				
o-Toluidine	285	1,810			233	7,790		
	ca. (280)[16]	*ca.* (1,600)[16]			*ca.* (230)[16]	*ca.* (7,100)[16]		
p-Nitrotoluene			275	10,410			215	7,790
			(285)[10]	(9,250)[10]			(217)[10]	(6,700)[10]
2-OCH_3-5-NO_2-Aniline[8]	370	3,560	304	4,760	257[b]	13,240	226	10,560
	(367)	(4,330)	(309.5)	(5,170)	(256)[b]	(10,040)	(222)	(10,680)
m-Nitroaniline[11a]	370	1,358	275[b]	4,000	235	17,200		
	(358)[9]	(1,450)[9]	(280)[9]	(4,800)[9]				
o-Anidisine[11b]	284	3,110			236	8,100		
p-Nitroanisole[12]			306	10,780			224	7,690
			(317)[8]	(11,000)[8]			(227)[8]	(7,000)[8]
2-Br-5-NO_2-Aniline	370	2,308	285[b]	5,500	253.5	13,210	229	13,950
	(357)[b]	(1,980)	(290)	(5,200)	(250)	(8,420)	(224)	(11,100)
m-Nitroaniline[11a]	370	1,358	275[b]	4,000	235	17,200		
	(358)[9]	(1,450)[9]	(280)[9]	(4,800)[9]				
o-Bromoaniline	293	2,700			237	8,580		
	299[c]	3,110[c]						
p-Nitrobromobenzene[13,14]			276	11,380			215	7,760
			270[c]	11,500[c]				
4-COOH-3-NO_2-Aniline			282	13,050	253[b]	9,600		
m-Nitroaniline[11a]	370	1,358	275[b]	4,000	235	17,200		
	(358)[9]	(1,450)[9]	(280)[9]	(4,800)[9]				
o-Nitrobenzoic acid			*ca.* 250[12]	3,500[12]				
			(266)[12]	(5,300)[12]				
p-Aminobenzoic acid			285	17,500			219	9,260
			(288)[14]	(19,000)[14]			(219.5)[10]	(9,900)[10]

[a] All data are from this study unless indicated otherwise. The values in parentheses are for an aqueous solvent. [b] The mean value of a shoulder or broad band. [c] In hexane.[14] The shift is in the correct direction in going to the less polar solvent.

one substituent is a *meta*-orienting group, that there is a relationship of their ultraviolet spectra to the spectra of their disubstituted constituents.



III

A trisubstituted benzene Its disubstituted constituents

As compounds I and II fall in the class reported by Doub and Vandenbelt, the spectra of I and II were compared with those of their disubstituted constituents. Typical spectra for compounds of type I and II and of their respective constituents are shown in Figs. 1 to 4. The spectral characteristics for all of the compounds studied are given in Tables I and II. The bands are assigned on the basis of three considerations[17]: (1) First use the criteria of Doub and Vandenbelt,[10] although these authors pointed out[18] that the intensity criteria do not always strictly apply, especially in the case of the secondary bands. In most instances, our assignments agree with those of Doub and Vandenbelt. (2) A more polar solvent will produce a bathochromic shift of the first primary band and a hypsochromic

(8) L. Doub and J. M. Vandenbelt, *J. Am. Chem. Soc.*, **77**, 4535 (1955).

(9) L. Doub and J. M. Vandenbelt, *J. Am. Chem. Soc.*, **71**, 2414 (1949).

(10) L. Doub and J. M. Vandenbelt, *J. Am. Chem. Soc.*, **69**, 2714 (1947).

(11) (a) R. A. Morton and A. J. McGookin, *J. Chem. Soc.*, 901 (1934). (b) I. P. Grammaticakis, *Bull. soc. chim. France*, **18**, (5) 220 (1951).

(12) W. F. Forbes, *Can. J. Chem.*, **36**, 1350 (1958).

(13) H. E. Ungnade, *J. Am. Chem. Soc.*, **76**, 1601 (1954).

(14) A. Burawoy and A. R. Thompson, *J. Chem. Soc.*, 4314 (1956); G. Förster and J. Wagner, *Z. für physik. Chem.*, **B35**, 343 (1937).

(15) W. F. Forbes, A. S. Ralph, and R. Gosine, *Can. J. Chem.*, **36**, 869 (1958).

(16) L. Dede and A. Rosenberg, *Ber.*, **67**, 147 (1934). These authors report a solvent effect in agreement with that noted in the present paper.

(17) Other descriptions have been used, such as X and X′ bands, R, B, and K bands, N → V, N → R, and others [*cf.* E. A. Braude, *Determination of Organic Structures by Physical Methods* edited by E. A. Braude and F. C. Nachod, Academic Press, N. Y., 1955, Chap. 4].

(18) Footnote 3 of ref. 9.

TABLE II

SPECTRAL CHARACTERISTICS OF THE NONSWEET *m*-NITROANILINES AND THEIR DISUBSTITUTED CONSTITUENTS[a]

(Wave Lengths in mμ)

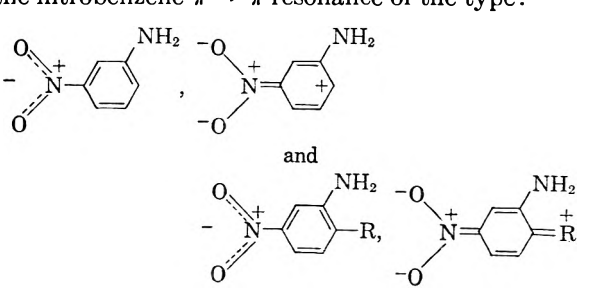
Compound	Secondary Band		First Primary Band		Second Primary Band		Third Primary Band	
	λ_m	ϵ	λ_m	ϵ	λ_m	ϵ	λ_m	ϵ
4-CH_3-3-NO_2-Aniline	366	1,395			234.5	15,500		
	(356)[b]	(1,462)			(228)	(15,200)		
m-Nitroaniline[11a]	370	1,358	275[b]	4,000	235	17,200		
	(358)[9]	(1,450)[9]	(280)[9]	(4,800)[9]				
o-Nitrotoluene	332.5	1,800	257	5,720				
	(325)[9]	(1,300)[9]	(266)[9]	(5,300)[9]			(202.5)[9]	(13,000)[9]
p-Toluidine[16]	289	1,515			234	9,120		
	(286)[10]	(1,600)[10]			(232)[10]	(8,900)[10]		
4-OCH_3-3-NO_2-Aniline	385	1,400			233	13,420		
	(390)	(1,923)			(228)	(15,910)		
m-Nitroaniline[11a]	370	1,358	275[b]	4,000	235	17,200		
	(358)[9]	(1,450)[9]	(280)[9]	(4,800)[9]				
o-Nitroanisole	324	2,370	259	3,220				
	(338)[8]	(2,800)[8]	(267)[8]	(4,000)[8]			(211)[8]	(15,000)[8]
p-Anisidine[11b]	300	2,138			235	9,250		
4-Br-3-NO_2-Aniline	365	1,199			241	18,250		
	(355)[b]	(1,107)			(236.5)	(15,450)		
m-Nitroaniline[11a]	370	1,358	275[b]	4,000	235	17,200		
	(358)[9]	(1,450)[9]	(280)[9]	(4,800)[9]				
o-Nitrobromobenzene[13]	295	1,380	253	2,980				
p-Bromoaniline	296	1,440			244	12,580		
	(290)[10]	(1,340)[10]			(239.5)[10]	(12,800)[10]		
2-COOH-5-NO_2-Aniline	400	2,830	265	11,000	242	19,690		
m-Nitroaniline[11a]	370	1,358	275[b]	4,000	235	17,200		
	(358)[9]	(1,450)[9]	(280)[9]	(4,800)[9]				
Anthranilic acid	333	4,400	247	6,880				
	(327)[9]	(1,940)[9]	(248)[9]	(3,900)[9]				
p-Nitrobenzoic acid			261	12,040				
			(271)[15]	(10,000)[15]				

[a] All data are from this study unless indicated otherwise. The values in parentheses are for an aqueous solvent. [b] The mean value of a shoulder or broad band.

shift of the second and third primary bands. This criterion is based on empirical observations; however, explanations of solvent effects on successive absorption bands have been offered by others.[19] (3) Bands below 250 mμ are arbitrarily designated third primary bands. In some cases, as with compounds of type I, such an assignment is natural because the first and second primary bands are clearly observable.

An accounting of the four bands of these compounds can be given in terms of electronic transitions within the molecules. It can be seen in Tables I and II that *m*-nitroaniline, a constituent of all of the trisubstituted benzenes, has a band at 370 mμ. A similar band appears in the spectra of all but one of the trisubstituted benzenes. This band can be designated an $n \rightarrow \pi^*$ band on the basis[20] of its low intensity, its broadness in alcohol solvent, its disappearance in acid solution, the effect of an electron-withdrawing substituent, and the *blue-shift* in going to more polar solvents.[21] It is observed from the data in Tables I and II that with few exceptions, the secondary band suffers a *blue-shift* in going from an alcohol to an aqueous solvent (latter values are in parentheses). This *blue-shift* has been explained[22] as originating from the effect of solvent molecules orienting themselves around the solute molecules in a favorable orientation to the ground state charge distribution of the solute molecules. Upon excitation, the charge distributions of the solute molecules are markedly changed and the solvent molecules are no longer oriented for strong binding to the solute molecules. This produces a greater solvation energy for the ground state of the solute than for the excited state.

The first primary band can be associated with the nitrobenzene $\pi \rightarrow \pi$ resonance of the type:



(19) N. S. Bayliss and E. G. McRae, *J. Phys. Chem.*, 58, 1002, 1006 (1954).

(20) J. W. Sidman, *Chem. Rev.*, 58, 689 (1958).

(21) H. McConnell, *J. Chem. Phys.*, 20, 700 (1952).

In *m*-nitroaniline this band is only a shoulder at about 275 mμ. The presence of the electron-donating substituent R produces a bathochromic and hyperchromic shift, and is greatest for the 2-OCH_3 derivative. Furthermore, in the case of substituted *m*-nitoanilines, the band persists in acid solution, although the $^+NH_3$ group produces a small shift to shorter wavelengths. In fact, the band resembles very much that for the correspondingly substituted nitrobenzene in which there is no $^+NH_3$ group.[23] This band in the 2-COOH derivative is very similar to that in *p*-nitrobenzoic acid.

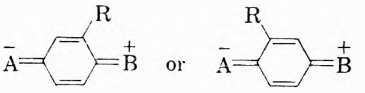
The *red-shift* of the primary band with change of solvent from ethanol to water has been explained in terms of increased solvation of the solute molecules in the excited state owing to their greater dipole moments.[19]

The second primary band apparently involves the lone-pair electrons on the amino nitrogen atom because, for all cases studied, it disappears in acid solution where the lone-pair electrons are not available for the transition. As this band too undergoes a *blue-shift* with a change to more polar solvents, it can be readily distinguished from the first primary band. On this basis, for example, the more intense bands of *o*-toluidine, *p*-toluidine, and *p*-bromoaniline are designated second rather than first primary bands, and that of anthranilic acid as a first rather than a second primary band.

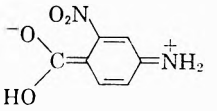
The third primary band is the least tenable assignment. It has been pointed out[24] that this band could possibly be the third primary band of benzene shifted to longer wave lengths. It is significant that a band in the 210–223 mμ region appears in the spectra of all of the substituted *m*-nitroanilines in acid solution.[23]

The first primary band is sensitive to the presence of a group *ortho* to the nitro group.[13,25] Thus, the band is either missing or is at shorter wavelengths and of much lower intensity for the *o*-substituted nitro compounds than for the *p*-substituted isomers. This is understandable in view of the coplanarity required for the nitro-phenyl group electronic interaction responsible for this band.

There is no readily apparent correlation between the spectra of the substituted *m*-nitroanilines and their tastes. It can be observed that only the sweet compounds have a first primary band above 280 mμ *and* a second primary band in the 230–260 mμ range. Considering the electronic transitions responsible for these two bands, one might deduce that intense sweetness is associated with a molecule having a flatness and a charge distribution as found in a *p*-disubstituted benzene with an electron-donor and an electron-withdrawing group plus a third group off center.



The sweetness of a molecule would then depend on the degree to which it approximates this structure. For example, *m*-nitroaniline, lacking a more electron-donating group than the hydrogen atom *para* to the nitro group, is only weakly sweet.[3] Furthermore, when R in I and II is an electron-donating group, I is the sweet isomer and II is nonsweet; but we have found in two cases that when R is an electron-withdrawing group (COOH or SO_2NH_2), II becomes the sweet isomer.



This possible taste-structure relationship is being explored further through a study of the molecular addition complex forming ability of these compounds and through an examination of the tastes of other structural systems approximating that of I and II.

The intensities of the second primary band (as the nonsweet isomers have no first primary band) of the 2- and 4-substituted 5-nitroanilines were measured in aqueous solutions with salt concentrations of 0.005*M*, 0.01*M*, 0.1*M*, and 1.0*M*. The molar extinction coefficients observed in water were unaffected by the presence of sodium chloride and magnesium chloride. However, potassium chloride produced a *decrease* in intensity of 5 to 10% for both isomers at each of the salt concentrations, and manganous chloride produced a variable 10% *increase* at the two higher salt concentrations. As these salt effects did not differ for the sweet and the nonsweet isomers, they were not investigated further at this time. These ions were chosen because of their key roles in nerve transmission and enzyme activations.

It is believed that the critical set of properties which determines the tastes of these compounds involves their loose complex-forming ability with some biological constituent in the tongue area. One does not expect a correlation with a single property of structure, basicity, or charge distribution, but with a combination of these and other factors. It is hoped that a factor analysis of the spectroscopic and other physicochemical properties of these compounds will provide a function which may be used for predicting the tastes of compounds, or at least give a clue as to why one isomer is several hundred times as sweet as sucrose while the other isomer is tasteless.

WASHINGTON 1, D. C.

(22) G. J. Brealey and M. Kasha, *J. Am. Chem. Soc.*, 77, 4462 (1955).

(23) A. R. Lawrence, Ph.D. thesis, Howard University, 1959.

(24) Page 2418 of ref. 9.

(25) G. S. Hammond and F. J. Modic, *J. Am. Chem. Soc.*, 75, 1385 (1953).

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

1,3-Diaxial Hydrogen Bonding and the Intramolecular Assistance of Solvolysis

ROBERT WEST, JAMES J. KORST,[1] AND WILLIAM S. JOHNSON

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The infrared spectra of some polycyclic 1,3-diols and 1,3-diol monoacetates, compounds I–VI, have been studied in the O—H stretching region under high resolution. Intramolecular hydrogen bonds from hydroxyl hydrogens to the ether oxygen of the acetate groups[2a] appear to be present in those monoacetates in which both groups are axial. In the diaxial diols the spectra indicate probable equilibrium between two different intramolecularly bonded species. The mechanism of hydroxyl participation in the solvolysis of the diaxial monoacetates is discussed.

In six-membered ring 1,3-diol monoesters which have the two functional groups rigidly held in the *cis*-diaxial relationship to one another, the ester group undergoes base-catalyzed methanolysis with surprising ease. This assistance by the hydroxyl group in facilitating solvolysis in such compounds was discovered independently by Henbest and Lovell[2] and by workers in these laboratories,[3] and accordingly may be called the "Henbest-Kupchan effect." Henbest and Lovell have also observed the infrared spectra of several 1,3-diaxial hydroxyesters in the cholestane and coprostane series.[2b] These spectra provide evidence for intramolecular hydrogen bonding of the hydroxyl hydrogen to the weakly basic alcohol oxygen of the ester group, and Henbest and Lovell suggest that this hydrogen bond formation is the factor responsible for the increased solvolysis rate of these compounds.

The importance of this unusual type of hydrogen bonding prompted us to study, at high resolution, the infrared spectra in the O—H region of some 1,3-diols and 1,3-hydroxyacetates of the bicyclononane and bicyclononene series (compounds I–VI).

EXPERIMENTAL

All of the compounds used in this study were prepared, purified, and characterized by methods described elsewhere.[4] The carbon tetrachloride solvent was used directly from freshly opened bottles of Merck and Co. reagent grade material; it contained negligible amounts of hydroxylic impurities. The spectra were determined using a Perkin-Elmer Model 112 single-beam double-pass spectrometer with calcium fluoride prism calibrated against ammonia and water vapor. Assignments are considered to be accurate to ± 3 cm.$^{-1}$ for sharp bands. Most of the compounds were studied both at 0.05M, using 1 mm. path length, and at 0.005M, using 10 mm. path length. Compounds II and IV were not soluble to the extent of 0.05M in carbon tetrachloride, and so were studied only at the lower concentration. Spectra in the 1700 cm.$^{-1}$ region were determined for some of the compounds as approximately 0.01M solutions in carbon tetrachloride.

All band maxima observed between 3100 and 3750 cm.$^{-1}$ are given following the names of the compounds below. Frequencies are given in cm.$^{-1}$, and the letters following the frequencies describe the bands as follows: s, strong; m, medium; w, weak; sh, shoulder; c, concentration-dependent band (intensity decreases upon dilution).

1β,6-*endo*-Dimethyl-6-*exo*-hydroxy-9α-acetoxy-2,3-(1′-methoxy-7′,8′-dihydro-6′,5′-naphtho)-Δ^2-bicyclo[3,3,1]-nonene[4b] (I), m.p. 131–132°, ν_{max} 3594 (s), 3480 (w).

1β,6-*endo*-Dimethyl-6-*exo*-9α-dihydroxy-2,3-(1′-methoxy-7′,8′-dihydro-6′,5′-naphtho)-Δ^2-bicyclo[3,3,1]nonene[4a] (II), m.p. 150.5–151°, ν_{max} 3628 (sh, m), 3607 (m), 3500 (s), 3300 (c).

1β,6-*endo*-Dimethyl-6-*exo*-hydroxy-9α-acetoxy-2,3-(1′-methoxy-5′β,6′β,7′,8′-tetrahydro-6′,5′-naphtho)-bicyclo-[3,3,1]nonane[4b] (III), m.p. 197–198°, ν_{max} 3593 (s), 3482 (w).

1β,6-*endo*-Dimethyl-6-*exo*-9α-dihydroxy-2,3-(1′-methoxy-5′β,6′β, 7′,8′-tetrahydro-6′,5′-naphtho)-bicyclo[3,3,1]nonane[4a] (IV), m.p. 212–218°, ν_{max} 3628 (sh, m), 3609 (m), 3510 (s), 3530 (c).

1β,6-*endo*-Dimethyl-6-*exo*-hydroxy-9β-acetoxy-2,3-(1′-methoxy-7′,8′-dihydro-6′,5,-naphtho)-Δ^2-bicyclo[3,3,1]-nonene[4b] (V), m.p. 195–198°, ν_{max} 3608(m), 3450 (c).

1β,6-*endo*-Dimethyl-6-*exo*-9β-dihydroxy-2,3-(1′-methoxy-7′, 8′-dihydro-6′, 5′-naphtho)-Δ^2-bicyclo [3,3,1]nonene[4a] (VI), m.p. 185–186.5°, ν_{max} 3618 (m), 3588 (m), 3300 (c).

DISCUSSION

The 1,3-diol monoacetates. The high resolution infrared spectra of the diaxial 1,3-hydroxy acetates I and III provide strong evidence in favor of intramolecular hydrogen bonding involving the hydroxyl group. Both compounds have a single strong O—H stretching absorption band at 3593–3594 cm^{-1}. The intensity of this bond is independent of concentration, and even at the maximum concentration used, 0.05M, there is no appearance of a concentration-dependent band attributable to intermolecular hydrogen bonding. In contrast the spectrum of the axial-equatorial hydroxy acetate V, which cannot be intramolecularly hydrogen bonded, has a sharp peak at 3607 cm.$^{-1}$ and a broad band at about 3450 cm.$^{-1}$, increasing in relative intensity with increasing concentration, characteristic of intermolecularly associated hydroxyl (Fig. 1).

A weak band at about 3480 cm.$^{-1}$ also appears in the spectra of compounds I and III. However, this band is not due to a hydrogen-oxygen stretch-

(1) Allied Chemical and Dye Company Fellow, 1958–1959.

(2) (a) H. B. Henbest and B. J. Lovell, *Chem. and Ind.*, 278 (1956); (b) H. B. Henbest and B. J. Lovell, *J. Chem. Soc.*, 1965 (1957).

(3) S. M. Kupchan and W. S. Johnson, *J. Am. Chem. Soc.*, **78**, 3864 (1956).

(4) (a) W. S. Johnson, J. Ackerman, J. F. Eastham, and H. A. DeWalt, Jr., *J. Am. Chem. Soc.* **78**, 6302 (1956); (b) W. S. Johnson, J. J. Korst, R. A. Clement, and J. Dutta, *J. Am. Chem. Soc.*, **82**, 614 (1960).

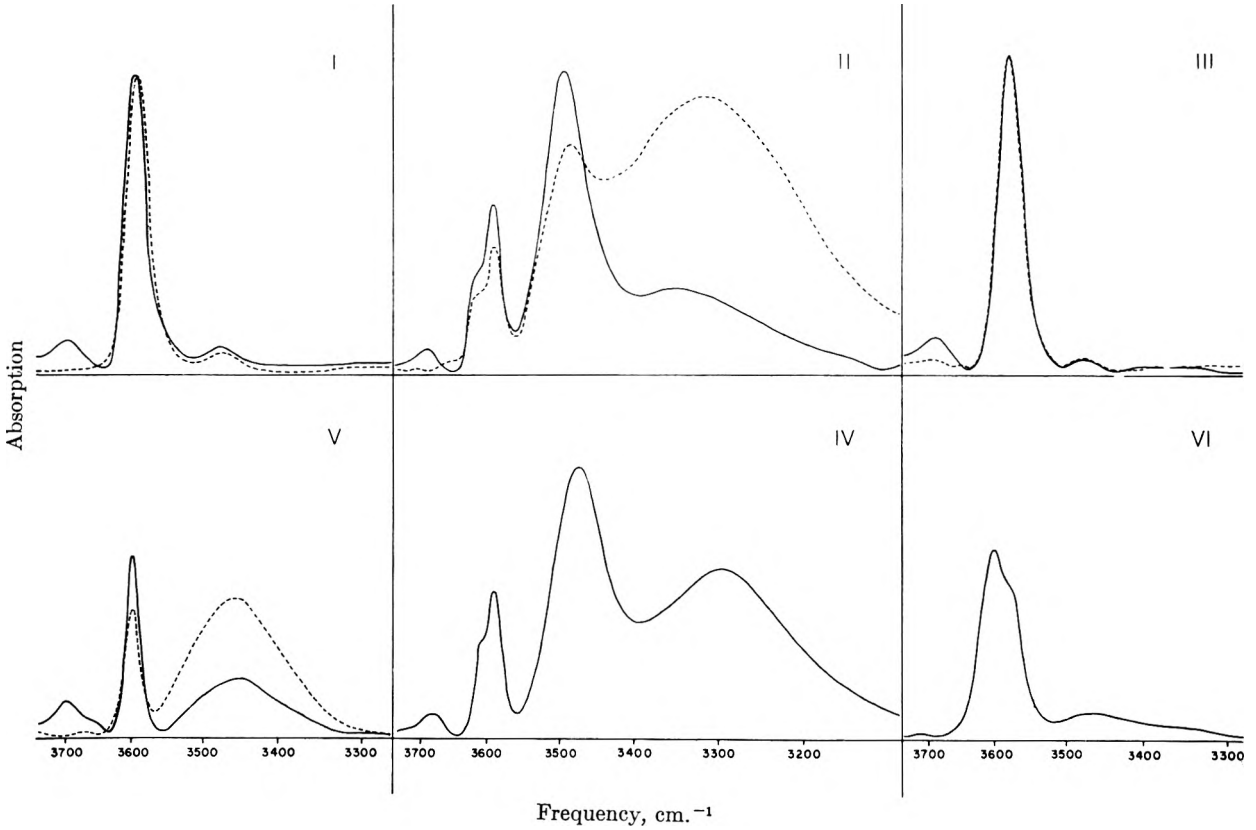
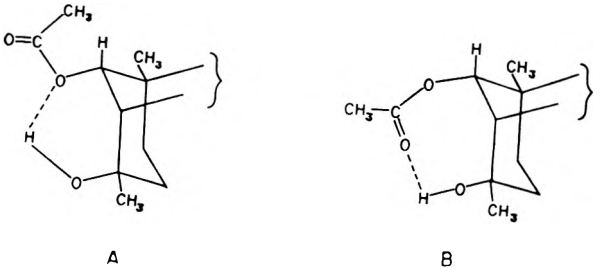


Fig. 1. Infrared spectra in the hydroxyl region. Solid lines, 0.005 *M*; broken lines, 0.05 *M*, in carbon tetrachloride

ing absorption, for when compound I was partially deuterated at the hydroxyl group by exchange with deuterium oxide in dioxane, the 3480 cm.$^{-1}$ band was not shifted. In contrast, the 3593 cm.$^{-1}$ O—H band exhibited a normal shift to 2637 cm^{-1}. The 3480 cm.$^{-1}$ band probably represents the first overtone of the strong carbonyl absorption at 1730 cm^{-1}.

The shift, $\Delta\nu$, of band position on hydrogen bond formation is approximately proportional to ΔH for the hydrogen bonding reaction.[5] The band at 3593 cm.$^{-1}$ in compounds I and III must therefore represent a very weakly bonded hydroxyl group, as $\Delta\nu$ is only 15 cm.$^{-1}$ from the position of the unassociated band (in compound V). The shift seems too small for a hydrogen bond to the carbonyl oxygen of the acetate group.[6] We believe that it indicates hydrogen bonding to the ether oxygen, as shown in structure A. As suggested by Henbest and Lovell for other compounds,[2b] hydrogen bonding to the more weakly basic ether oxygen atom probably takes place in I and III because of the large entropy effect favoring the six-membered ring hydrogen bonded system in A over the eight-membered ring system in B.

Further evidence for hydrogen bonding to the ether oxygen rather than to the carbonyl oxygen is given by the spectra of compounds I and III in

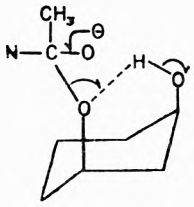


A B

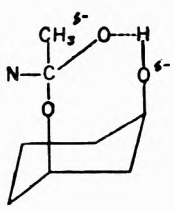
the 1700 cm.$^{-1}$ region. Intramolecular hydrogen bonding to carbonyl oxygen is known to lower the frequency of C=O stretching bands.[7] Compounds I and III, however, are observed to have carbonyl bands at unusually high frequencies. Compound V, which cannot be intramolecularly hydrogen bonded to either oxygen of the acetate group, has a broad carbonyl band centered at 1730 cm.$^{-1}$, while compounds I and III show sharp C=O bands near 1745 cm^{-1}.

Henbest has suggested that the intramolecular assistance of solvolysis in 1,3-diaxial hydroxy acetates involves an intramolecular solvation in the collapse (see arrows, formula C) of the reversibly formed adduct C between the ester and nucleophile (N^-). An alternative mechanism is conceivable, however, in view of the likely facile

(5) R. M. Badger, *J. Chem. Phys.*, 8, 288 (1940).
(6) M. St. C. Flett, *Spectrochim. Acta*, 10, 21 (1957).
(7) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, 2nd Edition, Methuen and Co., London, 1958, p. 142.



C



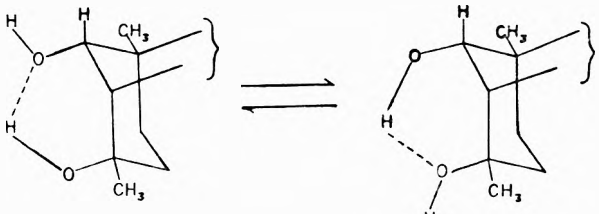
D

interconversion between structures A and B.[8] Hydrogen bonding to the carbonyl oxygen in species B would strongly polarize the C=O group and render it more susceptible to nucleophilic attack, by a sort of intramolecular acid catalysis (see formula D). Form B rather than A thus may be important in facilitation of solvolysis. In any case, the hydrogen bond to the ether oxygen in species A, prior to the solvolysis of the acetate group, seems too weak to have a significant influence on the rate of solvolysis. Which ever species is the important one in solvolysis, it seems likely that the hydrogen bond will become much stronger in the transition state, and that the increase in hydrogen bond energy in passing from the ground state to the transition state decreases the energy of activation for the reaction, thereby increasing the rate of solvolysis.

It may be possible to distinguish between the two mechanisms by appropriate kinetic measurements comparing the facilitation of 1,3-diaxial systems with eclipsed 1,2-systems wherein the entropy as well as enthalpy factors would favor the hydrogen to carbonyl oxygen interaction.

The 1,3-diols. The diols II and IV present very similar, and quite complicated, infrared spectra in the 3100–3800 cm.$^{-1}$ region (Fig. 1). Both show the following features: (a) a concentration-dependent band at about 3300 cm.$^{-1}$ which can be ascribed to intermolecular hydrogen bonding; (b) a strong concentration-independent band at about 3500 cm.$^{-1}$, in an appropriate position for an intramolecular hydrogen bond of moderate strength; and (c) two sharp, closely spaced bands, one at about 3608 and the other at about 3628 cm.$^{-1}$ The last two bands are in the right region for non-bonded hydroxyl groups. However, it seems quite unlikely that there are any substantial numbers of molecules of II or IV present which are not intramolecularly bonded, as even in the case of the weakly bonded acetates I and III no free hydroxyl vibrations are observed. We attribute the 3628 and 3608 cm.$^{-1}$ bands to secondary and tertiary hydroxyl groups, respectively, which are acting as bases in intramolecular hydrogen bond formation. The lower frequency band can be attributed to the tertiary hydroxyl, as in the non-bonded compound V the tertiary hydroxyl also absorbs at 3608 cm.$^{-1}$ It is well established that secondary hydroxyl groups absorb at higher frequencies than tertiary hydroxyls,[9] and Cole has recently shown that axial secondary hydroxyls absorb about 20 cm.$^{-1}$ higher than axial tertiary hydroxyls in triterpenoids.[10]

Our assignment implies the following equilibrium in diols II and IV:



E F

The relative intensities of the O—H bands suggest that the equilibrium constant for the reaction E⇌F lies in the neighborhood of 2. The ring formed by the hydrogen bond is six-membered in both E and F, so no large entropy effect is expected. The position of the equilibrium reflects the fact that the secondary hydroxyl is slightly more acidic, and less basic, than the tertiary hydroxyl group.[9] The bonded hydroxyl groups in forms E and F together contribute to the strong, broad peak at about 3500 cm.$^{-1}$ Finally, the presence of a concentration-dependent band at much lower frequency is not inconsistent with complete intramolecular hydrogen bonding in the diols, as that hydroxyl hydrogen which is not intramolecularly hydrogen bonded is available for intermolecular association.

One of the hydroxyl groups in compound VI is equatorial to ring A, which precludes intramolecular hydrogen bonding between the hydroxyl groups. It is somewhat surprising, then, to find that this compound has an absorption band at 3588 cm.$^{-1}$, indicating weak intramolecular hydrogen bonding. Probably the equatorial (secondary) hydroxyl group is partly or wholly intramolecularly hydrogen-bonded to the π-electrons of the double bond in ring B.[11]

Acknowledgment. This work was supported in part by a fellowship[1] and by grant from the U. S. Public Health Service and the National Science Foundation.

MADISON, WIS.

(8) The spectra give no indication of the presence of structure B, but an amount of B less than 1% of A at equilibrium cannot be excluded.

(9) L. P. Kuhn, *J. Am. Chem. Soc.*, 74, 2492 (1952).

(10) A. R. H. Cole, P. R. Jefferies, and G. T. A. Müller, *J. Chem. Soc.*, 1222 (1959).

(11) A number of instances of intramolecular hydrogen bonding to olefinic double bonds have been reported recently, including some closely related analogs such as *epi*-cholesterol. See P. von R. Schleyer, D. S. Trifan, and R. Backskai, *J. Am. Chem. Soc.*, 80, 6691 (1958); A. W. Baker and A. T. Shulgin, *J. Am. Chem. Soc.*, 81, 5358 (1958); R. West, *J. Am. Chem. Soc.*, 81, 1614 (1959).

[CONTRIBUTION FROM THE VENABLE CHEMICAL LABORATORIES, UNIVERSITY OF NORTH CAROLINA]

Ferrocenylazobenzenes. Resonance Interaction of Ferrocene with Substrates

WILLIAM F. LITTLE AND ALLEN K. CLARK[1]

Received February 29, 1960

A series of substituted *m*-ferrocenylazobenzenes and *p*-ferrocenylazobenzenes was prepared and the ultraviolet and visible spectra were obtained for purposes of interpreting resonance effects of the ferrocenyl substituent on the azo substrate. Strong bathochromic shifts for the *p*-ferrocenylazobenzenes compared to slight shifts for the *m*-ferrocenylazobenzenes indicate that the ferrocenyl substituent does interact with the substrates by resonance, and the electron donating character of this interaction is seen in the greatly exalted bathochromic shift for *p*-ferrocenyl-*p'*-nitroazobenzene. The *p*-ferrocenyl substituent causes a greater shift of the azobenzene absorption than does a *p*-phenyl substituent.

The high electron density in the aromatic rings of ferrocene is reflected in the reactivity of the ferrocene nucleus toward electrophiles. As a substituent, ferrocene exhibits electron donor properties. This has been shown quantitatively in the comparison of the base constants of *m*-ferrocenylaniline (*m*-aminophenylferrocene) and *p*-ferrocenylaniline (*p*-aminophenylferrocene) with aniline in 80% aqueous alcohol reported by Nesmeyanov[2]: aniline, 7.2×10^{-11}; *m*-ferrocenylaniline, 1.4×10^{-10}; *p*-ferrocenylaniline, 2.2×10^{-10}. The same interpretation is given to the results that *p*-ferrocenylphenol is a weaker acid than phenol and the ferrocenylbenzoic acids are weaker acids than benzoic acid.

A series of *m*- and *p*-ferrocenylazobenzenes were prepared for the purpose of observing resonance effects of the ferrocenyl substituent on the azobenzene substrates as exhibited in the shifts of the absorption maxima in the ultraviolet and visible spectra. The ferrocenylazobenzenes were conveniently prepared by condensation of the appropriate nitrosobenzenes with *m*- and *p*-aminophenylferrocene. *p*-Ferrocenylazobenzene was also prepared by direct arylation of the ferrocinium ion with a diazonium salt of *p*-aminoazobenzene. Table I lists the properties of the ferrocenylazobenzenes.

TABLE I

FERROCENYLAZOBENZENES

(Fc = FERROCENYL)

Compound	M.P.	Color	Yield, %	Formula	Nitrogen, % Calcd.	Nitrogen, % Found
p-Fc	122.8–123.8	Red	49	$C_{22}H_{18}N_2Fe$	7.65	7.43
p-Fc, *p'*-Cl[a]	217.5–218.7[b]	Red	82	$C_{22}H_{17}N_2ClFe$	6.99	7.15
p-Fc, *p'*-Br	216.5–218.0[b]	Red	78	$C_{22}H_{17}N_2BrFe$	6.29	6.23
p-Fc, *p'*-I	196.0–197.5	Red	80	$C_{22}H_{17}N_2IFe$	5.69	5.89
p-Fc, *m'*-Cl	134.0–136.0	Purple	56	$C_{22}H_{17}N_2ClFe$	6.99	7.18
p-Fc, *p'*-CH_3	180.8–181.8	Red	55	$C_{23}H_{20}N_2Fe$	7.38	7.44
p-Fc, *o'*-Cl	134.0–135.5	Black	60	$C_{22}H_{17}N_2ClFe$	6.99	6.95
p-Fc, *m'*-CF_3	116.5–118.0	Purple	47	$C_{23}H_{17}N_2F_3Fe$	6.45	6.53
p-Fc, *p'*-NO_2	260 (dec.)[b]	Green[c]	58	$C_{22}H_{17}N_3O_2Fe$	10.22	10.47
m-Fc	109.8–111.8	Orange-red	64	$C_{22}H_{18}N_2Fe$	7.65	7.81
m-Fc, *p'*-Cl	118.0–119.0	Red	55	$C_{22}H_{17}N_2ClFe$	6.99	7.18
m-Fe, *p'*-Br	117.0–119.0	Red	68	$C_{22}H_{17}N_2BrFe$	6.29	6.44
m-Fc, *p'*-I	153.0–155.0	Purple	68	$C_{22}H_{17}N_2IFe$	5.69	5.74
m-Fc, *m'*-Cl	66.0– 68.5	Red	39	$C_{22}H_{17}N_2ClFe$	6.99	7.16
m-Fc, *p'*-NO_2	166.0–168.0	Brown	45	$C_{22}H_{17}N_3O_2Fe$	10.22	10.38

[a] Calcd. for $C_{22}H_{17}N_2ClFe$: C, 65.94; H, 4.28. Found: C, 65.83, 65.60; H, 4.31, 4.46. [b] Uncorrected. [c] Reddish purple in solution.

DISCUSSION

The ultraviolet and visible spectra of the *p*-ferrocenylazobenzenes (Table II) show marked resonance interaction[3] between the *p*-ferrocenyl substituent and the azo system as reflected in the strong bathochromic shifts of the absorption maxima compared to the corresponding parent azobenzenes. *p*-Ferrocenylazobenzene, itself, shows maximum absorption in the ultraviolet at 350 mμ

(1) Union Carbide Fellow, 1958–59.

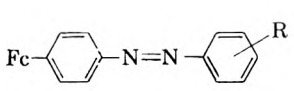
(2) A. N. Nesmeyanov, E. G. Perevalova, and R. V. Golovnya, *Doklady Akad. Nauk S.S.S.R.*, 103, 81 (1958); A. N. Nesmeyanov, *Proc. Roy. Soc., London*, 246, 495 (1958).

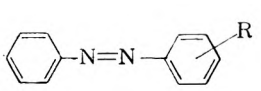
(3) A referee has pointed out that resonance interactions of phenyl substituents with the ferrocene ring have been previously reported and that many of these same conclusions were drawn in these reports: K. L. Rinehart, 135th Meeting of the American Chemical Society, Boston, Mass., April, 1959, Abstracts, p. 29; M. Cais and R. T. Lundquist, XVIIth International Congress of Pure and Applied Chemistry, Munich, August 1959, Abstracts p. 7.

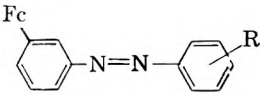
TABLE II

ULTRAVIOLET AND VISIBLE SPECTRA OF FERROCENYLAZOBENZENES

(Fc = ferrocenyl)







R	U.V. Max., mμ	ε	Vis. Max., mμ	ε	R	U.V. Max., mμ	ε	Vis. Max., mμ	ε	R	U.V. Max., mμ	ε	Vis. Max., mμ	ε
p-H	350	25100	488	4640	*p*-H	316	21200	441	519	*p*-H	317	23400	438	1420
					p-C_6H_5	342	30600	440	1030					
p-Cl	357	27600	499	5300	*p*-Cl	322	23900	442	623	*p*-Cl	325	25000	442	1530
p-Br	358	29100	500	5460	*p*-Br	324	25500	442	638	*p*-Br	326	26300	442	1610
p-I	361	31500	502	5730	*p*-I	329	27400	443	740	*p*-I	332	27600	442	1700
p-CH_3	353	28800	483	4950	*p*-CH_3	323	23800	439	676					
p-NO_2	376	25900	537	6080	*p*-NO_2	331	25500	457	638	*p*-NO_2	331	25000	450	1550
o-Cl	359	24500	506	5140	*o*-Cl	322	18600	450	481					
m-Cl	356	26000	504	5090	*m*-Cl	319	21700	443	499	*m*-Cl	319	22300	443	1350
p-Cl	357	27600	499	5300	*p*-Cl	322	23900	442	623					
m-CF_3	357	25100	507	5040	*m*-CF_3	315	21400	443	458					

compared to 316 mμ for azobenzene, a shift of 34 mμ. By comparison, the phenyl substituent in *p*-phenylazobenzene shifts the maximum of azobenzene to 342 mμ, a shift of 26 mμ, indicating a greater resonance interaction for the ferrocenyl substituent than for the phenyl group. In *m*-ferrocenylazobenzene, on the other hand, the ferrocenyl substituent cannot interact with the azo function, and, as expected, there is but a slight shift of the maximum absorption (317 mμ, a shift of one mμ) from that of azobenzene.

Similar effects are seen in the visible spectra, where the *p*-ferrocenyl substituent causes a bathochromic shift in the azobenzene absorption of 47 mμ, compared to slight hypsochromic shifts of 1 mμ for *p*-phenylazobenzene and 3 mμ for *m*-ferrocenylazobenzene.

It is interesting to compare the absorption maxima and extinction coefficients of ferrocenylazobenzene to those of ferrocene and azoferrocene. While ferrocenylazobenzene absorbs at 350 mμ (ε 25,100) in the ultraviolet and at 488 mμ (ε 5300) in the visible, ferrocene itself absorbs at the shorter wave lengths, 326 mμ and 440 mμ, with much smaller extinction coefficients, 50 and 87, respectively.[4] Nesmeyanov *et al.*, have prepared azoferrocene,[5] and have reported absorptions at 315 mμ (ε 350), 375 mμ (ε 76), and 510 mμ (ε 81).

Table II shows that ultraviolet extinction coefficients of the substituted azobenzenes are increased by the ferrocenyl substituent. Except for the ferrocenyl-*p'*-nitroazobenzenes, which show abnormally low extinction coefficients, the *p*-ferrocenyl group increases the extinction coefficients between 14 and 30%, while the *m*-ferrocenyl substituent appears responsible for smaller increases ranging from 1 to 10%. Similarly, the visible extinction coefficients of the substituted azobenzenes are between seven- and eleven-fold larger due to the *p*-ferrocenyl substituent, while the *m*-ferrocenyl group is responsible for extinction coefficients around 2.5 times larger than the correspondingly substituted azobenzenes not containing ferrocene.

Table III lists the spectral shifts brought about by substituents within the two series, the azobenzenes and the *p*-ferrocenylazobenzenes. From the listed data it can be seen that for those substituents with electron withdrawing inductive effects, the bathochromic shifts in the *p*-ferrocenylazobenzene series are slightly larger than the corresponding shifts in the azobenzene series. The only group with an electron donating inductive effect, the methyl group, shows a smaller shift in the *p*-ferrocenyl series. This suggests that the *p*-ferrocenyl group is electron releasing in its resonance interaction with the azo system. The effect is dramatic in the case of the *p*-nitro group, the only substituent listed that is electron withdrawing by resonance as well as by induction. The bathochromic shift in *p*-nitro-*p'*-ferrocenylazobenzene is far larger than the shifts caused by other substituents in the *p*-ferrocenyl series (26 mμ), and, relative to azobenzene, the shift is 60 mμ.

It can be seen from Table III that the *m*-CF_3 group also causes a marked bathochromic shift in both the ultraviolet and visible spectra of the *p'*-ferrocenylazobenzene series, though not so outstandingly large as that of the *p*-nitro group.

In the *m*-ferrocenylazobenzene series (Table II) the absorption maxima for the substituted *m*-ferrocenylazobenzenes are very nearly the same as the correspondingly substituted azobenzenes.

The magnitudes and directions of these spectral shifts suggest activated states that can be represented by the structures:

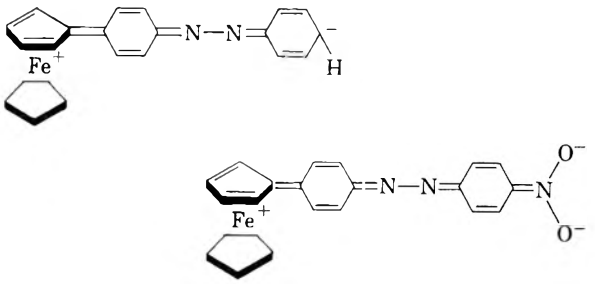
(4) G. Wilkinson, M. Rosenblum, M. C. Whiting, and R. B. Woodward, *J. Am. Chem. Soc.*, **74**, 2125 (1952).

(5) A. N. Nesmeyanov, E. G. Perevalova, and T. V. Nikitina, *Tetrahedron Letters*, **1**, 1 (1960).

TABLE III

SPECTRAL SHIFTS ARISING FROM SUBSTITUENTS IN AZOBENZENE AND *p'*-FERROCENYLAZOBENZENE

	Ultraviolet			Visible		
Group	a, Observed shift of azobenzene spectrum, mμ	b, Observed shift of *p'*-ferrocenyl-azobenzene spectrum, mμ	b − a	c, Observed shift of azobenzene spectrum, mμ	d, Observed shift of *p'*-ferro-cenylazobenzene spectrum, mμ	d − c
p-Cl	6	7	+1	1	11	+10
p-Br	8	8	0	1	12	+11
p-I	13	11	−2	2	14	+12
p-CH_3	7	3	−4	−2	−5	−3
p-NO_2	15	26	+11	16	49	+33
o-Cl	6	9	+3	9	18	+9
m-Cl	3	6	+3	9	16	+7
p-Cl	6	7	+1	1	11	+10
m-CF_3	−1	7	+8	2	19	+17



where the substituted ring takes on the character of a diene-iron complex.[6]

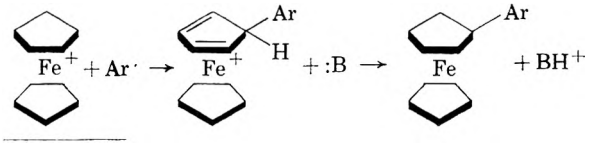
The use of the arylation of the ferrocinium ion in the direct preparation of *p*-ferrocenylazobenzene and *m*-nitrophenylferrocene from diazonium salts has led the authors to comment on the mechanism of this reaction as presented by Pauson.[7] Pauson has shown that traces of neutral ferrocene are necessary for the initiation of this reaction according to the mechanism:

$$Fc + ArN_2^+ \longrightarrow Fc^+ + Ar\cdot$$

$$Ar\cdot + Fc^+ \longrightarrow Fc^+Ar + H\cdot$$

$$H\cdot + Fc^+ \longrightarrow Fc + H^+$$

A more plausible modification of this scheme can be suggested wherein a base attack on the intermediate sigma complex, rather than loss of a hydrogen atom, is proposed[8]:



(6) Pauson has reported stable diene-iron complexes, though of a somewhat different nature from this, P. L. Pauson, *J. Chem. Soc.*, 642 (1958).

(7) P. L. Pauson, *Quart. Revs. (London)*, 9, 391 (1955).

(8) Rinehart[9] has discussed the nature of the intermediate sigma complexes in electrophilic substitution of ferrocene. While he has represented the intermediates as resonance forms with the seat of positive charge located principally in the rings, we prefer to represent these intermediates with the positive charge largely contained in the iron, in view of Pauson's stable diene-iron complexes.[6]

EXPERIMENTAL

Melting points are corrected.

p-Aminophenylferrocene and m-aminophenylferrocene. *p*-Aminophenylferrocene was prepared by hydrogenation of *p*-nitrophenylferrocene[10] with platinum oxide in alcohol at room temperature and 50 lb. pressure. The reduction required about 20 min. and crystallization from alcohol gave 90% yield of a product melting at 159–160°. Nesmeyanov[10] reported *p*-aminophenylferrocene from a tin–hydrochloric acid reduction of *p*-nitrophenylferrocene, m.p. 159–160.5°.[11] *m*-Aminophenylferrocene was prepared by hydrogenation of *m*-nitrophenylferrocene in a similar manner, m.p. 117–118°; reported[10] m.p. 112–113°. The benzoyl derivative of *m*-aminophenylferrocene was prepared, m.p. 207.0–209.5°.

Anal. Calcd. for $C_{23}H_{19}ONFe$: N, 3.68. Found: N, 3.82.

Nitrosobenzenes. Three methods were used for the preparation of substituted nitrosobenzenes. *Method 1.* Substituted nitro compounds were reduced to hydroxylamines with zinc and ammonium chloride, followed by oxidation to nitroso compounds with ferric chloride or dichromate.[12–14] This method was used for the preparation of nitrosobenzene, *p*-chloronitrosobenzene, *p*-bromonitrosobenzene, *p*-iodonitrosobenzene, and *o*-chloronitrosobenzene.

Method 2. Substituted aromatic amines were oxidized with Caro's acid.[14,15] This method was used for *m*-chloronitrosobenzene, *p*-methylnitrosobenzene, and *m*-trifluoromethylnitrosobenzene.

Method 3. *p*-Nitronitrosobenzene was prepared by peracetic acid oxidation of *p*-nitroaniline.[16]

Azobenzenes. The azobenzenes were prepared by dissolving equimolar quantities (usually about 0.004 mole) of the appropriate substituted aniline and the substituted nitroso compound in glacial acetic acid. The azo compounds were collected as precipitates after standing from 12 to 48 hr., and were recrystallized from water and alcohol. The compounds prepared from nitrosobenzene and the appropriate substituted anilines were: *m*-chloroazobenzene, m.p. 68–

(9) K. L. Rinehart, K. L. Motz, and S. Moon, *J. Am. Chem. Soc.*, **79**, 2750 (1957).

(10) A. N. Nesmeyanov, E. G. Perevalova, R. V. Golovnya, and L. S. Shilovtseva, *Doklady Akad. Nauk S.S.S.R.*, **102**, 535 (1955).

(11) V. Weinmayr, *J. Am. Chem. Soc.*, **77**, 3012 (1955).

(12) W. J. Wijs, S. E. Hoekstra, R. M. Ulmann, and E. Havinga, *Rec. trav. chim.*, **77**, 746 (1958).

(13) R. E. Lutz and M. R. Lytton, *J. Org. Chem.*, **2**, 68 (1937).

(14) C. H. Coleman, C. M. McCloskey, and F. A. Stuart, *Org. Syntheses*, Coll. Vol. III, 668 (1955).

(15) E. Bamberger and R. Hubner, *Ber.*, **36**, 3803 (1903).

(16) E. Hecker, *Ber.*, **88**, 1666 (1955).

69.5°, reported[17] m.p. 67.5°; *p*-chloroazobenzene, m.p. 88–89°, reported[17] m.p., 87.5°; *p*-bromoazobenzene, m.p. 88–90°, reported[17] m.p. 89°; *p*-iodoazobenzene, m.p. 105–107°, reported[18] m.p. 105°; *p*-methylazobenzene, m.p. 69–71°, reported[19] m.p. 71–72°; *p*-phenylazobenzene, m.p. 154–155°, reported[20] m.p. 150°, and *m*-trifluoromethylazobenzene, m.p. 38–39°, reported[21] m.p., 37°.

The azobenzenes prepared from aniline and the appropriate substituted nitrosobenzenes were: *p*-nitroazobenzene, m.p. 132–134°, reported[11] m.p. 134–135°; *m*-trifluoromethylazobenzene, m.p. 38–39°; and *o*-chloroazobenzene, m.p. 29–31°.

Anal. Calcd. for $C_{12}H_9N_2Cl$: C, 66.52; H, 4.19. Found: C, 66.60, 66.79; H, 4.28, 4.17.

Ferrocenylazobenzenes. The ferrocenylazobenzenes were prepared by the same methods as the azobenzenes, using in each case the aminophenylferrocene and a 10% excess of the appropriate nitroso compound. Their properties and analyses are listed in Table I. The ferrocenylazobenzenes dissolve in alcohol to give colored solutions varying from orange to reddish purple. They are soluble in concd. hydrochloric acid to form red solutions.

p-Ferrocenylazobenzene was also prepared directly from ferrocene and *p*-aminoazobenzene. A solution of 9.3 g. (0.05 mole) of ferrocene was prepared in 27 ml. of concd. sulfuric acid, to yield the ferrocinium ion, and this solution was poured on crushed ice. To this solution was added a solution of diazotized *p*-aminoazobenzene in acetic acid, prepared from 9.9 g. (0.05 mole) of *p*-aminoazobenzene in acetic acid with sulfuric acid and a 10% excess of sodium nitrite at −3°. The mixture was brought to room temperature with stirring overnight. Work-up involved chromatography on alumina (benzene). *p*-Ferrocenylazobenzene was obtained in 21% yield, based on recovery of 38% of the ferrocene. The infrared spectrum of this product was identical with that prepared from *p*-aminophenylferrocene; a mixed melting point showed no depression.

Several nitroso compounds failed to couple with the aminophenylferrocenes. *p*-Nitroso-*N*,*N*-dimethylaniline, *p*-nitrosoanisole, and *m*-nitrosotoluene yielded with the amino compounds intractable tars.

Attempts to diazotize *m*-aminophenylferrocene and *p*-aminophenylferrocene and to couple with *N*,*N*-dimethylaniline failed. In both cases it is doubtful that the diazonium salt was obtained. This is not surprising in view of the report of failures by Nesmeyanov[22] to diazotize *p*-aminophenylferrocene.

Spectra. The spectra were obtained with a Cary Model 14 instrument. The solutions were prepared in absolute alcohol in about $10^{-5}M$ for the ultraviolet spectra and about $10^{-4}M$ for the visible spectra and were allowed to stand overnight in the dark to assure the *trans* form of the azo compounds. Although attempts to detect *cis* and *trans* isomers of the ferrocenylazobenzenes by chromatography on alumina gave no evidence of these two types of isomers, it was deemed desirable to allow these solutions to stand in the dark overnight in view of reports of changes in the spectra of azobenzenes upon exposure to light.[23,24] In view of experience the authors have had with decomposition of solutions of acetylferrocene and other derivatives of ferrocene on standing in acetonitrile, the ferrocenylazobenzene solutions were examined for decomposition on standing. No changes were observed in either the absorption maxima or the extinction coefficients of these solutions over a period of several days.

Acknowledgment. The authors would like to thank the University of North Carolina Research Council for financial assistance with some of the analyses.

CHAPEL HILL, N. C.

(17) E. Bamberger, *Ber.*, 29, 102 (1896)
(18) E. Noelting and P. Werner, *Ber.*, 23, 3252 (1903).
(19) C. Mills, *J. Chem. Soc.*, 67, 925 (1895).
(20) P. Greiss, *Ber.*, 9, 132 (1876).
(21) V. P. Chernetskii, L. M. Vagupolskii, and S. B. Serebryanyi, *Zhur. Obshcheĭ Khim.*, 25, 2161 (1955); *Chem. Abstr.*, 50, 8661 (1956).
(22) A. N. Nesmeyanov, E. G. Perevalova, L. S. Shilovtseva, and Yu A. Ustynyuk, *Doklady Akad. Nauk S.S.S.R.*, 124, 331 (1951).
(23) W. R. Brode, J. H. Gould, and G. M. Wyman, *J. Am. Chem. Soc.*, 74, 4641 (1952).
(24) K. Veno and S. Akiyoshi, *J. Am. Chem. Soc.*, 76, 3667 (1954).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Alkali Catalyzed Aldol Condensation of Bisacetylferrocene with Benzaldehyde to Form Mono- and Dibenzaldehyde Derivatives[1]

T. ARTHUR MASHBURN, JR., CHARLES E. CAIN,[2] AND CHARLES R. HAUSER

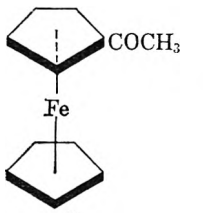
Received April 4, 1960

Treatment of mixtures of bisacetylferrocene and benzaldehyde with 5% aqueous-ethanolic sodium hydroxide produced a yellow product and a red product, which were evidently mono- and dibenzaldehyde derivatives respectively. The structure of the red product was established as the dibenzal derivative of bisacetylferrocene but that of the yellow product was not determined. Some evidence was obtained that the latter compound had a cyclic vinyl ether structure.

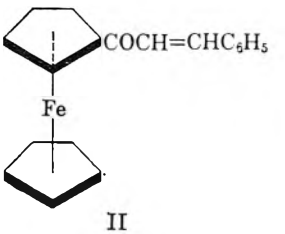
It has previously been shown[3] that acetylferrocene (I) and benzaldehyde undergo the alkali catalyzed aldol type of condensation accompanied by the elimination of water to form the benzal derivative II.

It therefore seemed possible that bisacetylferrocene (III)[4] and benzaldehyde would undergo this

(1) Supported in part by the Office of Ordnance Research, U. S. Army.
(2) Esso Research and Engineering Company Fellow, 1957–1958.
(3) C. R. Hauser and J. K. Lindsay, *J. Org. Chem.*, 22, 482 (1957).
(4) We are indebted to Dr. R. L. Pruett, Union Carbide Chemicals Company, South Charleston, W. Va., for a generous sample of this compound.

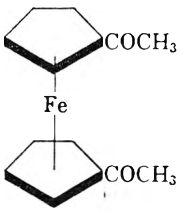


I

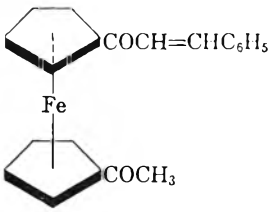


II

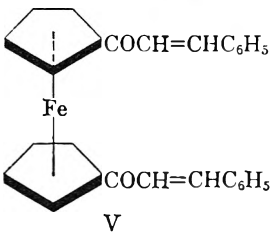
type of condensation to give the mono- and dibenzal derivatives IV and V respectively.



III



IV



V

Actually treatment of mixtures of diketone III and benzaldehyde with 5% aqueous–ethanolic sodium hydroxide produced a yellow product and a red product, the analyses of which were satisfactory for mono- and dibenzaldehyde derivatives, respectively. As might be expected on this basis, the proportion of the yellow product decreased and that of the red product increased as the number of molecular equivalents of benzaldehyde were increased (Table I).

TABLE I

YIELDS OF YELLOW AND RED PRODUCTS FROM BISACETYLFERROCENE (III) WITH VARIOUS EQUIVALENTS OF BENZALDEHYDE

C_6H_5CHO Equiv.	Yellow Prod., Yield, %[a]	Red Prod. (V) Yield, %
1	66–68	6–13
2	60	23
4	22	72
6	5	75

[a] Calculated as a monobenzaldehyde derivative.

Evidence was obtained that the red product was indeed the dibenzal derivative V but that the yellow product was an isomer or a polymer of structure IV. In Table II are summarized some significant bands of the infrared absorption spectra of the red and yellow products and of certain related compounds.

It can be seen from Table II that the infrared spectrum of the red product was almost identical

TABLE II

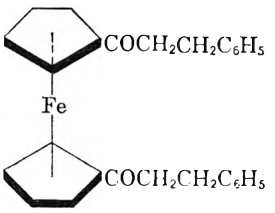
INFRARED ABSORPTION SPECTRA OF THE RED AND YELLOW PRODUCTS AND RELATED COMPOUNDS (μ)

Red Product V[a]	Benzal Derivative II[a]	Benzalacetophenone[b]	Saturated Ketone VI[c]	Saturated Ketone VII[c]	Yellow Product[a]
—	—	—	—	—	3.24
6.03	6.03	6.0	5.87	5.88	6.00
6.23	6.23	6.2	—	—	—
—	—	—	6.77	6.79	—
—	—	—	7.15	7.15	—
7.75	7.75	7.6	7.65	7.64	7.80
—	—	—	—	—	8.05
—	9.0	—	—	8.95	—
—	9.98	—	—	9.90	—
10.20	10.20	10.30	10.09	10.11	10.10
—	—	—	11.27	11.36	11.24
14.3, 14.6	14.1, 14.6	13.5, 14.5	—	—	14.16

[a] Infrared spectrum determined in potassium bromide pellet. [b] Ref. 5. [c] Infrared spectrum determined in carbon tetrachloride solution.

with that of the benzal derivative of monoacetylferrocene (II) and similar to that of benzalacetophenone,[5] both of which are structurally analogous to V. All three compounds showed bands at 6.2 μ and at about 14 μ, which may be ascribed to the conjugated carbon-carbon double bond[6] and to the monosubstituted benzene ring[7] respectively. The 9–10 μ bands exhibited by II but not by the red product (or benzalacetophenone) are attributed[8] to the unsubstituted cyclopentadienyl ring of II.

Further support that the red product had structure V was obtained by its molecular weight and by hydrogenation of the carbon-carbon double bond over palladium-charcoal, about 1.5 molecular equivalents of hydrogen being absorbed. The product was presumably the saturated ketone VI (51%), since its infrared spectrum showed carbonyl absorption at 5.88 μ and no band in the region of 6.2 μ for a carbon-carbon double bond conjugated with the carbonyl group (see Table II).



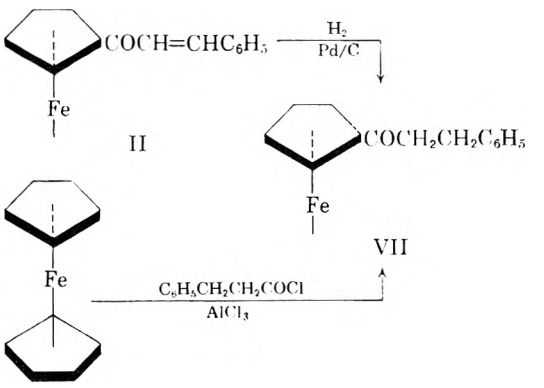
VI

As a model for such a hydrogenation, benzal derivative II was treated similarly, approximately one molecular equivalent of hydrogen being absorbed. The resulting saturated ketone VII (89%)

(5) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley and Sons, New York, 1958, p. 89.
(6) See ref. 5, p. 136.
(7) See ref. 5, p. 76.
(8) See P. L. Pauson, *Quart. Revs.* (*London*), 9, 391 (1955).

was independently synthesized from ferrocene and hydrocinnamoyl chloride (Scheme A).

Scheme A

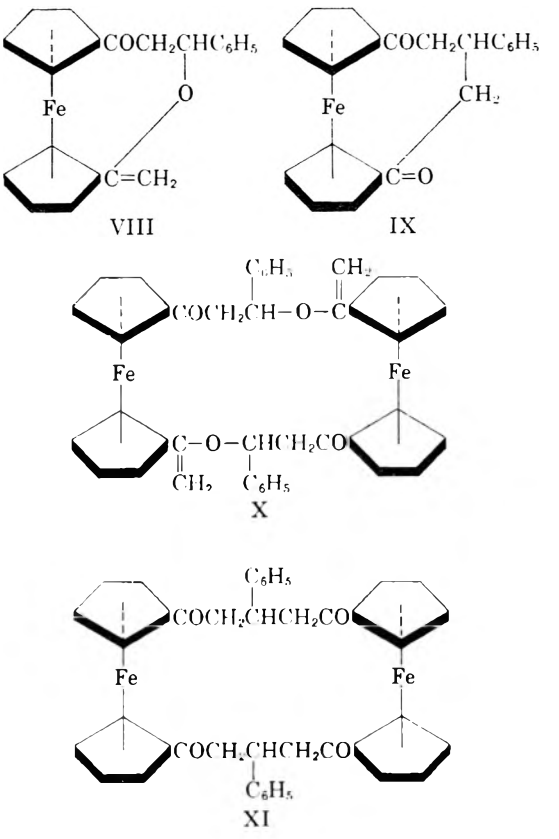


The infrared spectra of the two saturated ketones were almost identical, except for the usual absence of the 9–10 μ bands in the spectrum of VI[8] (see Table II). As these spectra were determined in carbon tetrachloride solution, the phenyl absorption was obscured by the solvent. The spectrum of ketone VII was also determined in a potassium bromide pellet, in which strong phenyl absorption was observed in the 14 μ region. These results are considered to establish the structure of the red product as V.

Incidentally, the method of preparation of benzal derivative II from monoacetylferrocene (I) and benzaldehyde was improved to give II in yields of 94–96% instead of the 65–69% yields reported earlier.[3]

It can further be seen from Table II that the infrared spectrum of the yellow product was not consistent with structure IV. Thus, although a carbonyl band was shown at 6.0 μ, no band was observed in the region of 6.2 μ for a conjugated carbon-carbon double bond. Instead, several bands appeared that were not exhibited by the α,β-unsaturated carbonyl compounds. As the analysis of the yellow compound called for a monobenzaldehyde derivative, an isomer or polymer of IV is suggested. A conceivable isomer would be VIII or IX, which might have arisen through intramolecular conjugate addition involving the oxygen or carbon resonance forms of the intermediate anion respectively. A conceivable dimer would be X or XI, which might have arisen through intermolecular conjugate addition of the two resonance forms of the anion.

As VIII and IX may correspond to an eight- or nine-membered ring and X and XI to a 16- to 18-membered ring, the latter might appear more likely even though an intermolecular condensation would first be required. Of course all the cyclizations would require the *cis*-configuration (*i.e.*, with the two groups on the same side) which appears to be the normal configuration of at least certain ferrocene derivatives.[9] Even if some ferrocene compounds



were normally in the *trans*-configuration, there seems to be free rotation around the iron in solution at normal temperatures.[10,11]

Because the yellow product had a relatively high melting point (>300°) and a relatively low solubility in such solvents as refluxing ethanol, benzene, carbon tetrachloride, tetrahydrofuran, and dimethylformamide, a dimer or even a higher polymer was indicated. Unfortunately, attempts to determine the molecular weight of the yellow product were unsatisfactory because of its insolubility in the usual cryoscopic and ebullioscopic solvents.

Although the structure of the yellow product was not established, its infrared spectra appeared to indicate the presence of a large ring ether group as in VIII and X but not in IX and XI (see Table II). Thus, the product showed a strong band at 8.05 μ, which corresponds to bands in the region of 7.87–8.1 μ reported for this type of group.[12] Moreover, the product gave weak bands at 3.24 μ and 11.24 μ, which seem attributable to the α,α-disubstituted ethylenic linkage found in VIII and X, as bands in these regions among others have been observed for compounds having such a group.[13] While the former band might also have been due to carbon-

(9) See D. A. Semenov and J. D. Roberts, *J. Am. Chem. Soc.*, **79**, 2741 (1957).

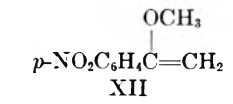
(10) See M. Rosenblum and R. B. Woodward, *J. Am. Chem. Soc.*, **80**, 5443 (1958).

(11) Yu T. Struchkov, *Zhur. Obshchei Khim.*, **27**, 2039 (1957).

(12) See ref. 5, page 114.

(13) See ref. 5, page 51.

hydrogen stretching in the ferrocene nucleus,[8] the nonferrocene type of vinyl ether XII[14] likewise showed a band at 3.23 μ (and at 3.55 μ) for the methylene double bond group. The band for the vinyl ether group in XII appeared at 9.0 μ, but this shift in value might be attributable to the presence of the nitro group.



XII

Indirect evidence was obtained that the yellow product had only one ketone group per ferrocene nucleus in agreement with structures VIII and X. Thus, the product gave a monophenylhydrazone and a mono-2,4-dinitrophenylhydrazone on treatment with large excesses of phenylhydrazine and 2,4-dinitrophenylhydrazine respectively. No diphenylhydrazone or di-2,4-dinitrophenylhydrazone was found.

It should be mentioned that when a suspension of the yellow product in glacial acetic acid containing 5% hydrochloric acid was heated at reflux temperature for two hours under dry nitrogen, decomposition occurred. However, no pure compound was isolated.

EXPERIMENTAL[15]

Condensation of bisacetylferrocene (III) *with benzaldehyde.* This condensation was effected with various molecular equivalents of benzaldehyde by means of dilute aqueous–ethanolic sodium hydroxide to form yellow and red products, the yields of which are summarized in Table I. Experiments are described below employing 1 and 6 equivalents of the aldehyde.

(*A*) *With one equivalent of benzaldehyde. Preparation of yellow product.* To a stirred solution of 1.6 g. (0.04 mole) of sodium hydroxide in 10 ml. of water and 125 ml. of 95% ethanol was added 10.8 g. (0.04 mole) of bisacetylferrocene (III). As soon as the diketone had dissolved, a cold water bath (approximately 15°) was placed around the flask, and 4.2 g. (0.04 mole) of freshly distilled benzaldehyde was slowly added to the solution. The resulting deep red solution was stirred for 90 min., during which time a pink precipitate formed. Stirring was stopped and the solution was allowed to stand overnight in the refrigerator. The pink-yellow solid was collected and washed with water until the washings were neutral to litmus. Recrystallization from ethanol-benzene gave 9.6 g. (66%) of the yellow compound as golden feathers, m.p. >300°, the analysis of which was satisfactory for a monobenzaldehyde derivative of bisacetylferrocene.

Anal. Calcd. for $C_{21}H_{18}O_2Fe$: C, 70.41; H, 5.06; Fe, 15.53 Found: C, 70.38; H, 5.11; Fe, 15.74.

Concentration of the filtrate precipitated 1.0 g (6%) of the bis-α,β-unsaturated ketone V as small, red crystals, m.p. 206–209°.

(*B*) *With six equivalents of benzoldehyde. Preparation of bis-α,β-unsaturated ketone* V. To a stirred solution of 6 g. (0.150 mole) of sodium hydroxide in 75 ml. of water and 100 ml. of 95% ethanol was added 5.4 g. (0.02 mole) of bisacetylferrocene (III) in 50 ml. of 95% ethanol, followed by 11.5 g. (0.12 mole) of freshly distilled benzaldehyde. The resulting deep red solution was stirred for 6 hr. During this time a very flocculant, red precipitate formed. The stirring was stopped, and the solution was allowed to stand overnight in the refrigerator. The red precipitate was collected and washed with water until the washings were neutral to litmus. The red powder, on recrystallization from ethanol-water, gave 6.7 g. (75%) of the bis-α,β-unsaturated ketone V as red needles, m.p. 208–210°.

Anal. Calcd. for $C_{25}H_{22}O_2Fe$: C, 75.34; H, 4.94; Fe, 12.51. Found: C, 75.06; H, 4.99; Fe, 13.34. *Mol. wt.*[16] Calcd. 446.3. Found: 462.

In addition, there was isolated a very small quantity (approximately 0.3 g.) of the yellow product, m.p. >300°. Mixed melting points and infrared spectra showed these two products to be identical with those isolated under (A).

Hydrogenation of bis-α,β-unsaturated ketone V. To a deep red solution of 1 g. of the unsaturated ketone V in 225 ml. of absolute ethanol was added 400 mg. of 5% palladium on charcoal. The resulting, rapidly stirred mixture was saturated with hydrogen at room temperature (approximately 28°) and atmospheric pressure. After 4 hr. the uptake of hydrogen, having reached approximately 75% of the theoretical, ceased and the reaction was stopped. The mixture was filtered and the filtrate was concentrated to yield a crude red-orange powder. This powder was recrystallized four times from ethanol to give 0.5 g. (51%) of the reduced ketone, presumably, VI, as red-orange needles, m.p. 130–130.5°.

Anal. Calcd. for $C_{28}H_{26}O_2Fe$: C, 74.5; H, 6.04; Fe, 12.4. Found: C, 73.90; H, 5.95; Fe, 12.02.

Hydrogenation of benzalacetoferrocene (II) *to form saturated ketone* VII. The benzal derivative II was prepared by a modification of the earlier procedure.[3]

To a stirred solution of 2.18 g. (0.055 mole) of sodium hydroxide in 20 ml. of water and 10 ml. of 95% ethanol at 30° was added a mixture of 9.8 g. (0.043 mole) monoacetylferrocene and 4.9 g. (0.048 mole) of freshly distilled benzaldehyde in 25 ml. of 95% ethanol. This mixture was stirred for about 10 min. The resulting thick mixture was allowed to stand for 1.5 hr., filtered, and the solid washed with water until the washings were neutral to litmus. The solid was recrystallized from 95% ethanol to give 13.0 g. (96%) of benzalacetoferrocene (II) as red crystals, m.p. 137–139°. Mixed melting points and infrared spectra showed this sample to be identical with an authentic one.

To the deep red solution of 1 g. of unsaturated ketone II in 150 ml. of absolute ethanol was added 500 mg. of 5% palladium on charcoal. The resulting, rapidly stirred mixture was saturated with hydrogen at 30° and atmospheric pressure. After 3 hr. the uptake of hydrogen, having reached approximately 100% of theory, ceased. The mixture was filtered, and the filtrate was concentrated to precipitate 0.88 g. (89%) of the saturated ketone VII as dark red needles, m.p. 85–85.5°. Recrystallization from *n*-hexane failed to raise the melting point.

Anal. Calcd. for $C_{19}H_{18}OFe$: C, 71.6; H, 5.7; Fe, 17.5. Found: C, 71.53; H, 5.35; Fe, 16.7.

Independent synthesis of saturated ketone VII. To a rapidly stirred, cooled solution of 10 g. (0.054 mole) of ferrocene and 9.04 g. (0.054 mole) of hydrocinnamoyl chloride in 200 ml. of anhydrous ethylene chloride was added 15.7 g. (0.108 mole) of anhydrous aluminum chloride at such a rate that the temperature did not rise above 8°. The resulting deep purple solution was stirred at 0° for one-half hour and then refluxed for 4 hr. Ice and excess hydrochloric acid were added, and the two layers were separated. The aqueous layer was extracted twice with small portions of methylene

(14) We are indebted to Dr. Frank G. Young of Union Carbide Chemicals Co., South Charleston, W. Va., for the infrared spectrum of this compound.

(15) Analyses are by Galbraith Laboratories, Knoxville, Tenn. Melting points are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Model 21 Spectrophotometer.

(16) Determined using Cottrill boiling point apparatus.

chloride, and the extracts were added to the ethylene chloride layer. The combined chlorocarbon layers were washed with water until neutral, and dried over Drierite. The solvents were removed to leave a red, mobile oil which very slowly crystallized. This crystalline solid was collected and recrystallized twice from hexane to give 7.0 g. (41%) of ketone VII, m.p. 85.5–86°, as small orange-red needles. Further recrystallizations did not raise the melting point. Mixed melting points and infrared spectra showed that this compound was identical with that obtained from the hydrogenation of the benzal derivative II.

Monophenylhydrazone of yellow product. To a solution of 1 g. of the yellow product in 250 ml. of boiling absolute ethanol was added 4 g. of phenylhydrazine. This solution was heated on the steam bath for 30 min., and then 3.5 ml. of concd. hydrochloric acid was added. The solution was cooled in the refrigerator overnight to precipitate a brown powder. Recrystallization from absolute ethanol gave 0.3 g. (25%) of tan needles, m.p. 200–201°, the analysis of which was satisfactory for a monophenylhydrazone of a monobenzaldehyde derivative of bisacetylferrocene.

Anal. Calcd. for $C_{27}H_{24}N_2OFe$: C, 72.10; H, 5.35; N, 6.24; Fe, 12.4. Found: C, 72.22; H, 4.96; N, 6.12; Fe, 12.02.

Mono-2,4-dinitrophenylhydrazone of yellow product. To a solution of 1 g. of the yellow product in 100 ml. of absolute ethanol was added 2 g. of 2,4-dinitrophenylhydrazine in 25 ml. of absolute ethanol. This solution was heated on the steam bath for 10 min., and then 3 ml. of concd. hydrochloric acid was added. The solution was cooled in the refrigerator to precipitate 1 g. (66%) of purple needles, m.p. >300°, the analysis of which was satisfactory for a mono-2,4-dinitrophenylhydrazone of a monobenzaldehyde derivative of bisacetylferrocene.

Anal. Calcd. for $C_{27}H_{22}N_4O_5Fe$: C, 60.24; H, 4.12; N, 10.41; Fe, 10.37. Found: C, 59.98; H, 3.84; N, 10.08; Fe, 10.27.

DURHAM, N. C.

[CONTRIBUTION FROM THE RESEARCH DIVISION, WYANDOTTE CHEMICALS CORP.]

Ferrocenes. I. Synthesis of Siloxanylferrocenes[1,2]

ROBERT L. SCHAAF, PETER T. KAN, CARL T. LENK, AND EVA P. DECK

Received April 11, 1960

The reaction of cyclopentadienyllithium with dimethyldichlorosilane, 1,3-dichlorotetramethyldisiloxane, and 1,5-dichlorohexamethyltrisiloxane gave monochloro derivatives which furnished unsymmetrical cyclopentadienylsiloxanes upon treatment either with a sodium silanolate or with water and a chlorosilane. From the cyclopentadienylsiloxanes, a series of siloxanylferrocenes was prepared by treatment with butyllithium and ferrous chloride. Similarly, 1,1′-bis(3-phenyltetramethyldisiloxanyl)-*x*,*x*′-dimethylferrocene and 1,1′-bis(chloromethyldimethylsilyl)ferrocene were synthesized. From the latter, 1,1′-bis(aminomethyldimethylsilyl)ferrocene dihydrochloride was prepared.

Silicon-substituted ferrocenes previously described have been mono- or bis(triarylsilyl)ferrocenes or trialkylsilylferrocenes and were prepared either by addition of a trisubstituted chlorosilane to metalated ferrocene[3–5] or by treatment of a trisubstituted-silyl cyclopentadiene successively with butyllithium and ferrous chloride.[5] By application of the latter method to cyclopentadienylsiloxanes we have prepared a series of siloxanylferrocenes. A major part of this paper describes the synthesis of the precursor cyclopentadienylsiloxanes, which, like the siloxanylferrocenes, are a class of compound not previously described in literature.

A compound desired for the synthesis of cyclopentadienylsiloxanes was cyclopentadienyldimethylchlorosilane (Ia). The reaction of cyclopentadienylmagnesium bromide with dimethyldichlorosilane in benzene has been described, but despite a 75% excess of dimethyldichlorosilane, the main product, obtained in about 40% yield, was bis(cyclopentadienyl)dimethylsilane[6] and not Ia. A by-product, obtained in 11% yield and which was not specifically named or characterized, was called cyclopentadienyldimethylchlorosilane in a related patent,[7] but the reported boiling point, 80–83°/0.7 mm., is too high for the monomer. Cyclopentadienyltrichlorosilane, b.p. 50–55°/10 mm., has been described, prepared in 56% yield from cyclopentadienylsodium and a five- to seven-fold excess of silicon tetrachloride in xylene.[8]

When cyclopentadienyllithium was treated with two moles of dimethyldichlorosilane in ether, cyclopentadienyldimethylchlorosilane[9] (Ia) was obtained in 69% yield. Regarding the mode of addition, it would be logical to add the cyclopentadienyllithium to the dimethyldichlorosilane, but the order of addition was not important to good yield or

(1) Presented at the 135th National Meeting of the American Chemical Society, Boston, Mass., April 1959.

(2) This investigation was conducted under contract with Materials Laboratory, Wright Air Development Division, Dayton, Ohio.

(3) R. A. Benkeser, D. Goggin, and G. Schroll, *J. Am. Chem. Soc.*, **76**, 4025 (1954); R. A. Benkeser, U. S. Patent 2,831,880 (Apr. 22, 1958).

(4) M. Rausch, M. Vogel, and H. Rosenberg, *J. Org. Chem.*, 22, 900 (1957).

(5) S. I. Goldberg, D. W. Mayo, M. Vogel, H. Rosenberg, and M. Rausch, *J. Org. Chem.*, 24, 824 (1959).

(6) K. C. Frisch, *J. Am. Chem. Soc.*, 75, 6050 (1953).

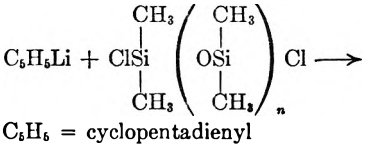
(7) R. W. Martin, U. S. Patent 2,667,501 (Jan. 26, 1954).

(8) Enjay Company, Inc., *High Purity Dicyclopentadiene, Technical Bulletin No. 12*, 18.

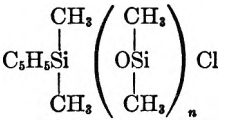
(9) Throughout this paper compounds containing a monosubstituted cyclpentadiene ring are referred to without designation of the relative position of the substituent and double bonds in the ring. The position of attachment is not important to the investigation, inasmuch as the final products prepared from the cyclopentadiene compounds are ferrocenes, in which the ring positions are equivalent.

purity. When methyltrichlorosilane was used, cyclopentadienylmethyldichlorosilane (II) was obtained in 55% yield. The preparation of II from cyclopentadienylmagnesium bromide was claimed in a patent,[7] but physical data were not given, and the reported boiling point (137–140°/0.7 mm.) of the diacetoxy derivative by which the compound was identified seems to be too high for the monomer. Methylcyclopentadienyllithium with dimethyldichlorosilane furnished methylcyclopentadienyldimethylchlorosilane (III) in 71% yield.

When 1,3-dichlorotetramethyldisiloxane and 1,5-dichlorohexamethyltrisiloxane were employed in place of dimethyldichlorosilane, cyclopentadienyllithium reacted to give the desired cyclopentadienylchlorosiloxanes, Ib and Ic, respectively.

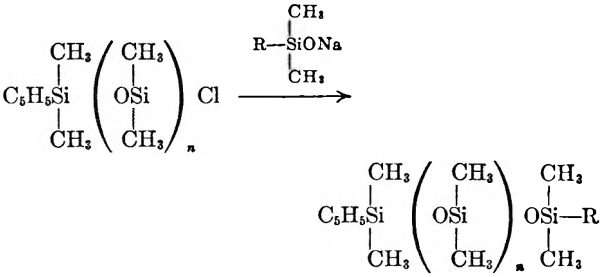


C_5H_5 = cyclopentadienyl



Ia. $n = 0$
Ib. $n = 1$
Ic. $n = 2$

Of the general methods available for the preparation of unsymmetrical siloxanes from halosilanes,[10] the reaction with metal silanolates[11] is the most straightforward. Treatment of compounds Ia-Ic and III with sodium phenyldimethylsilanolate in ether gave 61–80% yields of the desired siloxanes, IVa-IVc, and 1-(methylcyclopentadienyl)-3-phenyltetramethyldisiloxane (V), respectively. Similarly, cyclopentadienylpentamethyldisiloxane (IVd) was formed from Ia and sodium trimethylsilanolate.



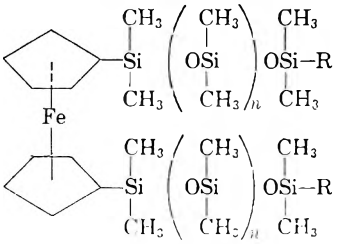
C_5H_5 = cyclopentadienyl

IVa. R = C_6H_5, $n = 0$
IVb. R = C_6H_5, $n = 1$
IVc. R = C_6H_5, $n = 2$
IVd. R = CH_3, $n = 0$

Another method for the preparation of cyclopentadienylsiloxanes was based upon the *in situ* formation of cyclopentadienyldimethylsilanol from Ia. After Ia in cold dioxane-ether had been treated with two moles of pyridine and one mole of water in order to form the silanol, the subsequent addition of one mole of trimethylchlorosilane furnished pure cyclopentadienylpentamethyldisiloxane (IVd) in 53% yield. By this method (Method B) three cyclopentadienyldisiloxanes, IVa, IVd, and 1-cyclopentadienyl - 3 - (dichlorophenyl)tetramethyldisiloxane (IVe), were prepared in 46–66% yields.

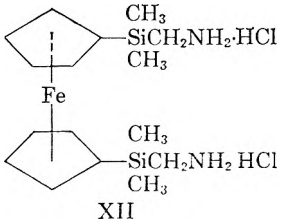
Triphenylsilanol reacted slowly with Ia in ether in the presence of pyridine to give 1-cyclopentadienyl-1,1-dimethyl-3,3,3-triphenyldisiloxane (VI) in 57% yield.

From the above cyclopentadienylsiloxanes (IVa-IVe, V, and VI), the corresponding siloxanylferrocenes VIIa-VIIe, 1,1′-bis(3-phenyltetramethyldisiloxanyl)-x,x′-dimethylferrocene (VIII), and 1,1′-bis(3,3,3 - triphenyl - 1,1 - dimethyldisiloxanyl)ferrocene (IX) were prepared by conversion to the lithio derivative with butyllithium in ether followed by treatment of the lithio derivative in tetrahydrofuran with ferrous chloride. With these reagents Goldberg, *et al.*, prepared 1,1′-bis(trimethylsilyl)ferrocene in 50% yield from trimethylsilylcyclopentadiene.[5] Yields of siloxanylferrocenes were 36–59%.



VIIa. R = C_6H_5, $n = 0$
VIIb. R = C_6H_5, $n = 1$
VIIc. R = C_6H_5, $n = 2$
VIId. R = CH_3, $n = 0$
VIIe. R = $C_6H_3Cl_2$, $n = 0$
$C_6H_3Cl_2$ = *x,x*-dichlorophenyl

The conversion to ferrocenes was also successful when the substituent on the cyclopentadienyl ring contained a chloromethyl group. With butyllithium and ferrous chloride, crude cyclopentadienylchloromethyldimethylsilane, obtained in 72% yield from chloromethyldimethylchlorosilane, was converted to 1,1′-bis(chloromethyldimethylsilyl)ferrocene (X) in 39% yield. Compound X in very crude form (86% yield) could be converted to the corresponding diamine dihydrochloride (XII) in 45% yield *via* the bis(phthalimide) (XI).[12]



XII

(10) General methods have been described or referred to by W. H. Daudt and J. F. Hyde, *J. Am. Chem. Soc.*, **74**, 386 (1952).

(11) J. F. Hyde, O. K. Johannson, W. H. Daudt, R. F. Fleming, H. B. Laudenslager, and M. P. Roche, *J. Am. Chem. Soc.*, **75**, 5615 (1953).

(12) S. Gabriel, *Ber.*, **20**, 2224 (1887); H. R. Ing and R. H. F. Manski, *J. Chem. Soc.*, 2348 (1926).

TABLE I

CYCLOPENTADIENYLCHLOROSILANES AND CYCLOPENTADIENYLCHLOROSILOXANES

Compound	Formula	Yield, %	B.P./mm.[a]	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found	Silicon, % Calcd.	Silicon, % Found
Ia	$C_7H_{11}ClSi$	69	37–40/7–4.5	52.97	53.08	6.99	6.87	22.34	22.36	17.70	17.81
Ib	$C_9H_{17}ClOSi_2$	57	62–82/3–4	46.42	46.19	7.36	7.68	15.23	15.4	24.12	24.41
Ic	$C_{11}H_{23}ClO_2Si_3$	40[b]	62–100/1.5–2	43.03	43.44	7.55	7.28	11.55	11.53	27.45	26.71
II	$C_6H_8Cl_2Si$	55	36–50/3.5	40.23	39.81	4.50	4.81	39.59	39.09	15.68	15.66
III	$C_8H_{13}ClSi$	71	75–90/20	55.63	55.35	7.59	7.93	20.53	20.42	16.25	16.11

[a] The wide boiling ranges but satisfactory analyses suggest some dimer may be present. [b] In subsequent runs, the yield varied from 9–26%.

TABLE II

CYCLOPENTADIENYLSILOXANES

Compound	Formula	Method[a]	Yield, %	B.P./mm.	n_D^{25}	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Silicon, % Calcd.	Silicon, % Found
IVa	$C_{15}H_{22}OSi_2$	A	80	83–86/0.03–0.05	1.5004	65.63	65.81	8.08	8.07	20.46	20.33
		B	66	81–89/0.2	1.4987						
IVb	$C_{17}H_{28}O_2Si_3$	A	76	107–112/0.04–0.07	1.4797	58.56	58.39	8.09	8.09	24.17	24.53
IVc	$C_{19}H_{34}O_3Si_4$	A	61	116–144/0.09	1.4653	53.97	53.53	8.11	8.09	26.57	26.64
IVd	$C_{10}H_{20}OSi_2$	A	66	82–83/21	1.4391	56.53	56.83	9.49	9.76	26.45	26.05
		B	53	78–81/20	1.4390	56.53	56.37	9.49	9.39		
IVe	$C_{15}H_{20}Cl_2OSi_2$	B	46	102/0.03	1.5245	52.46	52.42	5.87	5.64	16.36	16.43
										20.65[b]	20.63[b]
V	$C_{16}H_{24}OSi_2$	A	79	82–85/0.16	1.4968	66.60	66.24	8.38	8.96	19.47	19.27
VI	$C_{25}H_{26}OSi_2$	[a]	57	156–159/0.05	1.5788	75.32	74.94	6.57	6.79	14.09	13.96

[a] See Experimental. [b] Chlorine, %.

EXPERIMENTAL[13]

Cyclopentadienylchlorosilanes and cyclopentadienylchlorosiloxanes (Table I). The following procedure for the preparation of 1-cyclopentadienyl-3-chlorotetramethyldisiloxane (Ib) is representative of the procedures employed for the preparation of the compounds listed in Table I. A solution of *n*-butyllithium prepared[14] from 0.9 mole of *n*-butyl bromide was added dropwise during a 1-hr. period to a stirred solution of 59.5 g. (0.9 mole) of cyclopentadiene in 500 ml. of anhydrous ether under nitrogen in an ice bath. After the mixture was stirred an additional 1.5 hr. without the bath, a mixture of 365 g. (1.8 moles) of 1,3-dichlorotetramethyldisiloxane[15] in 350 ml. of ether was added in one portion and the mixture refluxed overnight. The volume of the mixture was reduced by vacuum distillation, the mixture filtered through a fritted glass filter, and the solid washed with ether. After removal of volatile material from the filtrate under vacuum, distillation of the residue through a 20-cm. Vigreux column gave a fraction, 203 g., b.p. 46°/14 mm.–75°/6 mm., and a second fraction, 95.1 g., b.p. 71–100°/4 mm. By redistillation of the first fraction, 197 g. (54%) of 1,3-dichlorotetramethyldisiloxane, b.p. 42–46°/22 mm., was recovered. The second fraction, redistilled for analysis, furnished 76.4 g. (36%) of Ib, b.p. 62–82°/3–4 mm. In a repeat run, the yield of material b.p. 53°/1.5 mm. to 60°/0.7 mm. was 57%.

When tetrahydrofuran was substituted for ether in the above procedure and the mode of addition was cyclopentadienyllithium to dichlorosiloxane, compound Ib, b.p. 51–71°/1.5 mm., was obtained in 15% yield. The temperature of the refluxing reaction mixture was 55°.

Cyclopentadienyldimethylchlorosilane (Ia) was prepared as described for Ib and by variations of the method as shown in Table IV.

For conversion of cyclopentadienyllithium to Ic, the reaction time was doubled (40 hr.) and the product, obtained in 40% yield, was not redistilled before analysis. A repeat run gave a 25% yield of Ic, b.p. 72–86°/1.2 mm. When the reaction time was 20 hr., yields of 19, 26, and 9% were obtained.

For the isolation of II, the following procedure was used. After the mixture had refluxed overnight, the precipitate was allowed to settle, the clear layer was forced with nitrogen into distillation equipment, and the solid was washed with petroleum ether and finally filtered. Removal of solvent from the decanted solution and washes and distillation of the residue through a 30-cm. Vigreux column furnished II (55%), b.p. 35–42°/3.5 mm. In an initial run, the product (41%), b.p. 36–50°/3.5 mm., was subjected to elemental analysis (Table I).

Cyclopentadienylsiloxanes from sodium silanolates (Table II, Method A). Cyclopentadienylpentamethyldisiloxane (IVd) and the cyclopentadienylphenylsiloxanes IVa–IVc and V were prepared by similar procedures from the required chlorosilanes and sodium silanolates (sodium trimethylsilanolate[11] and sodium phenyldimethylsilanolate[11]). The following procedure for the preparation of 1-cyclopentadienyl-3-phenyltetramethyldisiloxane (IVa) is typical. Cyclopentadienyldimethylchlorosilane (Ia) (39.7 g.; 0.25 mole) in 100 ml. of anhydrous ether was stirred under nitro-

(13) All melting points and boiling points were uncorrected. Analyses of ferrocenes were by the Schwartzkopf Microanalytical Laboratory, Woodside 77, New York. Other analyses were by Spang Microanalytical Laboratory, Ann Arbor, Mich. Distillations were in general performed under nitrogen, and products were stored under nitrogen in amber bottles. Heating of mixtures containing cyclopentadiene compounds was kept to a practical minimum during isolations, in an effort to avoid dimerization.

(14) R. G. Jones and H. Gilman, *Organic Reactions*, 6, 339 (1951).

(15) British Thomson-Houston Co., Ltd., Brit. Patent 631,018 (Oct. 25, 1949).

TABLE III

SILOXANYLFERROCENES

Compound	Formula	Yield, %	B.P./Mm.	n_D^{25}	d_4^{25}	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Iron, % Calcd.	Iron, % Found	Silicon, % Calcd.	Silicon, % Found
VIIa	$C_{30}H_{42}FeO_2Si_4$	59	200–205/0.03[a]	1.5473	1.1063	59.76	59.94	7.02	6.93	9.26	9.36[c]		
VIIb	$C_{34}H_{54}FeO_4Si_6$	50	220–223/0.15	1.5162	1.0796	54.36	54.35	7.25	7.34	7.43	7.59	22.44	22.02
VIIc	$C_{38}H_{66}FeO_6Si_8$	36	245–255/0.04	1.4850		50.74	50.72	7.40	7.51	6.21	5.95	24.98	25.11
VIId	$C_{20}H_{38}FeO_2Si_4$	55	107–110/0.01	1.4940	1.0308	50.18	50.19	8.00	8.18	11.66	11.60	23.47	23.44
VIIe	$C_{20}H_{38}Cl_4FeO_2Si_4$	47	263–265/0.12	1.5675	1.2591	48.65	48.87	5.17	5.20	7.54	7.48	15.17	15.05
												19.15[d]	19.15[d]
VIII	$C_{32}H_{46}FeO_2Si_4$	52	205–215/0.07	1.5428	1.0863	60.92	61.40	7.35	7.42	8.85	8.6	17.81	17.8
IX	$C_{65}H_{50}FeO_2Si_4$	37	[b]			70.56	70.43	5.92	5.70	6.56	6.50		

[a] M.p. 18–19.5°. [b] M.p. 148.5–150°. [c] On material m.p. 19.5–20°. [d] Chlorine, %.

TABLE IV

PREPARATION OF CYCLOPENTADIENYLDIMETHYLCHLOROSILANE (Ia)

Reactant Ratio[a]	Mode of Addition	Yield, %	B.P./Mm.	Hydrolyzable Chlorine, %[b]
1:5	Indirect[c]	58	62–69/22	
1:5	Direct	57	63–75/24	21.5
1:2	Indirect	53	62–74/24[d]	22.0
1:2	Direct	60	63–75/24[d]	20.4
1:2	Direct	67	31–38/5	22.3
1:2	Direct	69	37–40/7–4.5	22.4

[a] Ratio of cyclopentadiene to dimethyldichlorosilane. [b] Calcd. for $C_7H_{11}ClSi$: 22.34%. [c] Cyclopentadienyllithium to dimethyldichlorosilane. [d] Continued distillation up to 20° above this range gave a fraction which upon redistillation furnished additional product (7–18%) boiling within this range; the stated yield includes this material, which contained 20–21.6% hydrolyzable chlorine.

gen in an ice bath while a solution of 43.5 g. (0.25 mole) of sodium phenyldimethylsilanolate in 100 ml. of anhydrous ether was added during a 5-min. period. The mixture was allowed to come to room temperature while it was stirred overnight. Precipitated solid was removed by centrifugation and washed with ether, and the combined filtrate and washes were evaporated *in vacuo*. Distillation of the residue gave 55.0 g. (80%) of compound IVa.

The tetrasiloxane IVc, b.p. 124–144°/0.06 mm., was obtained in 61% yield after two distillations, and was distilled again before it was analyzed.

Compound IVd, prepared in 66% yield, b.p. 76–81°/21 mm., was redistilled through a 25-cm. column for analysis.

Cyclopentadienylsiloxanes from chlorosilanes (Table II, Method B). The procedure given below for the preparation of cyclopentadienylpentamethyldisiloxane (IVd) is representative for those compounds in Table II prepared by Method B. Trimethylchlorosilane, phenyldimethylchlorosilane,[16] and *x,x*-dichlorophenyldimethylchlorosilane[16] were freshly distilled. A solution of 15.9 g. (0.1 mole) of cyclopentadienyldimethylchlorosilane (Ia) in a mixture of 50 ml. of anhydrous ether and 50 ml. of anhydrous dioxane was stirred under nitrogen in an ice bath while 15.8 g. (0.2 mole) of pyridine was added during a 5-min. period. After 10 min., 1.8 ml. (0.1 mole) of water in a mixture of 25 ml. of ether and 25 ml. of dioxane was added in one portion and followed 45 min. later by 10.7 g. (0.1 mole) of trimethylchlorosilane in 25 ml. of ether, added in a slow stream. The mixture was stirred overnight and the precipitated solid was removed by filtration and washed with ether. The filtrate was evaporated *in vacuo* and the residue distilled; there was less than 1 ml. of liquid remaining after the main fraction (15.8 g.), b.p. 60–84°/20 mm., n_D^{25} 1.4386, was collected. Redistillation of the main fraction gave 11.2 g. (53%) of IVd.

For the preparation of the 3-phenyl compound (IVa) hydrolyzable chlorine analyses of Ia and phenyldimethylchlorosilane were made, and the amounts of each chlorosilane employed were such that the quantities of hydrolyzable chlorine in each amount were equal. This was also true in the case of the 3-(*x,x*-dichlorophenyl) compound (IVe); in this instance a center cut from the second distillation of the product, b.p. 100–103°/0.03 mm., was taken for elemental analysis.

1-Cyclopentadienyl-1,1-dimethyl-3,3,3-triphenyldisiloxane (VI). Cyclopentadienyldimethylchlorosilane (Ia) (52.9 g., 0.333 mole) in 400 ml. of ether was cooled in an ice bath under nitrogen, and treated with 26.4 g. (0.333 mole) of pyridine. Triphenylsilanol (97.5 g., 0.353 mole) was then

(16) Technical grade; Dow Corning Corporation, Midland, Mich.

washed into the mixture with 100 ml. of ether, and the reaction mixture was refluxed overnight. Solids were removed by filtration and were washed with petroleum ether (b.p. 30–60°) and with ether. The filtrate and washes were combined and evaporated *in vacuo*, the residue was extracted with 200 ml. of petroleum ether, and the insoluble, unchanged triphenylsilanol (29 g.) was removed by filtration and washed with 100 ml. of petroleum ether. By distillation of the combined extract and washes, 83.4 g. of liquid, b.p. 160°/0.13 mm. to 165°/0.07 mm., was obtained. Redistillation furnished VI, Table II.

Siloxanylferrocenes (Table III). The method for the preparation of the ferrocenes listed in Table III is illustrated by the synthesis of 1,1′-bis[3-(*x*,*x*-dichlorophenyl)tetramethyldisiloxanyl]ferrocene (VIIe). *n*-Butyllithium solution, prepared[14] from 0.175 mole of *n*-butyl bromide, was added during a 1.5-hr. period to a solution of 60 g (0.175 mole) of 1-cyclopentadienyl-3-(*x*,*x*-dichlorophenyl)tetramethyldisiloxane (IVe) in 175 ml. of anhydrous ether with stirring under a blanket of nitrogen. The mixture was stirred and refluxed overnight and then cooled. Ferrous chloride solution, which had been freshly prepared[17] from 9.5 g. (0.0585 mole) of ferric chloride and 1.65 g. of 325-mesh reduced iron, was washed into the stirred mixture with 175 ml. of anhydrous tetrahydrofuran. Solvent was removed by distillation until the boiling point of the distillate was 55°, and the mixture was stirred and refluxed overnight under nitrogen. The reaction mixture was then evaporated *in vacuo* and the residue extracted with petroleum ether. Removal of solvent from the extract and fractionation of the residue gave 30.9 g. (47%) of VIIe, b.p. 263–265°/0.12 mm.

Compound VIIa prepared in this manner melted at 18–19.5°; a sample, m.p. 19.5–20°, n_D^{25} 1.5474, was obtained by distillation through a 60-cm. column packed with glass helices.

In the preparation of VIIb, VIId, and IX the ferrous chloride solution was added 2 to 3 hr. after completion of the addition of *n*-butyllithium solution. For analysis of VIId, the first of two distillation fractions was taken: fraction 1 (41%), b.p. 107–109°/0.01 mm., and fraction 2 (14%), b.p. 106–110°/0.03–0.07 mm.

The reaction of *n*-butyllithium with VI was conducted in an ice bath. For subsequent isolation of IX, the final reaction mixture was evaporated to dryness under vacuum, the residue was extracted with boiling heptane, and the extracts were taken to dryness. By crystallization of the residue from hexane, the desired IX (37%), m.p. 146–149°, was obtained. It was recrystallized from acetone for analysis (Table III).

1,1′-Bis(chloromethyldimethylsilyl)ferrocene (X). Cyclopentadienyllithium in ether (1200 ml.) was prepared in the usual manner from 66.1 g. (1 mole) of cyclopentadiene and *n*-butyllithium, prepared[14] from 1 mole of *n*-butyl bromide. To the solution of cyclopentadienyllithium was added in one portion 143 g. (1 mole) of chloromethyldimethylchlorosilane[18] in 200 ml. of ether under nitrogen. The mixture was refluxed overnight, filtered, and the fitrate stripped of solvent *in vacuo*. The residual liquid was distilled through a 15-cm. Vigreux column to give 125 g. (72%) of crude cyclopentadienylchloromethyldimethylsilane, b.p. 48–52°/1.5 mm.

A solution of *n*-butyllithium prepared from 0.78 mole of *n*-butyl bromide was added dropwise during a 30-min. period to a stirred solution of 121 g. (0.70 mole) of this crude material in 350 ml. of tetrahydrofuran, kept at −20 to −30° under nitrogen. The mixture was stirred for an additional 45 min. at −30°. A slurry of ferrous chloride and tetrahydrofuran, freshly prepared[17] from 39.3 g. (0.243 mole) of ferric chloride and 7.2 g. of iron powder in 150 ml. of tetrahydrofuran, was cooled to −30° and added in one portion to the above mixture. The mixture was stirred overnight as it was allowed to warm to room temperature, and volatile materials were then removed *in vacuo*. The residue was mixed with petroleum ether until solids formed, the insoluble solids were filtered and washed thoroughly with petroleum ether, and the filtrate was evaporated *in vacuo*. The residue was then dissolved in 100 ml. of petroleum ether, refrigerated overnight, and filtered. Volatile material was removed from the filtrate under vacuum, and unchanged cyclopentadienylchloromethyldimethylsilane was removed by evaporation at 75°/0.5 mm. The residue, 106 g., which solidified upon refrigeration, was used for preparation of the bis(phthalimide) (XI), below. For purification, a portion of the solidified residue was extracted with petroleum ether, the extract evaporated to dryness and the residue crystallized from 2-propanol. Including material isolated by concentration of the mother liquor, the total yield of the ferrocene, m.p. 38–41°, was 39%. An analytical sample, m.p. 41–42°, was prepared by two recrystallizations from 2-propanol.

Anal. Calcd. for $C_{16}H_{24}Cl_2FeSi_2$: C, 48.13; H, 6.06; Cl, 17.76; Fe, 13.99. Found: C, 48.08; H, 5.92; Cl, 17.15; Fe, 14.05.

In an initial experiment an attempt was made to purify the compound by distillation, but decomposition was evident, and the orange-brown fraction, b.p. 125–135°/0.1 mm., contained 13.4% chlorine.

1,1′-Bis(phthalimidomethyldimethylsilyl)ferrocene (XI). A mixture of 231 g. (0.58 mole) of crude X and 236 g. (1.27 mole) of potassium phthalimide in 800 ml. of dimethylformamide was stirred at 90–110° for 4 hr., cooled, and filtered. Solvent was evaporated from the filtrate, and the residue was extracted with benzene. Removal of solvent from the extract and recrystallization of the resulting residue from 2-propanol furnished 198 g. (55%) of crude XI, m.p. 145–149°. After two recrystallizations, the product was analyzed. *Anal.* Found: N, 4.6%. In an initial experiment on a smaller scale, the yield of material m.p. 143–145° was 35%, and recrystallized XI melted 149–150°.

Anal. Calcd. for $C_{32}H_{32}FeN_2O_4Si_2$: C, 61.93; H, 5.20; N, 4.52. Found: C, 61.55; H, 5.37; N, 4.74.

1,1′-Bis(aminomethyldimethylsilyl)ferrocene dihydrochloride (XII). To a refluxing slurry of 192 g. (0.311 mole) of XI and 700 ml. of methanol was added 74 g. (1.26 moles) of 85% hydrazine hydrate. Refluxing was continued overnight. Concentrated hydrochloric acid (105 ml.; 1.06 moles) was then added dropwise during a 30-min. period, and refluxing was continued an additional 2 hr. The mixture was cooled, filtered, and the filtrate stripped of solvent. Extraction with benzene caused the residue to crystallize. The crystals were dissolved in water, the solution filtered, and the filtrate extracted with chloroform. The aqueous solution was evaporated to dryness. The residue was dissolved in hot methanol, the solution cooled and filtered to remove hydrazine hydrochloride, and the methanol evaporated from the filtrate; this procedure was repeated three times. Finally, the product was recrystallized from 2:1 2-propanol-methanol to give 108.3 g. (81%) of XII. It decomposed above 185°, without melting.

Anal. Calcd. for $C_{16}H_{30}Cl_2FeN_2Si_2$: C, 44.35; H, 6.98; Cl, 16.36; N, 6.47. Found: C, 44.45; H, 6.77; Cl, 16.71; N, 6.91.

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[CONTRIBUTION FROM THE CHEMICAL RESEARCH LABORATORIES, THE LUBRIZOL CORP.]

Novel Method for the Preparation of O,O-Dialkyl Phosphorochloridothionates[1]

N. A. MEINHARDT, SAMUEL Z. CARDON,[2] AND P. W. VOGEL

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O,O-Dialkyl phosphorochloridothionates may be prepared by the reaction of *O,O*-dialkyl hydrogen phosphorodithioates with hydrogen chloride in the presence of hydrogen sulfide acceptors. Acetonitrile, benzonitrile, ethyl, phenyl and benzyl thiocyanates, and ethyl isothiocyanate function as the hydrogen sulfide acceptors in the reaction.

The preparation of *O,O*-dialkyl phosphorochloridothionates has received considerable study as evidenced by the literature reports and patents issued on the subject.[3-18] Three general methods have been used in the preparation of the *O,O*-dialkyl phosphorochloridithionates as shown in equations (1),[1-10,14] (2),[17] and (5).[3,5-7,11-13,15,16,18]

$$2ROH + PSCl_3 \longrightarrow (RO)_2PSCl + 2HCl \quad (1)$$

$$2ROH + PCl_3 + S \longrightarrow (RO)_2PSCl + 2HCl \quad (2)$$

$$2(RO)_2PSSH + 3Cl_2 \longrightarrow 2(RO)_2PSCl + S_2Cl_2 + 2HCl \quad (3)$$

A fourth method based upon the double decomposition of *O,O*-dialkyl hydrogen phosphorodithioates with hydrogen chloride appeared to be feasible for the preparation of the *O,O*-dialkyl phosphorochloridothionates, since this reaction was known to occur with diphenylphosphinodithioic acid,[19] as in equation (4). However, the elimination of hydrogen

$$(C_6H_5)_2PSSH + HCl \xrightarrow{150-200^\circ} (C_6H_5)_2PSCl + H_2S \quad (4)$$

sulfide in this reaction takes place at temperatures in excess of 150°, which makes it impractical for use with the ester acid.

It has now been found that in the presence of a hydrogen sulfide acceptor,[20] the elimination of hydrogen sulfide in the double decomposition reaction between hydrogen chloride and *O,O*-dialkyl hydrogen phosphorodithioates takes place smoothly in ethyl ether at the reflux temperature. The hydrogen sulfide acceptors used in this study were acetonitrile, benzonitrile, ethyl, phenyl and benzyl thiocyanates, and ethyl isothiocyanate. In addition to the *O,O*-dialkyl phosphorochloridothionates, which were obtained in yields as high as 88%, there were also obtained the products which would be produced by the addition of hydrogen sulfide to the acceptor molecules in accordance with equations (5) and (6). Ethyl isothiocyanate did not function as a hydrogen sulfide acceptor in ethyl ether. In dioxane, at 100°, the reaction between *O,O*-diethyl hydrogen phosphorodithioate, hydrogen chloride, and ethyl isothiocyanate yielded 39% of *O,O*-diethyl phosphorochloridothionate and 83% of ethylamine hydrochloride. The amine salt was probably formed through decomposition of the intermediate dithiocarbamic acid, equations (7) and (8).

$$(RO)_2PSSH + R'CN + HCl \longrightarrow (RO)_2PSCl + R'CSNH_2 \quad (5)$$

$$(RO)_2PSSH + R'SCN + HCl \longrightarrow (RO)_2PSCl + R'SCSNH_2 \quad (6)$$

$$(C_2H_5O)_2PSSH + C_2H_5NCS + HCl \longrightarrow (C_2H_5O)_2PSCl + [C_2H_5NHCS_2H] \quad (7)$$

$$[C_2H_5NHCS_2H] + HCl \longrightarrow C_2H_5NH_3^+Cl^- + CS_2 \quad (8)$$

The yields of *O,O*-diethyl phosphorochloridothionate and the coproducts obtained with the hydrogen

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sulfide acceptors used in this reaction are shown in Table I.

TABLE I

YIELDS OF *O,O*-DIETHYL PHOSPHOROCHLORIDOTHIONATE AND COPRODUCTS OBTAINED WITH HYDROGEN SULFIDE ACCEPTORS

Acceptor	Yield of $(C_2H_5O)_2PSCl$, %	Coproduct	Yield, %
CH_3CN	74	CH_3CSNH_2	51
C_6H_5CN	74	$C_6H_5CSNH_2$	77
C_2H_5SCN	73	$C_2H_5SCSNH_2$	91
C_6H_5SCN	88	$C_6H_5SCSNH_2$	94
$C_6H_5CH_2SCN$	85	$C_6H_5CH_2SCSNH_2$	90

Phenyl isothiocyanate, potassium cyanide, and octene-1 did not serve as hydrogen sulfide acceptors in this reaction.

O,O-Di-*n*-propyl, *O,O*-diisopropyl, *O,O*-di-*n*-butyl, and *O,O*-di-*sec*-butyl phosphorochloridothionates were also prepared by this method, using benzyl thiocyanate as the coreactant. The yields and physical constants of these materials are shown in Table II.

Other materials used were commercially available reagents.

Preparation of O,O-dialkyl phosphorochloridothionates. Hydrogen chloride was bubbled through a solution of the *O,O*-dialkyl hydrogen phosphorodithioate (0.5 mole) and the hydrogen sulfide acceptor (0.5 mole) in 200 ml. of ethyl ether at the reflux temperature for 2 hr. The ether was removed by distillation at reduced pressure. The solid residue was extracted with 250-ml. portions of petroleum ether (b.p. 30–60°) four times. The combined extracts were dried over anhydrous sodium carbonate. The sodium carbonate was removed by filtration and the filtrate was distilled under reduced pressure over calcium carbonate chips.

The yields of *O,O*-diethyl phosphorochloridothionate obtained are shown in Table I. Typical analyses for this compound, as obtained, are: b.p. 34–35° at 0.5 mm.; n_D^{25} 1.4688 (reported 1.4685[3]).

Anal. Calcd. for $C_4H_{10}PSCl$: Cl, 18.8; P, 16.4; S, 17.0. Found: Cl, 19.2; P, 16.2; S, 16.9.

The yields of the other *O,O*-dialkyl phosphorochloridothionates prepared are shown in Table II.

The solid residue from the petroleum ether extractions was recrystallized to obtain the coproduct of the reaction. The yields are shown in Table I. The products were identified as follows:

Thioacetamide was recrystallized from isopropyl ether, m.p. 113–116° (reported[22] m.p. 115–116°), a mixed melting point with an authentic sample of thioacetamide showed no depression.

TABLE II

O,O-DIALKYL PHOSPHOROCHLORIDOTHIONATES FROM THE REACTION OF *O,O*-DIALKYL HYDROGEN PHOSPHORODITHIOATES WITH HYDROGEN CHLORIDE AND BENZYL THIOCYANATE

$$(RO)_2PSSH + C_6H_5CH_2SCN + HCl \longrightarrow (RO)_2PSCl + C_6H_5CH_2SCSNH_2$$[a]

R	Yield, %	B.P.	Mm.	n_D^{25}	Phosphorus, % Found	Phosphorus, % Calcd.	Sulfur, % Found	Sulfur, % Calcd.	Chlorine, % Found	Chlorine, % Calcd.
n-C_3H_7	75.5	72	2	1.4701[b]	14.17	14.34	14.46	14.77	16.45	16.39
i-C_3H_7	81.0	61	3	1.4612[c]	14.32	14.34	15.05	14.77	16.30	16.39
n-C_4H_9	81.0	76	0.5	1.4697[d]	12.66	12.68	13.16	13.08	14.42	14.50
sec-C_4H_9	86.0	54	0.1	1.4692	12.65	12.68	13.30	13.08	14.55	14.50

[a] Yields of 85–95% of benzyl dithiocarbamate were obtained. [b] Reported[5] 1.4672. [c] Reported[5] 1.4601. [d] Reported[5] 1.4670.

The reaction sequence suggested for this reaction is shown in equation (9). The intermediate imino-ester hydrochloride postulated here is similar to

$$(RO)_2PSSH + R'CN + HCl \longrightarrow [(RO)_2PSSC(NH)R'\cdot HCl] \quad (9)$$
$$\downarrow$$
$$(RO)_2PSCl + R'CSNH_2$$

the imino-thioether hydrochloride isolated from the reaction of mercaptans with nitriles and hydrogen chloride.[21] The intermediate imino-thioester hydrochloride formed in the present reaction is apparently too unstable to be isolated, and breaks down immediately into the reaction products isolated.

EXPERIMENTAL

O,O-Dialkyl hydrogen phosphorodithioates were prepared by a previously described method.[4] The crude acids were purified by distillation at reduced pressure and then were 98% to 99% pure by titration.

Thiobenzamide was recrystallized from ether-petroleum ether (b.p. 30–60°), m.p. 114–116° (reported[22] m.p. 115–116°), a mixed melting point with an authentic sample showed no melting point depression.

Benzyl dithiocarbamate was recrystallized, successively, from ethyl acetate, isopropyl alcohol, and chloroform, m.p. 87–88°.

Anal. Calcd. for $C_8H_9NS_2$: S, 34.95; N, 7.66. Found: S, 35.19; N, 7.69.

Phenyl dithiocarbamate was recrystallized twice from chloroform, m.p. 109–110.5°.

Anal. Calcd. for $C_7H_7NS_2$: S, 37.88; N, 8.27. Found: S, 37.98; N, 8.30.

Ethyl dithiocarbamate was recrystallized from petroleum ether (b.p. 30–60°) m.p. 41.5–43° (reported[23] m.p. 42°).

Anal. Calcd. for $C_3H_7S_2N$: N, 11.58. Found: N, 11.65.

Ethylamine hydrochloride was recrystallized from isopropyl alcohol, m.p. 107–109°. A mixed melting point with an authentic sample of ethylamine hydrochloride showed no melting point depression.

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CLEVELAND 17, OHIO

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[CONTRIBUTION FROM THE CHEMICAL RESEARCH LABORATORIES, THE LUBRIZOL CORP.]

The Preparation of Mercaptans by the Saponification of *O,O,S*-Trialkyl Phosphorodithioates[1]

W. E. BACON, N. A. MEINHARDT, AND W. M. LESUER

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Saponification of *O,O,S*-trialkyl phosphorodithioates gave alkyl mercaptans and sulfides. Good yields of mercaptans were obtained when the *O*-alkyl group of the phosphorus triester was isopropyl or 2-ethylhexyl.

The facile preparation of *O,O,S*-trialkyl phosphorodithioates in high yields[1,2,3] makes these esters attractive starting materials for the preparation of alkyl mercaptans and sulfides. Earlier work in this laboratory has shown that alkoxide cleavage of the *O,O,S*-trialkyl phosphorodithioates yields alkyl sulfides exclusively.[3] The aqueous saponification of *O,O*-di-*n*-propyl-*S*-2-octyl phosphorodithioate and *O,O*-di-*n*-propyl-*S*-α-phenethyl phosphorodithioate was reported to give 29% yields of 2-octyl mercaptan and α-phenethyl mercaptan respectively.[2]

This investigation was a continuation of the study on the saponification of the *O,O,S*-trialkyl phosphorodithioates as a method for the preparation of mercaptans. This would be of particular utility in connection with the hydrolysis of the *O,O,S*-trialkyl phosphorodithioates prepared by the addition of *O,O*-dialkyl hydrogen phosphorodithioates to olefins. The addition exhibits the peroxide effect so that either *O,O*-dialkyl-*S*-*n*-alkyl phosphorodithioates or *O,O*-dialkyl-*S*-2-alkyl phosphorodithioates are available.[3]

This paper describes the aqueous, alcoholic, and glycolic saponification of *O,O,S*-trialkyl phosphorodithioates.

Aqueous saponification of O,O,S-trialkyl phosphorodithioates. There was a considerable variation in the ease of hydrolysis of the *O,O,S*-trialkyl phosphorodithioates in aqueous media. These results are indicated in Table I, in which the percent of ester recovered after ten-hour reflux in 30% aqueous sodium hydroxide is shown. It appears probable that solubility of the ester in the reaction mixture is not a primary factor in this hydrolysis study, as *O,O,S*-triethyl phosphorodithioate was largely unsaponified in the 30% aqueous system, while *O,O*-di-*n*-hexyl phosphorodithioate esters and *O,O*-di-2-ethylhexyl phosphorodithioate esters were readily saponified in the same system (Table II). It would be expected that the *n*-hexyl and 2-ethylhexyl derivatives would be considerably less soluble than the triethyl ester in the aqueous system.

TABLE I

SAPONIFICATION OF *O,O,S*-TRIALKYL PHOSPHORODITHIOATES IN 30% AQUEOUS SODIUM HYDROXIDE (10-HR. REFLUX) $(RO)_2PSSR'$

R	R′	Unchanged Ester, %	R	R′	Unchanged Ester, %
C_2H_5	C_2H_5	70	*i*-C_3H_7	*i*-C_3H_7	87
C_2H_5	*t*-C_4H_9	70	*i*-C_3H_7	2-C_8H_{17}	84
C_2H_5	2-C_8H_{17}	55	*i*-C_3H_7	$C_6H_5CH_2CH_2$	82
C_2H_5	$C_6H_5CH_2CH_2$	30	*i*-C_3H_7	$C_6H_5(CH_3)CH$	89
C_2H_5	$C_6H_5(CH_3)CH$	20	*n*-C_4H_9	$C_6H_5CH_2CH_2$	10

The products obtained by the aqueous hydrolysis of a series of *O,O,S*-trialkyl phosphorodithioates are shown in Table II. It can be seen that the *O,O*-di-*n*-alkyl phosphorodithioate esters tended to yield mixtures of mercaptan and sulfide. The *O,O*-diethyl phosphorodithioate derivatives hydrolyzed in the aqueous system to give the corresponding ethyl sulfides in up to 60% yield. However, increasing the chain length of the *n*-alkyl group appeared to result in the formation of a higher ratio of mercaptan to sulfide in the hydrolysis product. With these esters, the tendency to form mercaptan was also increased by the presence of branching in the alkyl groups attached to the sulfur.

O,O-Di-2-ethylhexyl-*S*-2-octyl phosphorodithioate and *O,O*-di-2-ethylhexyl-*S*-α-phenethyl phosphorodithioate hydrolyzed to yield 60% 2-octanethiol and 65% α-phenethyl mercaptan, respectively.

Ethanolic and glycolic saponification of O,O,S-trialkyl phosphorodithioates. The *O,O,S*-trialkyl phosphorodithioates which resisted saponification in the aqueous system were readily saponified by the use of 21% potassium hydroxide in 70 weight % ethanol or in a 34% solution of potassium hydroxide in ethylene glycol. The results of the ethanolic saponifications are shown in Table III. In these hydrolyses, the same trend was noted as in the aqueous saponifications. The *O,O*-diisopropyl phosphorodithioates yielded from 57% to 65% of mercaptans, with an attendant yield of 0 to 9% of the corresponding isopropyl sulfides.

(1) Paper V. "Chemistry of the Aliphatic Esters of the Phosphorodithioic Acids." For previous paper in this series see N. A. Meinhardt and P. W. Vogel, *J. Org. Chem.*, **24**, 1604 (1959).

(2) G. R. Norman, W. M. LeSuer, and T. W. Mastin, *J. Am. Chem. Soc.*, **74**, 161 (1952).

(3) W. E. Bacon and W. M. LeSuer, *J. Am. Chem. Soc.*, **76**, 670 (1954).

TABLE II

AQUEOUS SAPONIFICATION OF *O,O,S*-TRIALKYL PHOSPHORODITHIOATES

$$(RO)_2PSSR' + NaOH\ (30\%) \longrightarrow \begin{cases} R'SH + (RO)_2PSONa \\ R'SR + ROP(S)(ONa)_2 \end{cases}$$

R	R'	Yield, %		% Sulfur			
				R'SH[a]		R'SR[b]	
		R'SH	R'SR	Found	Calcd.	Found	Calcd.
C_2H_5	n-C_8H_{17}	0	48	—	—	18.10	18.20
n-C_4H_9	n-C_8H_{17}	37	35	21.70	21.90	15.92	15.80
C_2H_5	2-C_8H_{17}	14	49	21.74	21.90	18.25	18.40
n-C_4H_9	2-C_8H_{17}	46	21	21.73	21.90	15.57	15.85
n-C_6H_{13}	2-C_8H_{17}	30	18	21.65	21.90	13.80	13.90
2-Ethylhexyl	2-C_8H_{17}	60	5	21.73	21.90	12.60	12.40
C_2H_5	$C_6H_5CH_2CH_2$	48	19	[a]		19.10	19.26
n-C_4H_9	$C_6H_5CH_2CH_2$	43	28	22.90	23.20	16.48	16.50
n-C_6H_{13}	$C_6H_5CH_2CH_2$	40	17	23.15	23.20	14.52	14.40
C_2H_5	$C_6H_5(CH_3)CH$	0	60	—	—	19.10	19.20
n-C_4H_9	$C_6H_5(CH_3)CH$	51	20	23.00	23.20	16.35	16.50
n-C_6H_{13}	$C_6H_5(CH_3)CH$	51	8	23.02	23.20	14.34	14.40
2-Ethylhexyl	$C_6H_5(CH_3)CH$	65	0	23.13	23.20	—	—

[a] Mercaptans were also identified by conversion to the corresponding 2,4-dinitrophenyl alkyl sulfides.[4,5] [b] Sulfides were also converted to their sulfones for identification purposes.[3]

TABLE III

ETHANOLIC SAPONIFICATION OF *O,O,S*-TRIALKYL PHOSPHORODITHIOATES

$$(RO)_2PSSR' + KOH(21\%) \longrightarrow \begin{cases} R'SH + (RO)_2POSK \\ R'SR + ROP(S)(OK)_2 \end{cases}$$

R	R'	Yield, %		Sulfur, %			
				R'SH[a]		R'SR[b]	
		R'SH	R'SR	Found	Calcd.	Found	Calcd.
i-C_3H_7	n-C_8H_{17}	57	6	21.70	21.90	17.20	17.00
i-C_3H_7	2-C_8H_{17}	53	9	21.98	21.90	16.86	17.00
i-C_3H_7	$C_6H_5CH_2CH_2$	65	0	23.11	23.20	—	
i-C_3H_7	$C_6H_5(CH_3)CH$	65	6	23.00	23.20	17.85	17.75
C_2H_5	$C_6H_5CH_2CH_2$	57	24	23.00	23.20	19.00	19.20
C_2H_5	$C_6H_5(CH_3)CH$	44	20	[a]		[b]	
C_2H_5	Cyclohexyl	41	31	27.60	27.60	22.10	22.10
n-C_6H_{13}	n-C_8H_{17}	53	3	21.70	21.90	14.00	13.90

[a] Mercaptans were identified also by their 2,4-dinitrobenzene derivatives.[4,5] [b] Sulfides were also converted to their sulfones for identification purposes.[3]

The *O,O*-diethyl phosphorodithioate esters gave mixtures of mercaptan and the corresponding ethyl sulfide, although with a higher ratio of mercaptan to sulfide than was obtained from the same ester in the aqueous system. Thus, ethanolic hydrolysis of *O,O*-diethyl-*S*-α-phenethyl phosphorodithioate gave 44% α-phenethyl mercaptan and 20% ethyl α-phenethyl sulfide. In the aqueous saponification of the same ester only the sulfide was obtained, in 60% yield.

Diethyl sulfide, ethyl isopropyl sulfide, and ethyl *t*-butyl sulfide azeotrope with ethanol, which made their isolation difficult in the ethanolic saponifications. Therefore, *O,O,S*-triethyl phosphorodithioate (I), *O,O*-diethyl-*S*-isopropyl phosphorodithioate (II), and *O,O*-diethyl-*S*-*t*-butyl phosphorodithioate (III) were saponified by use of a 34% solution of potassium hydroxide in ethylene glycol. The results of these hydrolyses are shown in Table IV. The saponification of I yielded only diethyl sulfide, while the saponification of both II and III gave both mercaptan and sulfide.

It may be concluded from these studies that satisfactory yields of mercaptan may be obtained by the saponification of *O,O,S*-trialkyl phosphorodithioates in which the *O*-substituents are sterically hindered.

Peroxide effect in the addition of O,O-dialkyl hydrogen phosphorodithioates to olefins. As was reported previously, the addition of *O,O*-diethyl hydrogen phosphorodithioate to octene-1 and styrene is subject to the peroxide effect,[3] Equations (1) and (2). Utilization of the peroxide effect offers

(4) R. W. Bost, J. O. Turner, and R. D. Norton, *J. Am. Chem. Soc.*, 54, 1985 (1932).

(5) M. S. Kharasch, E. S. May, and F. R. Mayo, *J. Org. Chem.*, 3, 175 (1934).

TABLE IV

ETHYLENE GLYCOL SAPONIFICATION OF *O,O,S*-TRIALKYL PHOSPHORODITHIOATES

$$(RO)_2PSSR' + KOH(34\%) \longrightarrow \begin{cases} R'SH + (RO)_2PSOK \\ R'SR + ROP(S)(OK)_2 \end{cases}$$

R	R'	Yield, % R'SH[a]	Yield, % R'SR	Sulfur, % R'SR[b] Found	Sulfur, % R'SR[b] Calcd.
C_2H_5	C_2H_5	0	42	35.40	35.60
C_2H_5	*i*-C_3H_7	28	29	30.50	30.80
C_2H_5	*t*-C_4H_9	13	24	27.00	27.10

[a] Mercaptans were identified by their 2,4-dinitrobenzene derivatives.[4,5] [b] Sulfides were also converted to their sulfones for identification.[3]

$$(C_2H_5O)_2PSSH + C_6H_5CH{:}CH_2 \xrightarrow[\text{(crude)}]{} (C_2H_5O)_2PSSCH(CH_3)C_6H_5 \quad (1)$$

$$(C_2H_5O)_2PSSH + C_6H_5CH{:}CH_2 \xrightarrow[\text{(pure)}]{\text{peroxide}} (C_2H_5O)_2PSSCH_2CH_2C_6H_5 \quad (2)$$

a convenient route to certain *O,O*-dialkyl-*S*-*n*-alkyl phosphorodithioates. This method was used in the preparation of a series of the *O,O,S*-trialkyl phosphorodithioates used in this saponification study. The esters prepared and their analyses are shown in Table V.

O,O-dialkyl-*S*-2-octyl (or α-phenethyl) phosphorodithioates in this reaction.[2]

The structures of the adducts were established by the saponification of the triesters as reported here.

EXPERIMENTAL

O,O-Dialkyl hydrogen phosphorodithioates were prepared by previously reported methods.[6]

Purification of O,O-dialkyl hydrogen phosphorodithioate. The crude acid was dissolved in an equivalent quantity of 4*M* sodium hydroxide solution. The aqueous solution was extracted three times with naphtha (b.p. 90–120°), then acidified with an equivalent amount of hydrochloric acid. The *O,O*-dialkyl hydrogen phosphorodithioate was extracted with ethyl ether and the ethereal solution was dried over magnesium sulfate. The magnesium sulfate was removed by filtration and the ether was distilled.

O,O-Diethyl hydrogen phosphorodithioate, *O,O*-diisopropyl hydrogen phosphorodithioate and *O,O*-di-*n*-butyl hydrogen phosphorodithioate were then distilled under reduced pressure.

O,O-Diethyl hydrogen phosphorodithioate boiled at 66.1° (0.6 mm.).

Anal. Calcd. for $C_4H_{11}O_2PS_2$: P, 16.69; S, 34.4; neut. equiv., 186. Found: P, 16.6; S, 34.2; neut. equiv., 190.

O,O-Diisopropyl hydrogen phosphorodithioate boiled at 75–80° (2.0 mm.).

Anal. Calcd. for $C_6H_{15}O_2PS_2$: P, 14.5; S, 29.9; neut. equiv., 214. Found: P, 14.4; S, 29.4; neut. equiv., 211.

O,O-Di-n-butyl hydrogen phosphorodithioate boiled at 110–115° (1.5 mm.).

Anal. Calcd. for $C_8H_{19}O_2PS_2$: P, 12.8; S, 26.4; neut. equiv., 242. Found: P, 12.7; S, 26.1; neut. equiv., 243.

TABLE V

PEROXIDE EFFECT IN THE PREPARATION OF *O,O,S*-TRIALKYL PHOSPHORODITHIOATES

$$(RO)_2PSSH + \text{Olefin} \longrightarrow (RO)_2PSSR'$$

R	R'[a]	Method[b]	Yield, %	n_D^{20}	Phosphorus, % Found	Phosphorus, % Calcd.	Sulfur, % Found	Sulfur, % Calcd.
i-C_3H_7	$C_6H_5(CH_3)CH$	A	89	1.5374	9.45	9.75	20.1	20.2
i-C_3H_7	$C_6H_5CH_2CH_2$	B	89	1.5400	9.80	9.75	19.9	20.2
i-C_3H_7	2-C_8H_{17}	A	78	1.4834	9.82	9.52	20.0	19.6
i-C_3H_7	*n*-C_8H_{17}	B	68	1.4823	9.55	9.52	19.9	19.6
n-C_4H_9	$C_6H_5(CH_3)CH$	A	90	1.5341	8.82	8.95	18.7	18.5
n-C_4H_9	$C_6H_5CH_2CH_2$	B	94	1.5348	8.95	8.95	18.8	18.5
n-C_4H_9	*n*-C_8H_{17}	B	91	1.4915	8.71	8.73	18.0	18.0
n-C_6H_{13}	2-C_8H_{17}	A	70	1.4841	7.65	7.55	15.8	15.6
n-C_6H_{13}	*n*-C_8H_{17}	B	87	1.4859	7.38	7.55	15.5	15.6
n-C_6H_{13}	$C_6H_5(CH_3)CH$	A	82	1.5208	7.68	7.78	15.9	15.9
n-C_6H_{13}	$C_6H_5CH_2CH_2$	B	79	1.5222	7.58	7.78	16.1	15.9

[a] Structure assignments were made on the basis of the hydrolysis studies. Infrared spectra of the α-phenethyl esters exhibited absorptions at 9.5 (s) and 13.0 (m) μ, which were not present in the spectra of the β-phenethyl esters. The infrared spectra of the β-phenethyl esters exhibited absorptions at 13.3 (m) and 14.0 (w) μ, which were not present in the spectra of the α-phenethyl esters; (s = strong, m = medium, and w = weak.) Structural assignments for these absorptions will be the subject of another publication. No differences in the infrared spectra of the *n*-octyl and the 2-octyl esters were observed. [b] Method: A, crude $(RO)_2PSSH$ + olefin. B, purified $(RO)_2PSSH$ + olefin.

When purified *O,O*-dialkyl hydrogen phosphorodithioates were added to either octene-1 or styrene, the peroxide normally present in the olefin was sufficient to cause formation of the *O,O*-dialkyl-*S*-*n*-octyl (or β-phenethyl) phosphorodithioate. The crude acid contains a reducing agent which destroys the peroxide present in ordinary samples of olefin and results in the formation of

O,O-Di-n-hexyl hydrogen phosphorodithioate was heated to 100° at 0.5 mm. after the extraction procedure.

Anal. Calcd. for $C_{12}H_{27}O_2PS_2$: P, 10.4; S, 21.5; neut. equiv., 298. Found: P, 10.6; S, 21.1; neut. equiv., 308.

Octene-1 and *styrene* were commercial reagents, used as received.

(6) T. W. Mastin, G. R. Norman, and E. A. Weilmuenster, *J. Am. Chem. Soc.*, 67, 1662 (1945).

O,O,S-Trialkyl Phosphorodithioates were prepared as previously described.[2,3]

General procedure for the aqueous saponification of O,O,S-trialkyl phosphorodithioates. The *O,O,S*-trialkyl phosphorodithioate, 0.5 mole, was added rapidly to a 30% aqueous solution of sodium hydroxide, 2 moles, and heated under reflux for 10 hr. The reaction mixture was cooled to 30°, blown with carbon dioxide for 1 hr. and then steam distilled. The distillate was saturated with sodium chloride and extracted with benzene. The benzene layer was dried over magnesium sulfate. The magnesium sulfate was removed by filtration and the benzene distilled. The products were fractionated under reduced pressure.

Mercaptans were identified by elemental analysis, and the corresponding 2,4-dinitrophenyl alkyl sulfides[4,5] were prepared in order to confirm the structure of the products.

Sulfides were identified by elemental analysis and converted to the sulfones in order to confirm structures.

The esters saponified by this procedure and the products obtained are summarized in Table II.

General procedure for the ethanolic saponification of O,O,S-trialkyl phosphorodithioates. The *O,O,S*-trialkyl phosphorodithioate, 0.4 mole, was added rapidly to a solution of potassium hydroxide, 147 g. (2.6 moles) in 534 g. of 70% ethanol, and heated under reflux for 5 hr. The reaction solution was cooled to 30°, blown with carbon dioxide for 1 hr., and then steam distilled. The isolation and identification procedure used for the products was the same as in the aqueous saponification. The results are summarized in Table III.

General procedure for the glycolic saponification of O,O,S-trialkyl phosphorodithioates. The *O,O,S*-trialkyl phosphorodithioate, 0.5 mole, was added dropwise, to a 34% solution of potassium hydroxide, 0.9 mole, in ethylene glycol, at 140°. The reaction was exothermic and the temperature rose to 160° during the 1-hr. addition period. The products were collected as they distilled from the reaction mixture. The mixture of mercaptan and sulfide was dried over calcium chloride; the calcium chloride was removed by filtration and the products were separated by fractionation at atmospheric pressure. The products were identified by the methods outlined previously. The results of these experiments are shown in Table IV.

Infrared spectra of the esters were measured on the Perkin-Elmer Infracord, Model 137, as neat films on sodium chloride plates.

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CLEVELAND 17, OHIO

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

Phosphorus Compounds. II. Synthesis of Unsymmetrical Tertiary Phosphines[1,2]

WILLIAM J. BAILEY, SHELDON A. BUCKLER,[3] AND FRITZ MARKTSCHEFFEL[4]

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The reduction of benzyl-containing phosphonium compounds with lithium aluminum hydride has been used for the synthesis of two unsymmetrical tertiary phosphines. Thus ethylmethylphenylphosphine was prepared from dichlorophenylphosphine in an over-all yield of 59%. Similarly, ethylmethylpentylphosphine was prepared from dichloromethylphosphine in an over-all yield of 50%.

The methods available for the synthesis of unsymmetrical tertiary phosphines are long and tedious and in general result in poor yields. Kosolapoff[5] lists very few unsymmetrical tertiary phosphines and only one of these contains three aliphatic radicals. The most widely used method for their synthesis, introduced by Hofmann[6] and Michaelis,[7] was one in which the halogens of a phosphorus halide are replaced stepwise by treatment with Grignard reagents, organozinc compounds or organolithium compounds.[8] Although there are new procedures available for the preparation of the monosubstituted dichlorophosphines in good yields,[9-13] the synthesis of disubstituted monochlorophosphines is still somewhat unsatisfactory.[14,15]

The treatment of a phosphine with an alkyl halide appears to be a general synthetic procedure but gives satisfactory yields of an unsymmetrical tertiary phosphine only with unsymmetrical secondary phosphines.[6] Although there are new procedures available for the preparation of primary

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(1) Previous paper in this series, *J. Am. Chem. Soc.*, **79**, 3567 (1957).

(2) This work was done in fulfillment of a contract with the Army Chemical Corps.

(3) Member of the Armed Forces assigned to the Army Chemical Corps, 1954–1956.

(4) Chemical Corps Postdoctoral Fellow, 1957–1959.

(5) G. M. Kosolapoff, *Organophosphorus Compounds*, John Wiley and Sons, New York, N. Y., 1950, p. 37.

(6) A. W. Hofmann, *Ber.*, **6**, 292 (1873).

(7) A. Michaelis, *Ann.*, **315**, 53 (1901).

(8) W. C. Davies and F. G. Mann, *J. Chem. Soc.*, 276 (1944).

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(12) T. Weil, B. Prijs and H. Erlenmeyer, *Helv. Chim. Acta*, **35**, 1412 (1955); **36**, 1314 (1956).

(13) R. B. Fox, *J. Am. Chem. Soc.*, **72**, 4147 (1950).

(14) E. Wedekind, *Ber.*, **45**, 2933 (1912).

(15) A. Michaelis, *Ann.*, **315**, 43 (1901).

phosphines,[16,17] a general synthesis of secondary phosphines is not available.

A third method for the preparation of unsymmetrical phosphines, the pyrolysis of quaternary phosphonium halides, usually gives mixtures of products.[18,19]

The previous article in this series[1] reported the facile reduction of benzylphosphonium compounds with lithium aluminum hydride. It was likely, as only one benzyl group was removed at a time, that this reaction could be conveniently adapted to the synthesis of unsymmetrical tertiary phosphines. This method appeared to be attractive, not only because it gave high yields, but also because the starting material could be either phosphorus trichloride or a readily available monosubstituted dichlorophosphine. For these reasons the syntheses of two unsymmetrical tertiary phosphines were undertaken, one completely aliphatic and the other containing an aromatic ring.

The commercially available dichlorophenylphosphine was treated with an excess of benzylmagnesium chloride to produce dibenzylphenylphosphine, which was not isolated but was treated directly with methyl iodide to give an 82% over-all yield of dibenzylmethylphenylphosphonium iodide (I). The iodide I was reduced with a large excess of lithium aluminum hydride in tetrahydrofuran to give the corresponding phosphine, which was treated directly with ethyl iodide to give an 80% over-all yield of benzylethylmethylphenylphosphonium iodide (II). Reduction of II with lithium aluminum hydride gave the desired ethylmethylphenylphosphine (III) in a 90% yield. The phosphine III was characterized by conversion to the solid dimethylethylphenylphosphonium iodide (IV) in a 94% yield. The phosphine III was quite stable to air oxidation. It could be exposed to air with little or no change and air bubbled through a refluxing benzene solution of III produced only slow oxidation.

When dichloromethylphosphine was treated with benzylmagnesium chloride, the resulting dibenzylmethylphosphine was not isolated but was converted directly to the dibenzylethylmethylphosphonium iodide (V) in an 84% over-all yield by treatment with ethyl iodide. Reduction of V with lithium aluminum hydride, followed by treatment of the resulting phosphine with *n*-pentyl iodide, gave benzylethylmethylpentylphosphonium iodide (VI) in an 84% over-all yield. Reduction of VI with lithium aluminum hydride gave a 71% yield of the desired ethylmethylpentylphosphine (IX). In contrast to compound III, the aliphatic phosphine IX is extremely sensitive to air oxidation. The lower yield of IX is partially due to the difficulty in handling the phosphine. Even though atmospheric oxygen was carefully excluded, the distillation residue from IX always contained some phosphine oxide XII.

As in some cases it was difficult to remove all oxygen-containing material by simple distillation, treatment with metallic sodium was used. Curiously, addition of sodium produced a solid material and a blue color which faded on exposure to air. Hein, Plust, and Pohlemann[20] reported the formation of blue phosphyles, $R_3P\cdot \rightarrow O—Na$ by the treatment of arylphosphine oxides with sodium. Apparently the introduction of a single phenyl group, as in III, markedly lowers the reactivity toward oxygen. On a preparative scale, heating the phosphine IX in air produced an 85% yield of ethylmethylpentylphosphine oxide (XII). The structure of XII was indicated by reduction with lithium aluminum hydride, followed by direct alkylation of the intermediate phosphine with methyl bromide, to give a 52% yield of dimethylethylpentylphosphonium bromide (XI). XI also could be prepared in an 80% yield by direct alkylation of the phosphine IX.

Treatment of IX with methyl iodide similarly produced an 85% yield of the solid dimethylethylpentylphosphonium iodide (VIII), which also could be prepared in an 81% yield by direct reduction of VI with lithium aluminum hydride, followed by alkylation of the intermediate phosphine with methyl iodide.

Although no solid derivative could be prepared from IX with either picric acid or tetracyanoethylene, mercuric chloride formed both a 1:1 and a 1:2 adduct with IX, depending on the ratio of the reactants.

Several by-products were isolated from the preparation of the tertiary phosphines. In both cases toluene was isolated and characterized through its dinitro derivative. Vapor-phase chromatography indicated that a 96% yield of toluene was obtained from the reduction of VI. It can be speculated that the hydride attacks the benzyl carbon atom with the displacement of the phosphine or the addition of a hydride ion to the phosphorus atom with subsequent rearrangement to the products. The latter possibility would be similar to the mechanism proposed for the decomposition of phosphonium hydroxides[21] and halides.[22] The driving force for either mechanism would be the removal of the formal positive charge on the phosphorus atom. In several reductions small quantities of lower boiling secondary phosphines were detected by odor and vapor-phase chromatography. This observation suggests that some reductive method

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(18) J. Meisenheimer, *Ann.*, **449**, 213 (1906).
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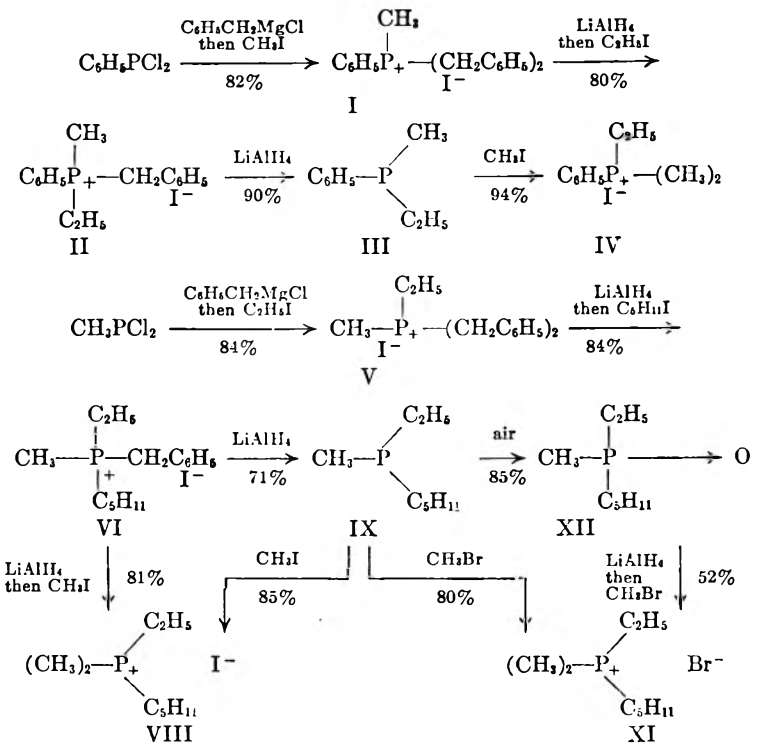

could be used for the synthesis of secondary phosphines. A second by-product isolated from the reductions of II and VI in quite large quantities was *n*-butyl alcohol, which was characterized by conversion to the corresponding 3,5-dinitrobenzoate and by vapor-phase chromatographic analysis. The production of the *n*-butyl alcohol from the tetrahydrofuran will be the subject of a separate report.

The synthesis of ethylmethylphenylphosphine (III) in an over-all yield of 59% and that of ethylmethylpentylphosphine (IX) in an over-all yield of 50% illustrates the versatility and usefulness of this procedure for the preparation of unsymmetrical tertiary phosphines.

EXPERIMENTAL[23]

All phosphines, solutions of phosphines, and Grignard reagents were prepared and handled in an atmosphere of nitrogen purified by passage of the commercial gas through a basic pyrogallol trap, a sulfuric acid trap, and then a tube filled with potassium hydroxide pellets and Drierite.

Dibenzylmethylphenylphosphonium iodide (I). To a solution of benzylmagnesium chloride [prepared in the usual way from 35.7 g. (1.47 g.-atoms) of magnesium, 184.0 g. (1.47 moles) of benzyl chloride, and 1300 ml. of anhydrous ether] cooled in an ice bath was added a solution of 125.5 g. (0.7 mole) of dichlorophenylphosphine (Eastman Kodak Company, technical grade) in 250 ml. of anhydrous ether with stirring and cooling over a period of 4 hr. After the mixture had been heated under reflux for 1 hr. and then allowed to stand for 15 hr., it was hydrolyzed by the cautious addition of 300 ml. of water and 250 ml. of a 20% ammonium chloride solution. The ether layer was separated, dried, and then treated with 200 g. (1.47 moles) of methyl iodide. After the solution was allowed to stand in a tightly stoppered flask for 48 hr., the crystalline solid which formed was removed by filtration and dried to give 266 g. (88%) of slightly impure iodide I, m.p. 201–205°. Recrystallization from a 3:1 mixture of ethanol and ethyl acetate gave 246 g. (82%) of pure dibenzylmethylphenylphosphonium iodide (I), m.p. 207–208° (reported[24] m.p. 206°).

Benzylethylmethylphenylphosphonium iodide (II). To a suspension of 108.0 g. (0.25 mole) of finely powdered dibenzylmethylphenylphosphonium iodide (I) in 900 ml. of dry tetrahydrofuran was added 9.5 g. (0.25 mole) of lithium aluminum hydride. After the mixture was heated under reflux for 30 hr., most of the tetrahydrofuran (750 ml.) was removed by distillation, and 950 ml. of a 20% sodium potassium tartrate solution was added cautiously with cooling in an ice bath. This mixture was then extracted with two 800-ml. portions of ether and the combined dry ether extracts were treated with 117 g. (0.75 mole) of ethyl iodide. After the solution was allowed to stand in a tightly stoppered flask for 9 days, the crystalline solid which deposited was collected, washed with ether, and air dried to obtain 74.0 g. (80%) of crude benzylethylmethylphenylphosphonium iodide (II), m.p. 164–166°. Recrystallization from water gave pure II, m.p. 165–166° (reported[24] m.p. 167–168°). When similar experiments were conducted with smaller quantities of lithium aluminum hydride or for shorter reflux periods, marked reduction in the yield was observed, together with recovery of unchanged starting material.

Ethylmethylphenylphosphine (III). To a suspension of 52.0 g. (0.14 mole) of finely powdered benzylethylmethylphenylphosphonium iodide (II) in 650 ml. of dry tetrahydrofuran was added 5.3 g. (0.14 mole) of lithium aluminum hydride. After the mixture was heated under reflux for 5.5 hr., most of the tetrahydrofuran was removed by distillation and 520 ml. of a 20% sodium potassium tartrate solution was added cautiously. The mixture was then extracted with two 400-ml. portions of ether, and the combined extracts were dried over anhydrous sodium sulfate. After the solvent

(23) The authors are grateful to Dr. Mary Aldrich, Kathryn Gerdeman, and Jane Swan for the analyses. All melting points and boiling points are uncorrected.

(24) J. Meisenheimer, *Ann.*, **449**, 213 (1926).

was removed by distillation, the residue was fractionated through a 12-inch Vigreux column to yield 15.6 g. of impure toluene, b.p. 45–65° (80 mm.), n_D^{25} 1.4667; 8.9 g. of impure *n*-butyl alcohol, b.p. 65–80° (12–25 mm.), n_D^{25} 1.4012; and 19.1 g. (90%) of slightly impure ethylmethylphenylphosphine (III), b.p. 82–83° (10 mm.), n_D^{25} 1.5522. Redistillation of the tertiary phosphine III gave an analytically pure sample, b.p. 93–94° (14 mm.), n_D^{25} 1.5524, d_{20}^{25} 0.954.

Anal. Calcd. for $C_9H_{13}P$: C, 71.03; H, 8.61. Found: C, 71.20; H, 8.42.

The toluene was further identified by conversion to a solid derivative, 2,4-dinitrotoluene, m.p. 70–71° (reported[25] m.p. 70–71°). A mixed melting point determination with an authentic sample showed no depression. Redistillation of the crude *n*-butyl alcohol at atmospheric pressure gave a fairly pure sample, b.p. 116–117°, n_D^{25} 1.3970 (reported[26] b.p. 117.4°, n_D^{20} 1.3993). A 3,5-dinitrobenzoate, m.p. 64–65° (reported[27] m.p. 64°), was prepared from the *n*-butyl alcohol by the procedure of Shriner and Fuson.[27] A mixed melting point determination with an authentic sample showed no depression.

Dimethylethylphenylphosphonium iodide (IV). To a suspension of 10.0 g. (0.027 mole) of finely powdered benzylethylmethylphenylphosphonium iodide (II) in 125 ml. of dry tetrahydrofuran was added 1.02 g. (0.027 mole) of lithium aluminum hydride. After the mixture was heated under reflux for 5.5 hr., most of the tetrahydrofuran was removed by distillation, and 100 ml. of a 20% sodium potassium tartrate solution was added cautiously. This mixture was then extracted with two 100-ml. portions of ether, and the combined extracts, together with 7.7 g. (0.054 mole) of methyl iodide, were allowed to stand in a tightly stoppered flask for 5 days. The oil which separated was dissolved in methanol, and the solvent was allowed to evaporate slowly to produce 7.46 g. (94%) of crystalline dimethylethylphenylphosphonium iodide (IV), m.p. 144–148°. Recrystallization from isopropyl alcohol gave an analytically pure sample, m.p. 148.5–150° (reported[28] m.p. 137°).

Anal. Calcd. for $C_{10}H_{16}IP$: C, 40.83; H, 5.48. Found: C, 40.57; H, 5.58

Dibenzylethylmethylphosphonium iodide (V). Benzylmagnesium chloride, prepared in the usual way from 37.7 g. (1.55 g.-atoms) of magnesium, 194 g. (1.55 moles) of benzyl chloride and 1350 ml. of anhydrous ether, was cooled in an ice bath, and a solution of 82.0 g. (0.7 mole) of freshly distilled dichloromethylphosphine, b.p. 77–79° (Army Chemical Center, Md.), in 200 ml. of ether was added with stirring and cooling over a period of 4 hr. The mixture was then heated under reflux for 1 hr. and hydrolyzed cautiously with 300 ml. of water and 300 ml. of a 20% ammonium chloride solution. The ether layer was combined with 435 g. (2.8 moles) of ethyl iodide and allowed to stand in a tightly stoppered flask for 14 days. The solution was then filtered to yield 225.5 g. (84%) of impure crystalline dibenzylethylmethylphosphonium iodide (V), m.p. 118–121°. Recrystallization from isopropyl alcohol–ethyl alcohol (3:1) gave an analytically pure sample, m.p. 122.5–123°.

Anal. Calcd. for $C_{17}H_{22}IP$: C, 53.13; H, 5.77. Found: C, 53.41; H, 5.86.

Benzylethylmethylpentylphosphonium iodide (VI). To a suspension of 120 g. (0.312 mole) of finely powdered dibenzylethylmethylphosphonium iodide (V) in 1440 ml. of freshly distilled dry tetrahydrofuran was added 11.85 g. (0.312 mole) of lithium aluminum hydride, and the mixture was heated under reflux for 6 hr. Most of the tetrahydrofuran was then removed by distillation and 1140 ml. of a 20% sodium potassium tartrate solution was added cautiously. This mixture was extracted with four 250-ml. portions of ether, and the combined extracts were dried over magnesium sulfate. After most of the ether was removed by distillation, a solution of 124 g. (0.624 mole) of *n*-pentyl iodide in 100 ml. of freshly distilled *n*-butyl ether was added to the residue. The solution immediately became milky and an oil separated. After the mixture had been heated under reflux for 24 hr., the supernatant liquid was removed by decantation. With cooling, the residual oil crystallized in an hour to yield, on filtration, 95 g. (84%) of crude white benzylethylmethylpentylphosphonium iodide (VI), m.p. 80–82°. Several recrystallizations from isopropyl alcohol–petroleum ether (b.p. 80–100°) gave an analytically pure sample, m.p. 90.5–92.0°.

Anal. Calcd. for $C_{15}H_{26}IP$: C, 49.46; H, 7.19. Found: C, 49.26; H, 7.20.

Benzylethylmethylpentylphosphonium bromide (VII). A suspension of 1.2 g. (0.0031 mole) of dibenzylethylmethylphosphonium iodide (V) in 150 ml. of freshly distilled tetrahydrofuran was reduced with 0.12 g. (0.0032 mole) of lithium aluminum hydride, and the reaction mixture was hydrolyzed as described above. After most of the ether had been removed from the solution containing the benzylethylmethylphosphine, 6.6 g. (0.044 mole) of *n*-pentyl bromide in 15 ml. of methanol was added. This mixture was heated under reflux for 24 hr., and then was allowed to stand for an additional 24 hr. to yield, after removal of the methanol, a semisolid material. Recrystallization from ethyl acetate yielded 0.5 g. (61%) of crude benzylethylmethylpentylphosphonium bromide (VII) in the form of white crystals, m.p. 123–127°. Two further recrystallizations from propanol–ethyl acetate (1:1) gave an analytically pure sample, m.p. 129–130.5°.

Anal. Calcd. for $C_{15}H_{26}BrP$: C, 56.78; H, 8.26. Found: C, 56.84; H, 8.01.

Dimethylethylpentylphosphonium iodide (VIII). *A. From benzylethylmethylpentylphosphonium iodide* (VI). To a suspension of 7.0 g. (0.0192 mole) of finely powdered benzylethylmethylpentylphosphonium iodide (VI) in 75 ml. of dry tetrahydrofuran was added 0.73 g. (0.0192 mole) of lithium aluminum hydride, and the mixture was heated under reflux for 7 hr. After most of the tetrahydrofuran had been removed by distillation, 70 ml. of a 20% sodium potassium tartrate solution was added to the residue. This mixture was extracted with two 80-ml. portions of ether and the combined extracts were treated with 11.4 g. (0.08 mole) of methyl iodide. After this solution was stored in a tightly stoppered flask for 3 days, the oil which formed was separated and dried *in vacuo* to give 4.81 g. of a crude solid. Recrystallization from 8 ml. of methylisobutylcarbinol–ethyl acetate (1:1) gave 4.48 g. (81%) of crystalline dimethylethylpentylphosphonium iodide (VIII), m.p. 106–108°. Two further recrystallizations gave an analytically pure sample, m.p. 108–109°.

Anal. Calcd. for $C_9H_{22}IP$: C, 37.51; H, 7.70. Found: C, 37.29; H, 7.59.

B. From ethylmethylpentylphosphine (IX). To 0.51 g. of ethylmethylpentylphosphine (IX) in 10 ml. of ether was added 1 ml. of methyl iodide in 20 ml. of ether with stirring and cooling with ice-water over a 30-min. period. The solution immediately turned milky and an oil, which solidified within 30 min., separated to give 0.85 g. (85%) of the crude iodide VIII. Recrystallization from propanol–ethyl acetate (1:2) gave fairly pure dimethylethylpentylphosphonium iodide (VIII), m.p. 108–108.5°. A mixed melting point determination with an authentic sample showed no depression.

Ethylmethylpentylphosphine (IX). To a suspension of 69 g. (0.19 mole) of finely powdered benzylethylmethylpentylphosphonium iodide (VI) in 1150 ml. of tetrahydrofuran

(25) E. A. Huntress and S. P. Mulliken, *Identification of Pure Organic Compounds*, John Wiley and Sons, New York, N. Y., 1941, p. 520.

(26) I. Heilbron, *Dictionary of Organic Compounds*, Oxford University Press, New York, N. Y., 1953, p. 388.

(27) R. L. Shriner and R. C. Fuson, *Identification of Organic Compounds*, 3rd edition, John Wiley and Sons, New York, N. Y., 1949.

(28) A. Michaelis, *Ann.*, 181, 362 (1876).

(freshly distilled from lithium aluminum hydride) was added 8.9 g. (0.23 mole) of lithium aluminum hydride, and the mixture was heated under reflux for 8 hr. After most of the tetrahydrofuran was removed by distillation over a 12-hr. period, the residue was treated cautiously with 600 ml. of a 25% sodium potassium tartrate solution with cooling and stirring. This mixture was then extracted with three 200-ml. portions of ether, which were removed through a glass tube by the application of an excess of nitrogen pressure. After the combined ether solutions were dried over anhydrous sodium sulfate, the ether and most of the tetrahydrofuran were removed by distillation through an 8-inch, helix-packed column. The residue was fractionated through the same column to give the following fractions:

Fraction	B.P., °	Mm.	Wt., g.	n_D^{25}
1	100–112	755	32.6	1.4489
2	112–114.5	755	7.0	1.4042
3	60–41	60–21	4.3	1.4081
4	68–73.5	21	19.5	1.4551
5	Residue	—	2.9	—

The impure ethylmethylpentylphosphine (IX), contained in fraction 4, was obtained in a 71% yield. Redistillation of fraction 4 through a 5-inch Podbielniak column (which had been alternately evacuated and flushed with nitrogen six times) yielded an analytically pure sample, b.p. 74–74.5° (22 mm.), n_D^{20} 1.4574. (Satisfactory analyses were obtained only if the combustion was carried out at 900°.)

Anal. Calcd. for $C_8H_{19}P$: C, 65.72; H, 13.09. Found: C, 65.53; H, 12.94.

Vapor-phase chromatography indicated that fractions 1 through 3 contained 16.5 g. (96%) of toluene, 20.5 g. of *n*-butyl alcohol, and 6.8 g. of tetrahydrofuran. The toluene was further identified as its 2,4-dinitro derivative, m.p. 70–71°, which did not depress the melting point of an authentic sample. The *n*-butyl alcohol was converted to its 3,5-dinitrobenzoate, m.p. 65.0–65.5°, which did not depress the melting point of an authentic sample.

Ethylmethylpentylphosphine-mercuric chloride addition compounds (X). When 0.4 g. (0.0027 mole) of ethylmethylpentylphosphine (IX) was added to a solution of 0.63 g. (0.0023 mole) of mercuric chloride in 20 ml. of ethanol, no precipitate was formed. Removal of the solvent on a steam bath produced a gray, sticky solid, m.p. 120–205°. Extraction of this solid with ethanol, followed by removal of the ethanol from the extracts on a steam bath, yielded a clear, sticky film, which was redissolved in hot ethanol. When the solution was allowed to cool to room temperature, an oil separated which solidified in the refrigerator. Three recrystallizations from ethanol produced white crystals of a 1:1 adduct of ethylmethylpentylphosphine and mercuric chloride (Xa), m.p. 67.5–68.5°.

Anal. Calcd. for $C_8H_{19}Cl_2HgP$: Cl, 16.97. Found: Cl, 16.77.

Repetition of the procedure described above, but with double the quantity of mercuric chloride, produced a 1:2 adduct of ethylmethylpentylphosphine and mercuric chloride (Xb), m.p. 155–155.5°. With continued heating, the molten Xb resolidified to produce a solid, which was recrystallized from ethanol to produce a pure sample of Xb, m.p. 210°.

Anal. Calcd. for $C_8H_{19}Cl_4Hg_2P$: Cl, 20.57; P, 4.59. Found: Cl, 20.59; P, 4.67.

Stoichiometric quantities of reactants are recommended, as purification of the adducts by recrystallization from ethanol is difficult. However, an excess of mercuric chloride can be conveniently removed by extraction with boiling water in which the adducts are only sparingly soluble.

Dimethylethylpentylphosphonium bromide (XI). To 0.8 g. (0.0054 mole) of ethylmethylpentylphosphine (IX) dissolved in 20 ml. of ether was added 3 ml. of methyl bromide at −15°. After the mixture was allowed to stand for 5 days at room temperature, the ether solution was decanted from an oil which solidified after being dried in a desiccator at 1 mm. pressure to produce 1.25 g. (80%) of very crude hygroscopic dimethylethylpentylphosphonium bromide (XI), m.p. 116–121°. Two recrystallizations from ethyl acetate–propanol (20:1) produced an analytically pure sample, m.p. 128–128.5°.

Anal. Calcd. for $C_9H_{22}BrP$: C, 44.81; H, 9.19. Found: C, 44.51; H, 9.19.

Ethylmethylpentylphosphine oxide (XII). After a mixture of 15 g. of ethylmethylpentylphosphine (IX) and the residue (2.9 g.) from the distillation of IX was heated for 4 hr. in the air, the reaction product was distilled at reduced pressure to yield 17 g. (86%) of crude ethylmethylpentylphosphine oxide (XII). Redistillation through an 8-inch, helix-packed column gave pure XII, b.p. 76–76.5° (0.4 mm.), n_D^{20} 1.4591, m.p. 8–9°, as a colorless, very hygroscopic liquid.

Anal. Calcd. for $C_8H_{19}OP$: C, 59.26; H, 11.81. Found: C, 59.37; H, 11.53.

Reduction of ethylmethylpentylphosphine oxide (XII) *with lithium aluminum hydride.* A solution of 1.14 g. (0.007 mole) of ethylmethylpentylphosphine oxide (XII) in 10 ml. of tetrahydrofuran was added to 0.3 g. of lithium aluminum hydride in 90 ml. of tetrahydrofuran. After the mixture had been heated under reflux for 5 hr., the mixture was worked up in the usual way, as described above. To the combined ether extracts was added 6 g. of methyl bromide, and the mixture was allowed to stand for 5 days at room temperature to yield 0.88 g. (52%) of crude dimethylethylpentylphosphonium bromide (XI), m.p. 110–114°. Three recrystallizations from propanol–ethyl acetate raised the melting point to 127.5–129°. A mixed melting point determination with an authentic sample of XI showed no depression.

College Park, Md.

[CONTRIBUTION FROM THE AERO-SPACE DIVISION, BOEING AIRPLANE CO.]

Derivatives of Triphenylphosphine and Triphenylphosphine Oxide

ALLEN E. SENEAR, WILLIAM VALIENT, AND JOSEPH WIRTH

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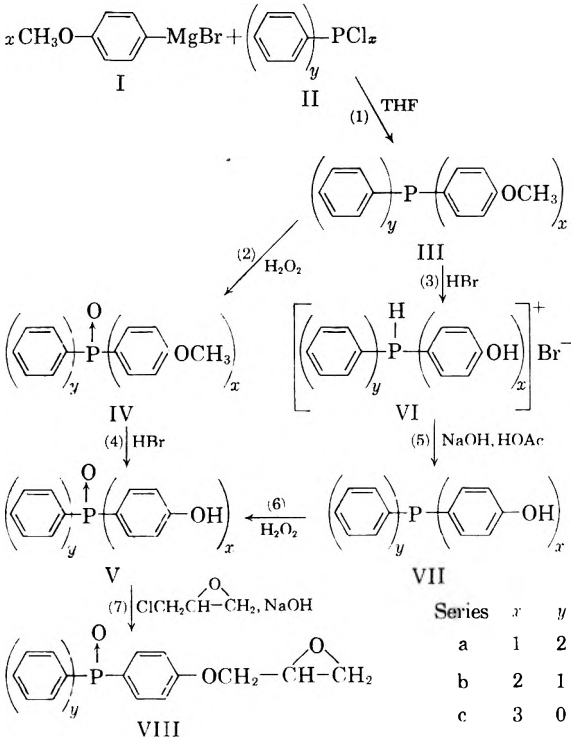
Synthesis of four monomers, *p*-styryldiphenylphosphine, *p*-glycidyloxyphenyldiphenylphosphine oxide, di(*p*-glycidyloxyphenyl)phenylphosphine oxide, and tri(*p*-glycidyloxyphenyl)phosphine oxide is described.

In view of the high thermal stability of triphenylphosphine oxide[1,2] we have undertaken the synthesis of a group of polymers containing this structure. In this paper we wish to describe the preparations and properties of a number of monomers required for this work.

The mono-, di-, and tri-*p*-hydroxy derivatives of triphenylphosphine and triphenylphosphine oxide were prepared as outlined below. Reactions of the hydroxyphenylphosphine oxides with epichlorohydrin yielded glycidyl ethers in which the triphenylphosphine oxide nucleus replaced the bisphenol A moiety of conventional epoxy resins. The



Series	*x*	*y*
a	1	2
b	2	1
c	3	0

Grignard synthesis of the mono-, di-, and tri-*p*-methoxy derivatives of triphenylphosphine went smoothly in tetrahydrofuran. Although the monofunctional product could be readily isolated by distillation, attempts to distill benzene extracts containing the di- and tri-functional compounds led to strongly exothermic decompositions beginning at about 225°. In large scale syntheses these became uncomfortably vigorous. Extraction with concentrated hydrochloric acid gave very satisfactory separations of products from accompanying tars and from *p,p'*-dimethoxybiphenyl, a principal by-product, and is therefore recommended in spite of its unpleasant features.

Demethylation by hydrobromic acid (reaction 3) proceeded smoothly, with no sign of phosphorus-phenyl cleavage.[3] Because the free hydroxyphosphines were difficult or impossible to recrystallize, they were isolated and purified as their hydrobromic acid salts.

The hydrogen peroxide oxidations of the methoxyphosphines (reaction 2) and of the hydroxyphosphines (reaction 6) proceeded smoothly in excellent yields. The phosphine oxides were nicely crystalline solids. To obtain satisfactory analyses it was necessary to dry them very thoroughly, as they held traces of solvent tenaciously.

As di(*p*-hydroxyphenyl)phenylphosphine (VIIb) and tri(*p*-hydroxyphenyl)phosphine (VIIc) could not be recrystallized, samples of them were oxidized to the corresponding hydroxyphosphine oxides (Vb and Vc) to establish their identity and purity (reaction 6). The products, obtained in excellent yield, were identical with those prepared by demethylation of the appropriate methoxyphosphine oxides (reaction 4).

The preparation of *p*-vinylphenyldiphenylphosphine (XIII) was carried out by reactions 8–11, following Neville.[4] Attempts to prepare it directly from *p*-styrylmagnesium chloride and diphenylchlorophosphine (reaction 12) led to immediate polymerization instead.[5]

Physical properties, yields, and analytical data for the compounds prepared are compiled in Table I. Those features of the infrared spectra used in confirming assigned structures are listed in Table

(1) G. N. Kosolapoff, *Organophosphorus Compounds*, John Wiley & Sons, New York, 1950, page 98.

(2) J. W. Dale, I. B. Johns, *et al.*, *Synthesis of 1000°F. Stable Fluids*, paper presented at the Conference on High Temperature Polymer & Fluid Research sponsored by the Wright Air Development Center, May 26–28, 1959.

(3) L. M. Kindley and L. P. Glekas, *Synthesis of Thermally Stable Epoxide Resins for Dielectric Applications*. Quarterly Progress Report No. 5 to Wright Air Development Center, Contract AF 33(616)-5518, September 1959.

(4) R. G. Neville, *J. Org. Chem.*, **21**, 111 (1959).

(5) See J. R. Leebrick and H. E. Ramsden, *J. Org. Chem.*, **23**, 935 (1959) for the preparation of *p*-styrylmagnesium chloride, and A. E. Senear, R. G. Neville, and J. Wirth, *J. Org. Chem.*, **25**, 807 (1960) for a similar resinification reaction with a chlorosilane.

TABLE I

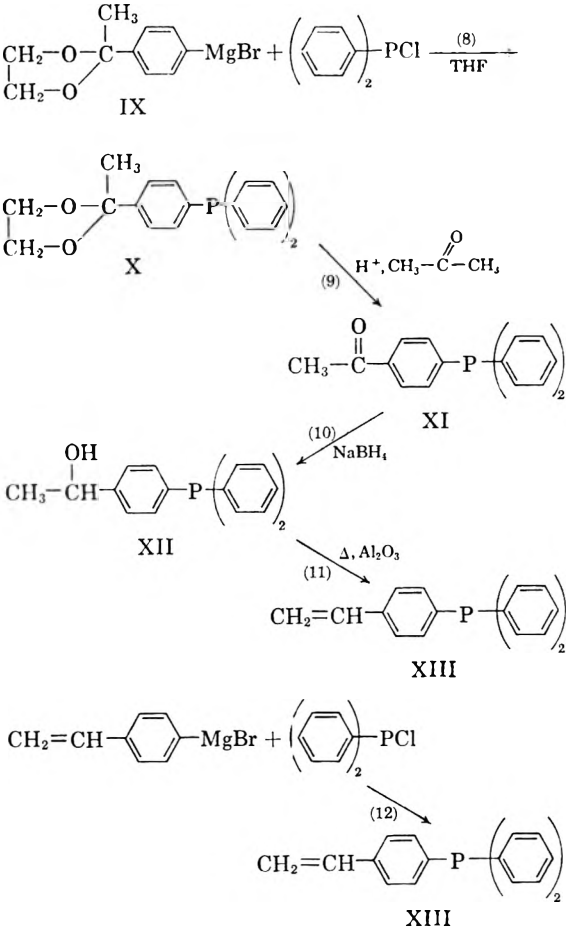
YIELDS, PHYSICAL PROPERTIES, ANALYSES

No.	Compound	Yield, %	M.P.[a]	Recry. Solvent	Calcd., % C	Calcd., % H	Calcd., % P	Found, % C	Found, % H	Found, % P[b]	Comments
IIIa	*p*-Methoxyphenyldiphenylphosphine	70	78–79	Methanol							Low melting form only analysed
			68–69	Methanol	78.07	5.86	10.60	78.14	5.90	10.88	See ref. 11
IIIb	Di(*p*-methoxyphenyl)phenylphosphine	75	89–90	Methanol	74.52	5.94	9.61	74.75	5.87	9.56	
IIIc	Tri(*p*-methoxyphenyl)phosphine	45	130–131	Methanol							Previously described, ref. 12
IVa	*p*-Methoxyphenyldiphenylphosphine oxide	93	117–118	Benzene-Pet. ether[d]	74.02	5.56	10.05	74.38	5.99	10.34	
IVb	Di(*p*-methoxyphenyl)phenylphosphine oxide	77	96–97	Benzene-Pet. ether[d]	70.99	5.66	9.16	71.21	5.93	9.06	
IVc	Tri(*p*-methoxyphenyl)phosphine oxide	90	143–144	Benzene	68.46	5.75	8.41	68.65	5.81	8.36	
VIa	*p*-Hydroxyphenyldiphenylphosphine hydrobromide	80	202–203	Methanol-HBr	60.19	4.49		60.26	4.58		Br, calcd. 22.25, found 22.03
VIb	Di(*p*-hydroxyphenyl)phosphine hydrobromide	70	220–221	Methanol-HBr	57.62	4.30		57.70	4.23		Br, calcd. 21.30, found 21.16
VIc	Tri(*p*-hydroxyphenyl)phosphine hydrobromide	70	227–228	Methanol-HBr	55.26	4.12	7.91	55.00	4.02	7.70	Br, calcd. 20.43, found 20.79
VIIa	*p*-Hydroxyphenyldiphenylphosphine	85	113–114	Benzene-Pet. ether[d]	77.65	5.43	11.13	77.97	4.84	10.88	Once recrystallized
			102.5–103.5	Benzene-Pet. ether[d]				77.43	5.23	[c]	After five recrystallizations
VIIb	Di(*p*-hydroxyphenyl)phenylphosphine	85	Oil								Yield based upon conversion to phosphine oxide
VIIc	Tri(*p*-hydroxyphenyl)phosphine	95	130–138								Could not be recrystallized
Va	*p*-Hydroxyphenyldiphenylphosphine oxide										
	(a) By oxidation	96	243–244	Methanol	73.45	5.14	10.53	73.20	5.00	10.66	
	(b) By hydrolysis	91									
Vb	Di(*p*-hydroxyphenyl)phenylphosphine oxide										
	(a) By oxidation	85	233–234	Methanol	69.68	4.87	9.98	69.45	4.95	9.81	
	(b) By hydrolysis	80									
Vc	Tri(*p*-hydroxyphenyl)phenylphosphine oxide										
	(a) By oxidation	95	273–275	Methanol	66.26	4.63	9.49	65.98	4.44	9.04	
	(b) By hydrolysis	95									
VIIIa	*p*-Glycidyloxyphenyldiphenylphosphine oxide		Oil								Epoxide equivalent, calcd. 350, found 453
VIIIb	Di(*p*-glycidyloxyphenyl)phenylphosphine oxide		Oil								Epoxide equivalent, calcd. 211, found 300
VIIIc	Tri(*p*-glycidyloxyphenyl)phosphine oxide		Oil								Epoxide equivalent, calcd. 165, found 210

TABLE I (*Continued*)

No.	Compound	Yield, %	M.P.[a]	Recry. Solvent	Calcd., % C	Calcd., % H	Calcd., % P	Found, % C	Found, % H	Found, % P[b]	Comments
X	2-Methyl-2-(4′-diphenylphosphinylphenyl)-1,3-dioxolane	71	73–74	Ethanol	75.84	6.08	8.89	76.15	6.24	9.32	Yield of oil, contaminated with XI
XI	*p*-Acetylphenyldiphenylphosphine	82	121–122	Acetone	78.93	5.63	10.18	78.90	5.96	10.24	Yield from oily intermediate (X)
XII	*p*-(1′-Hydroxyethyl)phenyldiphenylphosphine	99	Oil								
XIII	*p*-Styryldiphenylphosphine	38	75.0–75.5	Methanol	83.31	5.94	10.74	83.28	6.22	10.62	Yield based on acetyl compound (XI)

[a] Melting point of analytical sample. [b] Phosphorus analyses by Schöniger method, see K. Fleisher, *et al.*, *Anal. Chem.*, **30**, 152 (1958). [c] Formation of a precipitate following solution of the magnesium ammonium phosphate and fading of the titration end-point interfered with this phosphorus determination. [d] B.p. 30–60°.



II. The spectra were determined using potassium bromide pellets, and measured in a Perkin-Elmer Model 12 single beam spectrophotometer with sodium chloride optics.

EXPERIMENTAL[6]

Diphenylchlorophosphine (IIa).[7] In a 5-l. flask attached to a 2-foot, unwrapped Vigreux column were mixed 4650 g. (26.0 moles) of phenyldichlorophosphine[8] (IIb) and 175 g. of anhydrous aluminum chloride. The mixture was heated so that phosphorus trichloride distilled off the top of the column at 85–95° as it was formed by redistribution. After 20 hr. 700 ml. (8.0 moles) had been collected. The pot residue was distilled *in vacuo* through a fractionating column to yield 1015 ml. (7.5 moles) of unchanged phenyldichlorophosphine, b.p. 90–95°/1 mm., followed by 1624 g. (7.35 moles) of diphenylchlorophosphine, b.p. 145–147°/1 mm., (79%, based on consumed starting material).[9]

p-Methoxyphenyldiphenylphosphine (IIIa). To the Grignard reagent prepared from 112 g. (0.60 moles) of *p*-bromoanisole in 250 ml. of tetrahydrofuran was added a solution

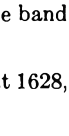
(6) All melting points were measured in glass capillaries immersed in a heated silicone bath, and are uncorrected.

(7) Although this compound has been described frequently [see reference 1, page 55, also F. G. Mann and I. T. Miller, *J. Chem. Soc.*, 4453 (1952) and B. A. Arbuzov and N. P. Grechlin, *Zhur Obschei Khim.*, **20**, 107 (1950); cf. *Chem. Abstr.*, **44**, 5832 (1950)], this method is presented as it conveniently furnishes a good yield with easily available starting material.

(8) Available from Victor Chemical Co., Chicago Heights, Ill.

TABLE II

INFRARED SPECTRA, CM.$^{-1}$

Compound	Phenyl, Monosubstituted	Phenyl *p*-Substituted	C—O, Ether or Phenolic	P—O	P—C_6H_5	—CH_3 bend	Aromatic C=C	OH Region	Comments
IIIa	696, 746	833	1247		1424	1451	1494, 1566, 1590		*p*-Substitution and methyl bending bands increase in intensity on going from mono- to trifunctional
IIIb	697, 753	831	1247		1429	1449	1494, 1566, 1592		
IIIc		831	1247		1437	1451	1494, 1566, 1590		
IVa	704, 728	838	1259	1174–1178	1426	1451	1499, 1563, 1596		
IVb	704, 726	831	1259	1175	1434	1455	1499, 1570, 1600		
IVc		805	1252	1176	1439	1455	1449, 1566, 1596		
VIa	683, 738	843	1117, 1294		1432		1497, 1577, 1600	3021	P-H at 2257
VIb	683, 746	846	1118, 1283		1424		1494, 1576, 1600	3067	P-H at 2328
VIc		830	1115, 1283		1424		1494, 1576, 1600	3130, 3257	P-H at 2358
VIIa	697, 743	833	1093, 1217		1426		1494, 1582, 1596	3280	
VIIb	697, 746	826	1093, 1245		1429		1503, 1582, 1604	3280	
VIIc		830	1115, 1247		1429		1497, 1583, 1604	3416	
Va	692, 729	836	1117, 1285	1158–1166	1429		1499, 1574, 1600	3021	
Vb	694, 728	831	1120, 1276	1156	1432		1497, 1586, 1604	3106	
Vc		831	1118, 1276	1171	1426		1997, 1582, 1604	3179	
VIIIa	709, 754	831	1026, 1258	1183	1437		1500, 1570, 1596	3390	Oxirane bands at 863, 919, 1163
VIIIb	700, 754	833	1026, 1255	1176	1434		1497, 1570, 1592	3205	Oxirane bands at 865, 919, 1163
VIIIc		831	1024, 1255	1176	1429		1503, 1574, 1596	3257	Oxirane bands at 863, 916, 1160
X	697, 746	831	1255		1429		1476, 1590		Ketal doublet at 1041, 1071
XI	697, 746	826	1265		1424		1476, 1592		C=O strong at 1680
XII	696, 746	830	1082		1426		1476, 1586	3311	Variable band at 2392[a]
XIII	696, 750	838			1426		1478, 1590		C=C at 1628,  at 919

[a] This band, absent in some preparations and very strong when treatment of the reaction mixture with acid was omitted, was attributed to residual B—H structures in the oily product. Its presence or absence did not materially affect the subsequent dehydration of the carbinol.

of 90 g. (0.40 mole) of diphenylchlorophosphine in 50 ml. of tetrahydrofuran.[10] The mixture was refluxed 1 hr. and poured over ice–hydrochloric acid. The product was extracted into benzene, washed, dried, and distilled to yield 97 g. of yellow oil, b.p. 195–225°/5 mm. Trituration with methanol caused the oil to crystallize, and recrystallization from 1 l. of methanol gave 82 g. (70%) of colorless crystals, m.p. 78–79°.[11]

Di(p-methoxyphenyl)phenylphosphine (IIIb). A mixture of 3.0 moles of *p*-methoxyphenylmagnesium bromide and 1.25 moles of phenyldichlorophosphine in 3 l. of tetrahydrofuran

(9) CAUTION: At the end of the distillation a waxy yellow solid collected in the still head. While hot, both this material and the still pot residue would ignite on contact with air. After cooling, air could be carefully admitted, and these materials rinsed out with acetone.

(10) Substitution of *p*-chloroanisole (Ansul Chemical Co.) gave comparable yields, and the Grignard formed readily in tetrahydrofuran. Tetrahydrofuran was preferred to ether, as it held complexes of the reaction products in solution, greatly facilitating working up the products.

(11) In our first preparation a metastable crystalline form, m.p. 68–69°, was isolated, recrystallized, and analysed. Both forms gave quantitative yields of *p*-methoxyphenyldiphenylphosphine oxide (IVa) upon oxidation, and had identical infrared spectra. The lower melting form yielded the higher melting one when seeded with the latter during recrystallization.

was refluxed 3 hr., poured over ice, and acidified with hydrochloric acid. After standing overnight to allow the tetrahydrofuran to evaporate, the product was taken up in benzene, washed with water, and extracted with four 1-l. portions of concd. hydrochloric acid. The acid extracts were cautiously neutralized with concd. ammonia giving an oil which solidified on cooling. The solid was filtered, washed, dried, and recrystallized from 2 l. of methanol to yield 271 g. (75%) of colorless crystals, m.p. 85–90°. Upon a second crystallization the melting point became 89–90°.

Tri(p-methoxyphenyl)phosphine (IIIc).[12] This compound was prepared in 45% yield by treating in tetrahydrofuran 6.0 moles of *p*-methoxyphenylmagnesium bromide[10] with 1.8 moles of phosphorus trichloride, and isolating the product by the procedure described above for the dimethoxy compound.

Mono-, di-, and tri-p-methoxy derivatives of triphenylphosphine oxide (IVa, b, c). To the methoxyphosphine suspended in 4–8 volumes of acetone was slowly added enough 10% hydrogen peroxide to furnish 1.1 moles of the latter per mole of phosphine.[13] During the vigorous exothermic reaction the solids dissolved. The acetone was allowed to evaporate, and the products taken up in benzene, washed peroxide free with ferrous ammonium sulfate solution, and dried. Evaporation of the benzene left the phosphine oxides as readily crystallizable oils. The mono- and trimethoxy compounds recrystallized easily. To avoid oiling out the dimethoxy derivative, careful addition of petroleum ether (b.p. 30–60°) to a dilute benzene solution at room temperature, followed by refrigeration was necessary; the yield was lowered by recrystallization losses.

p-Hydroxyphenyldiphenylphosphine hydrobromide (VIa). Fifty-nine grams (0.2 mole) of *p*-methoxyphenyldiphenylphosphine (IIIa) and 150 ml. of 48% hydrobromic acid were refluxed under nitrogen 4 hr. A 6.5-ml. sample (65%) of methyl bromide collected in a cold trap attached to the condenser top. On chilling 61.8 g. (80%) of crystalline product, m.p. 200–203°, came out of solution. Recrystallization from 160 ml. of methanol and 10 ml. of hydrobromic acid gave 55.1 g. (71%) of colorless crystals, m.p. 202.5–203.5° dec.

Di-(p-hydroxyphenyl)phenylphosphine hydrobromide (VIb) *and tri(p-hydroxyphenyl)phosphine hydrobromide* (VIc). These compounds were prepared in the same fashion as the mono functional analog, in yields of 70% following recrystallization.

p-Hydroxyphenyldiphenylphosphine (VIIa). The phosphine hydrobromide (VIa) prepared above was dissolved in 500 ml. of 3% sodium hydroxide solution. The free phosphine, precipitated by the slow addition of acetic acid, came down as an oil and then solidified. After 4 days *in vacuo* it melted over a wide range, 87–112°, and weighed 40.4 g. (theory is 36.7 g.). It was dissolved in 200 ml. of benzene and refluxed. By means of a Dean Stark trap 4.5 ml. of water was removed. After addition of 200 ml. of petroleum ether (b.p. 30–60°) to the dried benzene solution, chilling caused 31.3 g. (85%) of crystalline product, m.p. 110–112° to form. This represents an over-all yield of 60% from *p*-methoxyphenyldiphenylphosphine.

During the course of several recrystallizations from benzene-petroleum ether (b.p. 30–60°) the melting point of the hydroxyphenylphosphine dropped to 102.5–103.5°, and then remained constant. The infrared spectrum was unaltered during this change, and was in agreement with the proposed structure. Both forms were reconverted quantitatively to *p*-hydroxyphenyldiphenylphosphine hydrobromide (VIa) on recrystallization from methanol–hydrobromic acid, and yielded *p*-hydroxyphenyldiphenylphosphine oxide (Va) on oxidation.

Di(p-hydroxyphenyl)phenylphosphine (VIIb) *and tri(p-hydroxyphenyl)phosphine* (VIIc). The phosphine hydrobromides were converted to the free bases by solution in sodium hydroxide and precipitation with acetic acid. The dihydroxy compound was a noncrystallizable oil. The trifunctional product yielded a taffy-like precipitate which gradually solidified. After grinding with water, washing salt-free, and drying, it melted at 130–138°. Attempted recrystallization led to oils. The high yields, 85% and 95%, of the di- and trihydroxy phosphine oxides, obtained by oxidation (see below), confirm the compositions of these products.

p-Hydroxyphenyldiphenylphosphine oxide (Va). a. *By hydrolysis.* A suspension of 70.4 g. (0.23 mole) of *p*-methoxyphenyldiphenylphosphine oxide (IVa) in 250 ml. of 48% hydrobromic acid was refluxed 3.5 hr. Twelve milliliters (97%) of methyl bromide was isolated. After cooling, the acid phase was discarded, and the oily residue dissolved in dilute sodium hydroxide and precipitated with acetic acid. Recrystallization of the tan powder from 500 ml. of methanol gave 82.7 g. (91%) of crystals, m.p. 237–239°.

b. *By oxidation.* Addition of a slight excess of 10% hydrogen peroxide to a solution of *p*-(hydroxyphenyl)diphenylphosphine in six volumes of acetone produced a vigorous reaction. As the acetone evaporated a product, identical with the hydrolysis product above, crystallized out in 96% yield.

Di(p-hydroxyphenyl)phenylphosphine oxide (Vb) *and tri(p-hydroxyphenyl)phosphine oxide* (Vc). Hydrogen peroxide oxidation of the oily difunctional phenol (VIIb) produced the phosphine oxide in 85% yield, based on the hydrogen bromide salt precursor of the free base. Hydrobromic acid demethylation of di(*p*-methoxyphenyl)phenylphosphine oxide (IVb) gave the same product in 80% yield. Similarly tri(*p*-hydroxyphenyl)phosphine oxide was prepared in 95% yield both by oxidation of crude tri(*p*-hydroxyphenyl)-phosphine and by demethylation of tri(*p*-methoxyphenyl)-phosphine oxide.

Mono-, di-, and tri(p-glycidyloxy)triphenylphosphine oxide (VIIIa, b, c). Following the reactions of epichlorohydrin with the hydroxyphenylphosphine oxides as described by Lee and Neville for bisphenol A,[14] the products were taken up in benzene, and washed salt free. Solvent stripping *in vacuo* left viscous oils. The epoxide equivalents shown in Table I indicate that some opening of the epoxide ring had occurred during reaction. The products could be converted to tough, strong, adherent resins by reaction with such typical epoxy curing agents as amines, acid anhydrides, and boron trifluoride.

2-Methyl-2-(4'-diphenylphosphinylphenyl)-1,3-dioxolane (X). To the Grignard reagent from 529 g. (2.18 moles) of 2-(4'-bromophenyl)-2-methyl-1,3-dioxolane (IX)[4] and 58 g. (2.40 moles) of magnesium in 1.5 l. of tetrahydrofuran was added slowly a solution of 386 g. (1.75 moles) of diphenylchlorophosphine in 0.5 l. of tetrahydrofuran. After refluxing 1.5 hr. the solution was poured over cracked ice and the product extracted into benzene. Emulsification made this a tedious procedure. After drying, the benzene solution was distilled to yield a crystalline fraction, b.p. 120–130°/25 mm. (probably 2-phenyl-2-methyl-1,3-dioxolane), and a product-containing fraction, b.p. 200–300°/3.5 mm., weighing 423 g. (71%), mainly distilling at 235–255°/3.5 mm.

Trituration with 300 ml. of ethanol caused the oil to crystallize. The crystals, m.p. 63–70°, were shown by infrared spectroscopy to consist mainly of ketal (X), with some ketone (XI) as impurity, probably formed by hydrolysis during work-up. Although ketone-free ketal, m.p. 73–74° could be prepared by ethanol recrystallization, this product was converted directly to the ketone without purification.

p-Acetylphenyldiphenylphosphine (XI). The crude crystalline product from the previous reaction was dissolved in 2 l.

(12) F. G. Mann and E. Chaplin, *J. Chem. Soc.*, 527 (1937).

(13) R. Letsinger, J. Nazy, and A. Hussey, *J. Org. Chem.*, **23**, 1806 (1958).

(14) H. Lee and K. Neville, *Epoxy Resins.* McGraw-Hill Book Co., Inc., New York, 1957.

of acetone containing 10 g. of *p*-toluenesulfonic acid. Following 3 hr. of reflux the solution was neutralized with methanolic sodium hydroxide solution and, after filtering out sodium *p*-toluenesulfonate, concentrated to 800 ml. On chilling 220 g. of product, m.p. 117–119°, crystallized.

The ethanolic mother liquor from the ketal preparation was evaporated, and the residual oil treated with acetone and *p*-toluenesulfonic acid as described above to give an additional 35 g. of ketone. By concentration of the combined acetone mother liquors 48 g. of impure ketone was obtained, making the overall yield of ketone (XI) 58%, based upon the original diphenylchlorophosphine.

p-(1'-Hydroxyethyl)phenyldiphenylphosphine (XII). To a suspension of 254 g. (0.84 mole) of *p*-acetylphenyldiphenylphosphine (XI) in 1.2 l. of methanol was slowly added a solution of 32 g. (0.84 mole) of sodium borohydride in 0.5 l. of methanol. Mild cooling was needed to keep the temperature below 30°. After standing overnight 150 ml. of glacial acetic acid and 200 ml. of water were added. Four hours later 1.5 l. of water was added and the product was taken up in benzene and washed with dilute hydrochloric acid, dilute base, and water. Removal *in vacuo* of the benzene left 254 g. (99%) of a very viscous oil which resisted crystallization. The infrared spectrum (Table II) confirmed its structure.

p-Styryldiphenylphosphine (XIII). Over a 4-hr. period a solution of 253 g. (0.33 mole) of the carbinol (XII) in 250 ml. of toluene was dropped into a 40 cm. × 25 mm. column filled with 7–10 mesh activated alumina. The column was heated to 400°, with an exit pressure of 2–5 mm. and an inlet pressure of 15–20 mm. The tendency of the product to crystallize in the condenser below the column caused some difficulty.

From the Dry Ice trap protecting the vacuum pump approximately one-third of the toluene and 8 ml. (53%) of water were isolated. Addition of 500 ml. of methanol to the toluene solution of the product caused 46.2 gm. of white crystals, m.p. 74–76°, to form. By removing all the solvent *in vacuo* from the mother liquor, and treating the oily residue with methanol, an additional 34.1 g. of product was obtained, giving a total yield of 38%.

Acknowledgment. We wish to thank Dr. Murray Taylor of this laboratory for the microanalyses reported, and Mr. Harry Goldberg and Miss Carolyn Aldrich for measurements of infrared spectra.

SEATTLE, WASH.

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

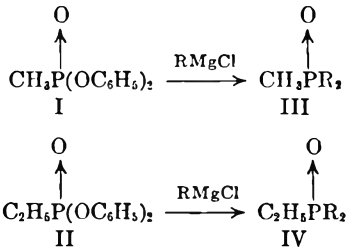
The Formation of Linear Polymers from Diene Monomers by a Cyclic Polymerization Mechanism. VII. Phosphorus-Containing Dienes[1]

K. DARRELL BERLIN[2] AND GEORGE B. BUTLER

Received May 9, 1960

Two unsymmetrical trialkylphosphine oxides, dimethallylmethylphosphine oxide and dimethallylethylphosphine oxide, have been synthesized. Polymerization of these monomers was initiated with α,α'-azobisisobutyronitrile and afforded soluble polymers. An intrinsic viscosity determination on a sample of poly(dimethallylmethylphosphine oxide) indicates it is of low molecular weight. Conversions to polymer are low for both oxides, and it is suggested that the presence of a large number of active hydrogen substituents may cause excessive degradative chain transfer.

The formation of linear polymers, *via* cyclic polymerization, from certain unsaturated, tertiary phosphine oxides has been reported from two independent studies.[3,4] Extension of this idea to include unsymmetrical trialkylphosphine oxides prompted this investigation. Dimethallylmethylphosphine oxide(III) and dimethallylethylphosphine oxide(II) were synthesized by treatment of the appropriate phosphonate with an excess of the methallyl Grignard reagent under forcing conditions. The yields approximated 50% in both cases. Preparation of diphenylmethylphosphonate (I)



R = Methallyl

was by the method recorded in the literature.[5] The scheme below afforded diphenyl ethylphosphonate (II)[6,7] in an overall yield of 36%.

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(1) This research was supported by the United States Air Force through the Air Force Office of Scientific Research of the Air Research and Development Command, under Contract Number AF 33(616)-5616, Part I. Reproduction in whole or in part is permitted for any purpose of the United States government.

(2) Post-doctoral Fellow, 1958–1960; present address: Department of Chemistry, Oklahoma State University, Stillwater, Okla.

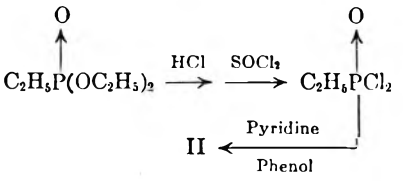
(3) K. D. Berlin and G. B. Butler, *J. Am. Chem. Soc.*, 82, 2712 (1960).

(4) C. G. Gebelein and E. Howard, Jr., Abstracts of Papers, Third Delaware Regional Valley Regional Meeting, Philadelphia, February 25, 1960, p. 79.

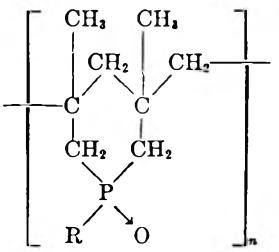
(5) P. W. Morgan and B. C. Herr, *J. Am. Chem. Soc.*, 74, 4526 (1952).

(6) A. E. Arbuzov and L. V. Nesterov, *Doklady Akad. Nauk S.S.S.R.* 92, 57 (1953); *C.A.* 48, 10538 (1954).

(7) A. E. Arbuzov and L. V. Nesterov, *Izvest Akad. Nauk S.S.S.R. Otdel Khim Nauk* 427 (1954); *Chem. Abstr.*, 49, 9541 (1955).

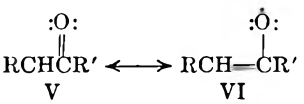


Treatment of dimethallylmethylphosphine oxide (III) in bulk with catalytic amounts (up to 5%) of benzoyl peroxide apparently initiated little or no polymerization as unreacted monomer could be recovered in high yield. This is in contrast to the behavior of diallyphenylphosphine oxide and dimethallylphenylphosphine oxide.[3] The highest conversions of the trialkylphosphine oxides III and IV to soluble polymers were obtained by using azobisisobutyronitrile (5%) at a temperature of 110°. That poly(dimethallylmethylphosphine oxide) was not of high molecular weight was inferred by a low value (0.042) for its intrinsic viscosity. Infrared data demonstrate the existence of a small amount of residual unsaturation. Intramolecular cyclization during propagation would give polymers of the following structure.



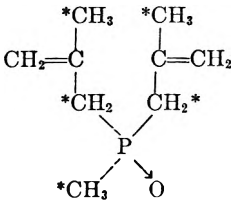
R = CH_3, C_2H_5

The small conversions of monomers with azobisisobutyronitrile as well as the negative results with benzoyl peroxide can probably be explained *in part* as another example of degradative chain transfer. In addition to the increased reactivity of hydrogen atoms on a carbon atom adjacent to a carbonyl function,[8,9,10] the stability of the radical resulting from hydrogen abstraction is well known.[11,12] Stabilization *via* the following contributing forms V and VI was postulated.[12] Alkylation



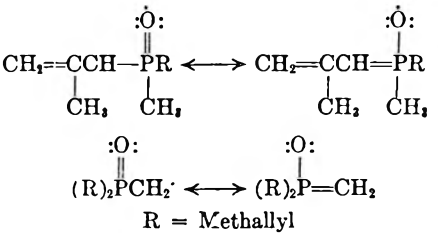
of certain phosphonates, such as tetraethyl methanediphosphonate, attests to the activating influence of a phosphoryl group on flanking methylene hydrogen atoms.[13,14]

The trialkylphosphine oxides encountered in this study possess hydrogen activated by unsaturated functions. For example, any of the carbon atoms marked by an asterisk in dimethallylmethylphosphine oxide (IIIa) might lose a hydrogen atom[15] to produce a radical which could be stabi-



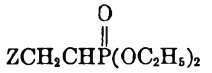
IIIa

lized through interaction with a carbon-carbon double bond and/or through an enolic structure involving the phosphoryl group. Delocalization of the former type is well known in the polymerization of allyl compounds.[16] The enolic forms would include species which may also contribute to the overall phenomena of autoinhibition:



R = Methallyl

Objections to this kind of delocalization have been expressed.[17] Attempts to copolymerize diethyl vinylphosphonate with styrene resulted in the incorporation of only a small amount of the phosphonate in the polymer. As a partial explanation it was suggested that the radical VII may not receive



VII

Z = Initiating radical

additional stabilization through enolic structures due to difficulty in creating carbon-phosphorus double bonds. A previous report indicated that the phosphonate did polymerize, however, but no conditions were presented.[18] Recent developments have established that carbon-phosphorus double bonds do exist and that the phosphorus-oxygen linkage does have some double-bond character

(8) N. G. Gaylord and F. R. Eirich, *J. Am. Chem. Soc.*, 74, 337 (1952).

(9) M. S. Kharasch, J. Kuderna, and W. Nudenberg, *J. Org. Chem.*, 18, 1225 (1953).

(10) P. Gray and A. Williams, *Chem. Revs.*, 59, 267 (1959).

(11) C. Walling, *Free Radicals in Solution*, John Wiley and Sons, Inc., New York, 1957, p. 276.

(12) T. M. Patrick, Jr., *J. Org. Chem.*, 17, 1269 (1952).

(13) G. M. Kosolapoff and J. S. Powell, *J. Am. Chem. Soc.*, 72, 4198 (1950).

(14) G. M. Kosolapoff, *J. Am. Chem. Soc.*, 75, 1500 (1953).

(15) This could result from abstraction of hydrogen by the radical produced by decomposition of the initiator or by the radical generated during propagation.

(16) R. C. Labile, *Chem. Revs.* 58, 807 (1958).

(17) C. L. Arcus and R. J. S. Matthews, *J. Chem. Soc.*, 4607 (1956).

(18) G. M. Kosolapoff, *J. Am. Chem. Soc.*, 70, 1971 (1948).

reminiscent of a carbonyl function.[19] More recently it was found that di-*n*-propenylphenylphosphine oxide and diisopropenylphenylphosphine oxide could not be obtained by a Grignard reaction as the oxides polymerized *in situ* to give both soluble and insoluble polymers.[4]

EXPERIMENTAL[20]

Diethyl ethylphosphonate. This chemical was obtained from the Victor Chemical Company.

Diphenyl methylphosphonate. Diphenyl methylphosphonate was prepared in a manner similar to that described in the literature[5] with a few modifications which improved the yield slightly.

A mixture consisting of 155.0 g. (0.5 mole) of triphenyl phosphite, 71.0 g. (0.5 mole) of methyl iodide, and several boiling chips, was warmed slowly until a reaction began. After 48 hr. at reflux, the mixture was allowed to cool to room temperature whereupon it solidified. The solid was washed with dry ether and was decomposed (cautiously) in the following manner: 200 ml. of 10% aqueous sodium hydroxide was added slowly with cooling and stirring; 200 ml. of 5% aqueous sodium hydroxide was added, and the entire mixture was transferred to a separatory funnel. When excessive base was used or when the decomposition was effected without cooling, the yield of phosphonate was decreased presumably through saponification. The brown-colored mixture was extracted rapidly with four 200-ml. portions of ether. The ether solution was dried over sodium sulfate. Evaporation of the ether left an oil which was fractionated to give 86.8 g. (70%) of colorless diphenyl methylphosphonate, b.p. 145–148° (0.4 mm.); n_D^{21} 1.5519. The reported boiling point is 151° (0.8 mm.).[5]

Dimethallylmethylphosphine oxide. The general procedure was the same as that described previously in the preparation of dimethallylphenylphosphine oxide.[3]

To the methallyl Grignard reagent, prepared from 72.0 g. (3.0 g. atom) of magnesium and 181.0 g. (2.0 moles) of methallyl chloride in 1200 ml. of dry ether, was added a solution of 49.6 g. (0.2 mole) of diphenyl methylphosphonate in 400 ml. of dry benzene. The reaction mixture was decomposed and worked up in the usual manner, and the organic solvents were distilled. Careful fractionation of the residual oil gave 19.0 g. (57.5%) of dimethallylmethylphosphine oxide which distilled at 135–141° (2 mm.). The average yield in several runs was 50%. The oxide is extremely hygroscopic and was dried in a vacuum oven over phosphorus pentoxide for a month. The infrared spectrum[21] has peaks which can be ascribed to aliphatic hydrogen (2900 cm.$^{-1}$), a carbon-carbon double bond (1645 cm.$^{-1}$), a methyl-phosphorus linkage (1290 cm.$^{-1}$), a phosphoryl group (1185 cm.$^{-1}$), and a terminal methylene function (890 cm.$^{-1}$). There is also absorption of medium intensity at 1450 (broad), 1370, and 715 cm.$^{-1}$ (broad) as well as a small peak for water.

Anal.[22] Calcd. for $C_9H_{17}OP$: C, 62.79; H, 9.88; P, 18.02. Found: C, 62.56; H, 9.82; P, 17.40, 17.98.

Diphenyl ethylphosphonate. Although this compound has been reported previously, the procedures have involved the preparation of several uncommon intermediates at high temperatures.[6,7] The following procedure does not give superior yields but it can be carried out with general laboratory equipment and readily available starting materials.

Diethyl ethylphosphonate (166.0 g., 1.0 mole) was hydrolyzed with boiling, concd. hydrochloric acid (150 ml.) over a 16-hr. period. To the mixture was added a solution of benzene-toluene (100 ml.–50 ml.), and the water was azeotroped from the reaction flask. A white solid separated from the mixture upon cooling. An excess of thionyl chloride (216 ml.) was added to the solid and, as a reaction appeared to occur immediately, the solution was allowed to stand at room temperature for 12 hr. and was then refluxed for 4 hr. Excess thionyl chloride was removed under aspirator pressure, and the residual oil was fractionated. The acid chloride, which was faint-yellow in color, distilled at 56–60° (2.5 mm.); yield, 92.0 g. (62.5%). Bands for aliphatic hydrogen (2950 cm.$^{-1}$) and a phosphoryl group (1275 cm.$^{-1}$ are present in the infrared spectrum. Absorption is also evident at 1460, 1245, 750, and 715 cm.$^{-1}$

To the acid chloride in 250 ml. of dry ether was added, with cooling and stirring, a solution of 116.5 g. (1.24 moles) of phenol in 97.9 g. (1.24 moles) of pyridine. A cloudiness appeared in the mixture, and a precipitate began to settle almost immediately. The addition required 1 hr. and stirring was continued for another 4 hr. at room temperature. The pyridine hydrochloride was filtered, and the ether was evaporated. Diphenyl ethylphosphonate distilled at 159–161° (1–2 mm.), n_D^{21} 1.5453; yield 94.2 g. (57% based on the acid chloride or 36% based on the diethyl ethylphosphonate converted). The reported boiling point is 202° (13 mm.), n_D^{20} 1.5451.[8] The results were obtained from only one run, and undoubtedly they could be improved by meticulous purification at each stage. The infrared spectrum of this phosphonate is similar to the spectrum of diphenyl methylphosphonate. The ethyl compound has bands which can be assigned to aromatic hydrogen (3050 cm.$^{-1}$), aliphatic hydrogen (2950 cm.$^{-1}$) and a phosphoryl function (1200 cm.$^{-1}$, broad). Bands of strong intensity are also present at 1290, 1270, 1160, 930, 770, and 690 cm.$^{-1}$ (probably monosubstituted phenyl).

Dimethallylethylphosphine oxide. The methallyl Grignard reagent was prepared[3] from 72.0 g. (3.0 g.-atoms) of magnesium and 181.0 g. (2.0 moles) of methallyl chloride in 1500 ml. of dry ether. To the Grignard mixture was added a solution of 52.0 g. (0.2 mole) of diphenyl ethylphosphonate in 175 ml. of dry benzene. The procedure from this point was identical with that described in the preparation of dimethallylphenylphosphine oxide.[3] Fractionation of the crude oil gave 16.0 g. (43%) of a colorless oil which distilled at 115–118° (0.3 mm.). In several runs the yields ranged from 40 to 50%. This oxide is also very hygroscopic, and the compound partially solidified after being placed in a vacuum oven with phosphorus pentoxide for one month. An infrared analysis revealed absorption for aliphatic hydrogen (2900 cm.$^{-1}$), a carbon-carbon double bond (1640 cm.$^{-1}$), a phosphoryl group (1180 cm.$^{-1}$), and a terminal methylene function (890 cm.$^{-1}$). There are bands at 1550, 1375, 1040, and 875 cm.$^{-1}$ of medium to strong intensity. The presence of water was indicated by a small peak near 3300 cm^{-1}.

Anal. Calcd. for $C_{10}H_{19}OP$: C, 64.51; H, 10.21; P, 16.66. Found: C, 64.49; H, 10.32; P, 16.46.

Polymerizations. Attempts to polymerize dimethallylmethylphosphine oxide in bulk failed with benzoyl peroxide at 75° at concentrations up to 5% catalyst and for as long as 30 days. Oils resulted from which a large amount of unchanged oxide could be recovered. This behavior was unlike that of diallylphenylphosphine oxide and dimethallylphenylphosphine oxide both of which polymerized under the above conditions.[3] It was possible to obtain soluble polymers from both of the trialkylphosphine oxides, however, and the data can be found in Table I.

Poly(dimethallylmethylphosphine oxide). A general procedure for the preparation of the polymers was as follows: A sample of monomer and catalyst were placed in a glass tube, one end of which was sealed. To the other end of the

(19) P. C. Crofts, *Quart. Revs.*, 12, 341 (1958), see pages 45–347.

(20) All melting points are corrected. All boiling points are uncorrected.

(21) The infrared spectra were recorded by Mr. Leo Pijanowski, Jr., and Miss Anna M. Yoakum on a Perkin-Elmer Model 21.

(22) The microanalyses were preformed by Galbraith Laboratories, Knoxville, Tenn.

TABLE I

POLYMERIZATION DATA

Monomer	Initiator	Wt. g. Monomer	Wt. g. Initiator	Temp.	Time	Intrinsic[b] Viscosity	Yield, %	M.P. of Polymer
I	[a]	6.5871	0.2632	110°	10 days	0.042	15.0	150–160°
I	[a]	9.8249	0.4910	110°	15 days	[c]	15.2	162–170°
II	[a]	12.1216	0.4848	110°	10 days	[c]	4.0	141–152°
II	[a]	12.3215	0.6160	110°	15 days	[c]	4.7	130–140°
II	[a]	6.3001	0.3150	110°	30 days	[c]	5.5	165–185°

[a] α,α'-Azodiisobutyronitrile. [b] In alcohol at 30°; concentrations of solutions were less than 1%, and the flow times were obtained in a modified Ubbelohde viscometer. [c] Not determined.

tube was attached a condenser and nitrogen inlet. The polymerization mixture was maintained at 110°. Partial purification of the polymers was achieved by dissolving the crude solid in a minimum of absolute alcohol and reprecipitating with dry ether. Poly(dimethallylmethylphosphine oxide) is soluble in alcohol and acetic acid. The infrared spectrum indicates the presence of some residual unsaturation by a small peak at 1640 cm.$^{-1}$ Additional data can be found in Table I. Although the polymer did not appear to be hygroscopic, the analytical results checked well for a monohydrate.

Anal. Calcd. for $(C_9H_{17}OP)_n$: C, 62.79; H, 9.88; Calcd. for $(C_9H_{17}OP\cdot H_2O)_n$: C, 59.99; H, 10.55; Found: C, 59.34, 59.95, H. 10.01, 9.89.

Poly(dimethallylethylphosphine oxide). The polymer was prepared and purified as described above; it is also soluble in alcohol and acetic acid. A small peak for the carbon-carbon double bond (1640 cm.$^{-1}$) can be found in the infrared spectrum, but no band is evident for a terminal methylene function (890 cm.$^{-1}$). Table I contains further experimental details. This polymer also had an analysis consistent with a monohydrate but it was not hygroscopic.

Anal. Calcd. for $(C_{10}H_{19}OP)_n$: C, 64.51; H, 10.21; P, 16.66. Calcd. for $(C_{10}H_{19}OP\cdot H_2O)_n$: C, 58.82; H, 9.31; P, 14.21. Found: C, 59.18, 59.17; H, 10.26, 9.99; P, 13.18.

GAINESVILLE, FLA.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, LAFAYETTE COLLEGE]

The Preparation of Aryl Difluoromethyl Ethers[1]

THOMAS G. MILLER AND JOHN W. THANASSI

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Aryl difluoromethyl ethers may be prepared in acceptable yields by the reaction of chlorodifluoromethane with phenols in an aqueous dioxane solvent and in the presence of an excess of sodium hydroxide. Aryl orthoformates are formed as by-products. Difluoromethylene, the reactive intermediate in the synthesis, affords only *O*-alkylation of the aryloxide ion in contrast to dichloromethylene which, in the Reimer-Tiemann synthesis, causes considerable C-alkylation.

Previous methods for the preparation of α-fluoroethers have involved replacement of chlorine and bromine in ethers by fluorine, addition of metal alcoholates to fluorine-containing olefins, electrochemical fluorination of ethers, and the reaction of metal alcoholates with saturated, fluorine-containing carbon compounds.[2] The latter method when used with halogenated ethanes and propanes often proceeds through a dehydrohalogenation step, and thus resembles the method of addition of metal alcoholates to fluoroolefins.[3] Alkyl difluoromethyl ethers have been prepared by the reaction of metal alcoholates with difluoromethylene generated by treatment of bromo- or chlorodifluoromethane with a strong base.[4] One aryl difluoromethyl ether, α,α-difluoroanisole, was reported to have been prepared in 28% yield from dibromodifluoromethane and potassium phenoxide.[5] The stoichiometry of this reaction is not obvious, and no equation was given in the brief note.

It has now been found that the reaction of phenols with chlorodifluoromethane, under conditions favorable for the Reimer-Tiemann reaction between phenols and chloroform, gives acceptable yields of aryl difluoromethyl ethers (Table I). Appreciable quantities of the corresponding orthoformate esters were also formed in the reaction and were isolated and characterized in several cases. In no instance could any carbonyl compounds be detected by testing the neutral products or the aqueous mother liquor with 2,4-dinitrophenylhydrazine reagent.[8]

(1) This work was supported by a grant, NSF-G6578, from the National Science Foundation.

(2) W. H. Pearlson in J. H. Simons (ed.), *Fluorine Chemistry*, Academic Press, Inc., New York, 1950, Vol. I, p. 486.

(3) (a) P. Tarrant and J. A. Young, *J. Am. Chem. Soc.*, **75**, 932 (1953); (b) E. T. McBee and R. O. Bolt, *Ind. Eng. Chem.*, **39**, 412 (1947).

(4) (a) A. L. Henne and M. A. Smook, *J. Am. Chem. Soc.*, **72**, 4378 (1950); (b) J. Hine and J. J. Porter, *J. Am. Chem. Soc.*, **79**, 5493 (1957).

(5) R. F. Clark and J. H. Simons, *J. Am. Chem. Soc.*, **77**, 6618 (1955).

TABLE I

ARYL DIFLUOROMETHYL ETHERS (AR-O-CHF_2)

Ar-	Yield, %	d_4^{20}	n_D^{20}	MR Calcd.[a]	MR Obs.
Phenyl-[b]	65	1.183	1.4473	32.71	32.57
p-Tolyl-	66	1.133	1.4531	37.55	37.74
p-Methoxyphenyl-	53	1.239	1.4671	38.99	38.99
p-Nitrophenyl	9.5	—	—	—	—
2,4-Xylyl-	56	1.119	1.4591	41.97	42.03
2,4-Dichlorophenyl-	44	1.441	1.4897	42.45	42.71
2-Naphthyl-	66	1.242	1.5527	[c]	50.02

[a] Atomic refractivities used, except for fluorine, are those of ref. 6. A value of 1.18 was used for fluorine (ref. 4b). [b] The authors of ref. 5 report d_{25} 1.171, n_D^{25} 1.4400, MR calcd. 32.35, MR obs. 32.58. Sources for the atomic refractivities used were not given. [c] It is difficult to calculate a meaningful value for the MR of new naphthalene derivatives, as the exaltation for the naphthalene ring varies widely with the substituents present (ref. 7). The physical constants obtained indicate an exaltation of 1.95 for the ring in the difluoromethyl ether.

The identity of the difluoromethyl ethers was established by means of the elemental analyses, molecular refractivities, and infrared spectra.[9] Satisfactory analytical results were difficult to obtain. This was due apparently to the nature of the compounds themselves, as agreement between duplicate analyses was usually poor. The infrared spectra are characterized in each case by three strong absorption bands at *ca.* 1220, 1130, and 1040 cm.$^{-1}$ Assignment of the 1130 cm.$^{-1}$ band to the C—F linkage and the 1220 cm.$^{-1}$ band to the Ar—O linkage can be made with confidence.[10] The absorption at 1040 cm.$^{-1}$ is probably the result of the combination of two or more separate bands.

Like the α,α-difluoroanisole reported by Clark and Simons,[5] the aryl difluoromethyl ethers listed in Table I are stable when purified, and can be stored for extended periods at room temperature without noticeable decomposition. Unpurified ethers, or those to which traces of strong acids have been added, decompose rapidly with evolution of hydrogen fluoride and development of a red coloration and black tars. No qualitative difference in stability was noted between the negatively substituted ethers and those having electron-donating substituents which would be expected to render the ether group more susceptible to attack by acids. As the method of preparation suggests, the ethers are relatively stable in the presence of hot, aqueous alkalies. In contrast, the alkyl counterparts usually decompose on standing[4a,b] although difluoromethyl isopropyl ether is reportedly stable at 50°.[11]

The reaction of chlorodifluoromethane with phenols under conditions favorable to the Reimer-Tiemann reaction affords a comparison of the behavior of the dihalomethylenes, difluoromethylene, and dichloromethylene.[12] The latter is accepted as the reactive intermediate in the Reimer-Tiemann reaction,[13] and the former has been demonstrated to be the electrophilic species in the reaction of sodium methoxide with chlorodifluoromethane.[4b] There is little doubt that difluoromethylene is also involved in the preparation of aryl difluoromethyl ethers, because yields of ethers and conversion of chlorodifluoromethane are both greatly reduced for a given reaction time, when only a small instead of a large excess of sodium hydroxide is used. As the analogy to the work of Hine and Porter is close,[4b] it seems probable that the following equations described the course of the reaction:

$$HCClF_2 + OH^- \rightleftharpoons H_2O + :CF_2 + Cl^-$$

$$ArO^- + :CF_2 \longrightarrow ArO\bar{C}F_2$$

$$ArO—\ddot{C}\bar{F}_2 + H_2O \longrightarrow ArOCHF_2 + OH^-$$

That nuclear alkylation of phenoxide ions occurs to a considerable extent with dichloromethylene and not at all with difluoromethylene may result because the latter is significantly less electrophilic than the former.[14] Only the more reactive alkyl halides are capable of effecting C-alkylation of phenols.[15] *O*-alkylation by dichloromethylene has not been excluded as a side reaction during the Reimer-Tiemann synthesis of hydroxyaldehydes. In fact, the isolation of the orthoformate ester from such a reaction definitely suggests this possibility.[16]

(6) K. Fajans in A. Weissberger (ed.), *Physical Methods of Organic Chemistry*, 2nd ed., Interscience Publishers, New York, 1949, Vol. 1, Part I, p. 1162.

(7) K. von Auwers and A. Fruhling, *Ann.*, 422, 192 (1921).

(8) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *The Systemic Identification of Organic Compounds*, 4th ed., John Wiley & Sons, Inc., New York, 1956, p. 111.

(9) The authors are indebted to Edward J. Pugh of the Kirby Health Center, Wilkes-Barre, Pa., for the infrared spectra.

(10) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, 2nd ed., John Wiley & Sons, New York 1958, p. 329, 117.

(11) J. Hine and K. Tanahe, *J. Am. Chem. Soc.*, 79, 2654 (1957).

(12) Aqueous dioxane, the solvent employed in this work, is not a commonly-used solvent for Reimer-Tiemann synthesis. In order to test the suitability of this medium, an experiment was carried out under the conditions described in the Experimental for the preparation of difluoromethyl ethers, in which an equimolar amount of chloroform was substituted for the chlorodifluoromethane and 2-naphthol was used as the phenolic reactant. The yield of purified 2-hydroxy-1-naphthaldehyde was 47%, which is comparable to the best yields obtained by others under different conditions—see A. Russell and L. B. Lockhart, *Org. Syntheses*, Coll. Vol. III, 463 (1955).

(13) H. Wynberg, *J. Am. Chem. Soc.*, 76, 4998 (1954).

(14) J. Hine and S. J. Ehrenson, *J. Am. Chem. Soc.*, 80, 824 (1958).

(15) L. F. Fieser in H. Gilman (ed.), *Organic Chemistry*, 2nd ed., John Wiley & Sons, Inc., New York, 1943, p. 190, and references therein.

(16) D. E. Armstrong and D. H. Richardson, *J. Chem. Soc.*, 496 (1933).

That dichloromethyl ethers are not isolated is readily explained by their known hydrolytic instability.[17] The occurrance of extensive *O*-alkylation by dichloromethylene during the Reimer-Tiemann synthesis would help to explain the customary low yields of hydroxyaldehyde and the recovery of large amounts of the phenol used as the starting material in the reaction.

A mixed dioxane-water solvent is necessary for the preparation of aryl difluoromethyl ethers by the method described in the Experimental.[18] In most cases the trihalomethane reacted completely, either by formation of the ether or by hydrolysis. One experiment in which the dioxane was omitted, however, gave only a negligible yield of neutral reaction products, and 73% of the chlorodifluoromethane passed was recovered unreacted. The exact role of the dioxane is unknown. Solubility considerations may be paramount; however, it has been found that hydrolysis rates of some haloforms are considerably greater in a 67% dioxane-water solution than in water alone, even under conditions where solubility is not a factor.[14] Utilization of the chlorodifluoromethane was also only 45% complete if the phenol were omitted from the reaction mixture.

The phenolic reactant was not in any case completely accounted for by recovered difluoromethyl ether and the orthoformate still-residues. As tests on all fractions for carbonyl compounds were negative, it appears likely that unaccounted-for phenols were unchanged and lost in the aqueous fractions.

EXPERIMENTAL[19]

General procedure for aryl difluoromethyl ethers. The following general procedure was used for the preparation of all of the aryl difluoromethyl ethers. Comments on individual preparations are given under separate headings.

A mixture of 0.51 mole of the phenol, 103 g. of sodium hydroxide, 125 ml. of water, and 150 ml. of dioxane was prepared in a four-necked flask equipped with thermometer, stirrer, gas-inlet tube extending below the liquid surface, and reflux condenser to which a Dry-Ice trap was connected through calcium chloride and Drierite drying tubes. The temperature was adjusted to 68–70° and chlorodifluoromethane was introduced, with vigorous agitation, at the rate of 0.91 g./min. until 65 g. had been added. The mixture was allowed to cool to room temperature, then diluted with 500 ml. of water. One hundred milliliters of ether was added and the mixture was filtered to remove precipitated inorganic salts which if not separated caused emulsification of the water and ether layers. After the organic layer was separated, the water layer was extracted with three 100-ml. portions of ether. The combined ether solutions were then extracted with five 100-ml. portions of water and dried over potassium carbonate. After distillation of the ether, the remaining liquid was fractionated through a 22-cm. column packed with stainless-steel sponge.

α,α-Difluoroanisole. No unchanged chlorodifluoromethane was recovered in the cold trap. Acidification of the aqueous, alkaline mother liquor produced 1 g. of unchanged phenol. The ether boiled at 37° (13 mm.), and had a hydrocarbon-like odor.

Anal. Calcd. for $C_7H_6F_2O$: C, 58.33; H, 4.20; F, 26.37. Found: C, 58.04; H, 4.42; F, 26.95.

The distillation residue contained an appreciable amount of a solid, presumably the ortho ester, which could not be purified due to decomposition accompanied by tar-formation and evolution of hydrogen fluoride by other compounds present.

α,α-Difluoro-4-methylanisole. Complete reaction of chlorodifluoromethane was indicated by the absence of the condensed gas in the Dry Ice trap, and no unchanged *p*-cresol was precipitated on acidification of the aqueous mother liquor. The ether, possessing a sweet fruity odor, boiled at 28–29° (3 mm.).

Anal. Calcd. for $C_8H_8F_2O$: C, 60.76; H, 5.10; F, 24.03. Found: C, 61.08; H, 5.08; F, 23.88.

The distillation residue of *ca.* 10 ml. solidified on cooling, but purification of the ortho ester could not be effected.

A second run, identical with the first except that the temperature was held at 50 ± 2° and rate of addition of chlorodifluoromethane was halved, yielded 53% of the ether. From the aqueous mother liquor 16.7 g. of unrecovered *p*-cresol was isolated by acidification and extraction with ether. The recovered phenol did not contain carbonyl compounds (test with 2,4-dinitrophenylhydrazine) or combined fluorine (ref. 8, p. 62).

A third run, carried out by the general procedure, except that no dioxane was used, resulted in recovery of 73% of the chlorodifluoromethane. The yield of crude, neutral products was 2.5 g.

2,4-Dichloro-α,α-difluoroanisole. A voluminous, white precipitate, the ortho ester (see below), appeared during the reaction of 2,4-dichlorophenol and chlorodifluoromethane. This was removed along with inorganic salts by filtration of the water-ether mixture (see general procedure). The ether boiled at 117° (42 mm.) and possessed a fruity odor. There was no unchanged 2,4-dichlorophenol in the aqueous mother liquor, and no chlorodifluoromethane was collected in the cold trap.

Anal. Calcd. for $C_7H_4Cl_2F_2O$: C, 39.46; H, 1.89; Cl, 33.29; F, 17.84. Found: C, 39.73; H, 2.28; Cl, 33.75; F, 17.53.

Tris(2,4-dichlorophenyl) orthoformate. The white solid which appeared during the preparation of 2,4-dichloro-α,α-difluoroanisole was removed by filtration and triturated with water to remove inorganic salts. A second portion of the orthoformate was recovered from the residue from the distillation of the corresponding difluoromethyl ether. The total weight of crude orthoformate was 55.4 g. Crystallization from ethyl acetate (low recovery) gave fine, white, hair-like crystals melting at 205.5–206° (reported,[20] m.p. 201–202°). The melting point was undepressed when this compound was mixed with a sample prepared by the method of ref. 20.

Anal. Calcd. for $C_{19}H_{10}Cl_6O_3$: C, 45.78; H, 2.02; Cl, 42.63. Found: C, 46.01; H, 2.18; Cl, 42.23.

2-Difluoromethoxynaphthalene. The neutral reaction products, after removal of the solvent ether, were dissolved in petroleum ether (b.p. 30–60°) and the solution chilled to 0°. The precipitated ortho ester was removed by filtration. Distillation of the petroleum ether from the filtrate and fractionation of the residue gave the difluoromethyl ether, b.p. 128–130° (14 mm.), a sweet-smelling liquid which solidified easily when chilled.

No unchanged chlorodifluoromethane was collected in

(17) C. Weygand and K. Vogel, *J. prakt. Chem.*, 155, 342 (1940).

(18) There is no particular reason to believe that solvents other than aqueous dioxane would not suffice. No others were examined, however.

(19) All melting and boiling points are corrected for stem exposure.

(20) A. Jonsson, *Acta Chem. Scand.*, 7, 596 (1953).

the cold trap, and only 2.2 g. of *n*-naphthol was recovered by acidification of the aqueous mother liquor.

Anal. Calcd. for $C_{11}H_8F_2O$: C, 68.02; H, 4.17; F, 19.57. Found: C, 68.38; H, 4.21; F, 18.92.

Tris(2-naphthyl) orthoformate. Crystallization of the crude orthoformate (for separation from the corresponding difluoromethyl ether, see above) from a mixture of toluene and hexane gave 5.2 g. of fine, white needles melting at 137–150°. The melting-point range was not narrowed by repeated crystallization from other solvents such as ethyl alcohol and isopropyl alcohol–toluene. Analytical data, solubility and chemical behavior, and the infrared spectrum are consistent with the assigned orthoformate structure.

Anal. Calcd. for $C_{31}H_{22}O_3$ C, 84.14; H, 5.02. Found: C, 84.05; H, 5.22.

α,α-Difluoro-2,4-dimethylanisole. The 2,4-xylenol was purchased from the Eastern Chemical Corp. At the end of the reaction there was no recovered chlorodifluoromethane in the cold trap, and the aqueous mother liquor gave no phenolic precipitate on acidification. The ether, a fruity-smelling liquid, boiled at 70° (12 mm.). A sizeable distillation residue underwent rapid decomposition, preventing isolation of the ortho ester.

Anal. Calcd. for $C_9H_{10}F_2O$: C, 62.78; H, 5.87; F, 22.07. Found: C, 62.58; H, 6.06; F, 21.82.

α,α-Difluoro-4-nitroanisole. The sodium salt of *p*-nitrophenol has very limited solubility in strong sodium hydroxide solutions. Consequently, agitation in this experiment was very inefficient, and the low yield of difluoromethyl ether obtained doubtless reflects this condition as well as any inherent lower reactivity of the *p*-nitrophenoxide ion. Twenty-one per cent of the chlorodifluoromethane was recovered unchanged in the cold trap, and acidification of the water layer yielded 50% of unchanged *p*-nitrophenol. The product was not distilled but was crystallized from petroleum ether (b.p. 30–60°) as shining, off-white plates, m.p. 32–32.5°.

Anal. Calcd. for $C_7H_5F_2NO_3$: C, 44.45; H, 2.67; F, 20.09; N, 7.41. Found: C, 44.68; H, 2.91; F, 20.37; N, 7.75.

1-Difluoromethoxy-4-methoxybenzene. Reaction of chlorodifluoromethane was complete as evidenced by the lack of any condensed gas in the cold trap. The product, a fruity-smelling liquid, boiled at 108° (29 mm.). A 10–12-g. residue remained after the distillation (see next section).

Anal. Calcd. for $C_8H_8F_2O_2$: C, 55.17; H, 4.63; F, 21.82. Found: C, 55.30; H, 4.87; F, 21.18.

Tris(p-methoxyphenyl) orthoformate. From the still residue left after distillation of the difluoromethyl ether 2 g. of the orthoester was isolated by crystallization from cyclohexane. The shining, white plates, melted at 50–51°.

Anal. Calcd. for $C_{22}H_{22}O_6$: C, 69.09; H, 5.80. Found: C, 68.82; H, 6.05.

EASTON, PA.

[CONTRIBUTION FROM ORGANIC CHEMISTRY BRANCH, CHEMISTRY DIVISION, U. S. NAVAL ORDNANCE TEST STATION]

Action of the Lewis Acids, Stannic Chloride and Boron Trifluoride, upon Nitrate Esters[1]

ROBERT BOSCHAN AND ABRAHAM LANDIS

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The action of the Lewis acids, stannic chloride and boron trifluoride, upon several representative nitrate esters, namely, *n*-butyl, isopropyl, benzyl, and triphenylmethyl nitrates, has been investigated. Products have been isolated and free-radical mechanisms have been postulated which fit the experimental observations.

In previous studies[2] involving the polymerization of glycidyl nitrate, it was found that denitration always occurred to some extent when this polymerization was catalyzed by stannic chloride. It seemed evident, therefore, that this observed denitration was due to some reaction involving the Lewis acid and the nitrate ester moiety of the glycidyl nitrate monomer or polymer. In an attempt to elucidate the nature of this Lewis acid nitrate ester interaction, a study of the action of stannic chloride and boron trifluoride upon model simple nitrate esters, namely, *n*-butyl, benzyl, isopropyl, and triphenylmethyl nitrate, was undertaken.

When equimolar amounts of *n*-butyl nitrate and stannic chloride were mixed at room temperature, a single phase resulted, and no immediate reaction was apparent. After about one hour, greenish-yellow crystals formed in the reaction mixture and gradually increased in amount. About four hours after mixing, a vigorous decomposition took place with evolution of much heat and gas. Infrared analysis of the gas fraction showed it to contain nitric oxide and possibly nitrous oxide. Since the gases were colorless, however, it was assumed that no nitrogen dioxide (or tetroxide) was present. Butyl butyrate was isolated in small amounts from the residue, which contained considerable amounts of tarry material. The greenish-yellow crystals which were deposited on the walls were identified as dinitrosyl hexachlorostannate, $(NO)_2SnCl_6$, by tin and chlorine analyses and by comparison of the x-ray powder patterns with that of an authentic sample prepared as described by Rheinboldt and Wasserfuhr[3] from nitrosyl chloride and stannic chloride.

Several attempts were made to determine the nature of any chemical change that might take place between the time of mixing of stannic chlo-

(1) Reported at the Tenth Meeting of the Joint Army–Navy–Air Force Solid Propellant Group at Wright Air Development Center, Dayton, Ohio, June 2–4, 1954.

(2) J. G. Meitner, C. J. Thelen, W. J. Murbach, and R. W. Van Dolah, unpublished work.

(3) H. Reinboldt and R. Wasserfuhr, *Chem. Ber.*, 60, 732 (1927).

ride and butyl nitrate and the time of the violet reactions.

The infrared spectrum of an equimolar mixture of butyl nitrate and stannic chloride remained essentially the same during the "induction period" of the reaction except for an over-all decrease in transmittance (due to fogging of the salt windows by stannic chloride). The only observed change was an increase in the peak at 2.9 μ in the OH stretch region.

Similarly, when aliquots of the reaction mixture taken during the induction period were poured into water and the organic materials extracted into petroleum ether, no substituents other than *n*-butyl nitrate could be found.

Other conceivable products, such as butyraldehyde, butyl butyrate, and butyl alcohol, would have been extracted into the petroleum ether. However there was no sign of any of these materials, and the infrared curve of all of these petroleum ether extracts was nearly identical with that of *n*-butyl nitrate. After the reaction had proceeded to the vigorous stage, water was added to the sirupy residue and the mixture extracted with petroleum ether to yield a material whose infrared spectrum was essentially that of *n*-butyl *n*-butyrate. Indeed, the only noticeable change was the production of a small amount of dinitrosyl hexachlorostannate in the gas phase above the reaction mixture. The fact that this reaction did occur in the gas phase was confirmed by conducting a run in a divided vessel where the liquids were not in contact with each other, but where their vapor phases could freely intermix. In this experiment, the reaction proceeded just as though the reactants were mixed, including the final violent reaction.

There appeared to be very little difference in the induction period of the reaction when the molar ratio of stannic chloride to butyl nitrate varied from 1:5 to 2:1.

The reaction of stannic chloride with benzyl nitrate was similar to that with butyl nitrate, except that the time between mixing and violent reaction was only a few minutes and their was no observed formation of dinitrosyl hexachlorostannate. The reaction seemed to be somewhat cleaner, as evidenced by higher yields of isolable products. Thus, benzaldehyde was isolated as its 2,4-dinitrophenylhydrazone in *ca.* 45% yield from this reaction. Benzaldehyde was likewise obtained as a product of the reaction of dinitrosyl hexachlorostannate upon benzyl nitrate.

The action of stannic chloride upon triphenylmethyl nitrate appeared to be somewhat anomolous. There appeared to be no interaction between stannic chloride and triphenylmethyl nitrate when the two were mixed; however, since these compounds are not miscible, a solvent (diethyl ether) was used. The reaction appeared to be cleaner than the other degradations studied, crude triphenylmethane being isolated in nearly quantitative yield.

The substitution of another powerful Lewis acid, boron trifluoride, for the stannic chloride led to analogous reactions with the nitrate esters of butyl alcohol, isopropyl alcohol, benzyl alcohol, and triphenyl carbinol. Thus, butyl butyrate was isolated in low yield from the reaction between *n*-butyl nitrate and boron trifluoride, benzaldehyde and benzoic acid from benzyl nitrate, triphenylmethane and triphenylcarbinol from triphenylmethyl nitrate, and acetone from isopropyl nitrate.

Any mechanism derived from the experimental facts can be, at best, highly speculative, but it seemed desirable to demonstrate that one could be derived which would fit the experimental observations. The choice between a free-radical and an ionic mechanism is not an obvious one. The observed induction periods and the explosions which occurred in certain instances seemed typical for a free-radical reaction, while the catalysis by strong electrophiles such as stannic chloride and boron trifluoride pointed to the possibility of an ionic type of formulation. The free radical mechanism is discussed here.

The reactions considered to be the important steps in the nitrate–ester–Lewis acid reaction are the following:

$$RCH_2ONO_2 + SnCl_4 \longrightarrow SnCl_4NO_2 + RCH_2O\cdot \quad (1)$$

$$SnCl_4NO_2 + RCH_2O\cdot \longrightarrow SnCl_4N(=O)(OH) + RCHO \quad (2)$$

I

$$SnCl_4N(=O)(OH) \longrightarrow SnCl_4 + NO + HO\cdot \quad (3)$$

$$NO + SnCl_4 \longrightarrow NOCl + \cdot SnCl_3 \quad (4)$$

$$2NOCl + SnCl_4 \longrightarrow (NO)_2SnCl_6 \quad (5)$$

$$RCH_2O\cdot + RCHO \longrightarrow RC(O\cdot)(H)-OCH_2R \quad (6)$$

$$RC(O\cdot)(H)-OCH_2R + SnCl_4NO_2 \longrightarrow RC(=O)-OCH_2R + SnCl_4N(=O)(OH) \quad (7)$$

It seems difficult to envision initiation to be other than the coordination of the nitrate ester group with the electrophile (stannic chloride in this case) and cleavage of the O—N bond as in step (1). For the propagation steps, the unstable intermediate I (reaction 2) has been postulated which can propagate by chain-branching step (3).

Additional chain-branching steps may be written, but these will not be considered here.

Termination steps may be induced from the initiation and propagation steps. Reactions (4) and (5) have been introduced to explain the formation of dinitrosyl hexachlorostannate.

The available evidence seems to point to a strong autocatalysis *via* various chain-branching steps. Thus the rate can become very fast after the reaction has proceeded only a very small extent.

The reaction of benzyl nitrate with stannic chloride to yield benzaldehyde may be formulated as in steps (1) and (2).

The products observed in the case of the boron trifluoride reactions can be explained by substitution of reactions similar to the initiation and propagation steps (1), (2) and (3).

The reaction between isopropyl nitrate and boron trifluoride was not very thoroughly investigated. The indications are that the reaction is fairly complex. However, acetone was identified as one of the products by its isolation in low yield as the 2,4-dinitrophenylhydrazone. The formation of acetone from isopropyl nitrate seems to be directly analogous to the formation of benzaldehyde from benzyl nitrate, and a similar sequence of reactions may be written.

The relatively high yields of triphenylmethane obtained from triphenylmethyl nitrate and either stannic chloride or boron trifluoride are attributed to the cleavage of the C—O bond of the triphenylmethyl nitrate in preference to the O—N bond, the resulting radical abstracting a hydrogen atom from the solvent:

$$(C_6H_5)_3CONO_2 + SnCl_4 \text{ (or } BF_3) \longrightarrow (C_6H_5)_3C\cdot + ONO_2SnCl_4 \text{ (or } ONO_2BF_3)$$

$$(C_6H_5)_3C\cdot + RH \longrightarrow (C_6H_5)_3CH + R\cdot$$

The triphenylcarbinol observed in the boron trifluoride-triphenylmethyl nitrate reaction very likely arose from the decomposition of the triphenylmethyl nitrate, as previously observed.[4,5]

Since this work was completed, an article has appeared in which the action of stannic chloride and of sulfuric acid upon ethyl nitrate was briefly studied.[6] The observations are very similar to those reported here, with the initial induction period and the final violent reaction yielding oxides of nitrogen.

EXPERIMENTAL

Reaction of n-butyl nitrate with stannic chloride. In order to have a sizable amount of the stannic chloride-butyl nitrate reaction product, twelve runs were made in the following manner: Stannic chloride, 13.02 g. (5.84 cc., 0.050 mole), and butyl nitrate, 5.97 g. (5.68 cc., 0.050 mole), were mixed and allowed to stand until the violent reaction took place (*ca.* 4 hr.). Each run was worked up as follows: The mixture was diluted with water and extracted with ether. To the mixture of ether, water, and reaction product was added solid sodium bicarbonate until carbon dioxide evolution ceased. The ether layer was removed, shaken once with saturated sodium bicarbonate solution, and dried over anhydrous magnesium sulfate. The ether extracts from all the runs were filtered and combined; and the ether was removed by distillation, the residue being transferred to a small distilling flask. In order to avoid polymerization observed in previous attempts to distill this product, the distillation was conducted at 1 mm. and the distillate, *ca.* 4.5 g., (10.4%) was collected in a Dry Ice trap, b.p. 30° (1 mm.), n_D^{20} 1.4047.[7] The infrared spectrum on this material was nearly identical with that of an authentic sample of *n*-butyl butyrate (prepared from *n*-butyl alcohol and *n*-butyryl chloride).

Saponification of stannic chloride-butyl nitrate reaction product. A sample of 1.00 g. of the product obtained above was added to a solution of 1.00 g. of sodium hydroxide and 20 cc. of water, and the mixture was refluxed 5 hr. The mixture was extracted with a total of 25 cc. of ether, and the extract was dried over anhydrous magnesium sulfate. The dried ether extract was filtered and the ether was removed by distillation. To the residue was added 1.00 g. of α-naphthyl isocyanate and this mixture was heated over the steam bath for 2 hr., after which time it was extracted with hot benzene. Evaporation of the benzene extract left an oil which gradually crystallized upon cooling. After one recrystallization from 10 cc. of ligroin (b.p. 60–80°) 0.48 g. of crystals, m.p. 65°, were collected, m.p. 70–71° after a second recrystallization, m.p. 70.5–71° when mixed with an authentic sample of *n*-butyl α-naphthyl urethan.

Isolation and characterization of the intermediate in the stannic chloride butyl nitrate reaction. The greenish-yellow solid from one of the butyl nitrate-stannic chloride runs was collected by filtering the reaction mixture through a sintered disk in a nitrogen atmosphere before the end of the induction period. This solid crystalline material vigorously evolved nitrogen dioxide upon addition of water. When aqueous silver nitrate was added to an acidified aqueous solution of this material, a precipitate of silver chloride appeared. Volhard titration of a sample showed it to contain 54.23% chlorine. A polarographic determination of tin showed the tin content to be 29.1 ± 0.9%.

Anal. Calcd. for $(NO)_2SnCl_6$: Cl, 54.34%; Sn, 30.32%.

Dinitrosyl hexachlorostannate. This compound was prepared by the procedure of Rheinboldt and Wasserfuhr.[8] To a solution of 0.05 mole (13.02 g., 5.84 cc.) of stannic chloride in 25 cc. of spectro grade carbon tetrachloride was added dropwise with agitation a solution of 0.20 mole (4.47 cc.) of purified nitrosyl chloride in 25 cc. of carbon tetrachloride. The nitrosyl chloride had been purified by two successive partial freezings and three distillations. A yellow-green precipitate appeared as the nitrosyl chloride was added. The product was filtered, taking precautions to exclude moisture, and was stored in a sealed ampoule. The x-ray powder pattern was identical with that of the product from the butyl nitrate-stannic chloride reaction.

Infrared study of the butyl nitrate-stannic chloride reaction. *n*-Butyl nitrate, 11.36 g. (0.10 mole), and stannic chloride, 11.68 g. (0.10 mole), were mixed and allowed to stand. Samples of 1.0 cc. of the mixture were removed at five different intervals throughout the induction period. To each sample was added 25 cc. of water and the mixture extracted with two 10-cc. portions of redistilled petroleum ether (b.p. 30–35°). The extracts were dried over anhydrous

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(6) R. A. Slavinskaya, *J. Gen. Chem. (U.S.S.R.)*, 27, 844 (1957).

(7) *Handbook of Chemistry and Physics*, 37th ed. 1955–56, Cleveland, Ohio, Chemical Rubber Publishing Co., p. 822, reported n_D^{20} for *n*-butyl butyrate 1.4049.

magnesium sulfate, filtered, and evaporated. The infrared curves on each extract were essentially the same and virtually identical with the spectrum of *n*-butyl nitrate.

After the violent reaction took place, the residue was extracted with petroleum ether and the nearly colorless extract was dried and evaporated. The infrared spectrum of the residue from this extraction indicated that it consisted essentially of *n*-butyl *n*-butyrate.

Reaction of benzyl nitrate with stannic chloride. Benzyl nitrate, 3.06 g. (0.02 mole), was placed in a glass ampoule and cooled for *ca.* 10 min. in Dry Ice. Stannic chloride, 2.34 cc. (5.21 g., 0.020 mole), was added; the mixture again cooled; and the ampoule sealed off while still immersed in Dry Ice. The mixture was allowed to warm to room temperature behind an explosion shield. As the stannic chloride melted into the benzyl nitrate, a dark layer developed. In a very short time, copious brown fumes (probably nitrogen dioxide) effervesced from the reaction mixture. Just as the gases filled the ampoule, there was a brilliant flash of light, followed by a loud detonation which powdered the glass in the ampoule, completely shattering it.

Products from the reaction of benzyl nitrate with stannic chloride. To 3.0 g. (0.20 mole) of benzyl nitrate was added 2.34 cc. (5.21 g., 0.020 mole) of stannic chloride. The induction period followed by vigorous effervescence, as previously described, was observed in a few minutes after mixing. Water was added and the mixture extracted with ether. The ether extract was dried and filtered and the ether distilled, leaving a residue smelling strongly of benzaldehyde. Addition of 2,4-dinitrophenylhydrazine reagent to an alcoholic solution of this residue precipitated 2.45 g. (44% based on benzaldehyde) of derivative, m.p. 220–223°; m.p. 230° after two recrystallizations from absolute ethanol; m.p. 230–235° when mixed with an authentic sample of benzaldehyde-2,4-dinitrophenylhydrazone.

Reaction of benzyl nitrate with dinitrosyl hexachlorostannate. To 4.0 g. of dinitrosyl hexachlorostannate was added 5.0 cc. of benzyl nitrate, and the mixture was allowed to stand for a week in a stoppered flask; it was then poured into water to decompose the residual solid material. The water solution was extracted with three portions (total 150 cc.) of petroleum ether (b.p. 30–60°), and the extracts dried and evaporated. The residue was made up to 100 cc. in a volumetric flask with absolute ethanol. A 20-cc. portion was treated with dinitrophenylhydrazine reagent to yield 0.43 g. of benzaldehyde-2,4-dinitrophenylhydrazone, m.p. 236–237°. This corresponds to a total of 2.15 g. of derivative or to 0.80 g. of benzaldehyde.

A polarographic determination of the product showed the ratio of benzyl nitrate to benzaldehyde to be 5:15. Thus, 4.12 g. of benzyl nitrate remained.

Reaction of triphenylmethyl nitrate with stannic chloride. Triphenylmethyl nitrate, 3.0 g. (0.098 mole), was dissolved in *ca.* 25 cc. of ether and 4 cc. of stannic chloride was carefully added. A vigorous reaction ensued (probably coordination of stannic chloride and diethyl ether); and after the stannic chloride was added, the ether was boiled for a few minutes, then poured into water. An oil formed which crystallized after *ca.* 1 hr. The crystals were filtered to yield 2.34 g. (97.5% crude yield) of dark crystals, m.p. 91°. The crystals were dissolved in hot alcohol, and the solution boiled with Norit, filtered, and cooled to yield 1.32 g. (55%) of white crystals, m.p. 93–94°. The melting point was unchanged when this material was mixed with an authentic sample of triphenylmethane (from hydrogenation of triphenylmethyl chloride).

Reaction of n-butyl nitrate with boron trifluoride. Into 3.0 ml. of *n*-butyl nitrate was passed a slow stream of boron trifluoride for *ca.* 3 hr. Ten cubic centimeters of petroleum ether was added and the mixture was cooled. Some semisolid material appeared at the bottom of the flask. When the petroleum ether was evaporated from this mixture, an exothermic reaction occurred accompanied by loss of nitrogen oxide. An infrared spectrum of the residue, 1.49 g., which had an ester odor, identified it as being principally *n*-butyl *n*-butyrate.

Reaction of boron trifluoride with benzyl nitrate. Into a mixture of 4.9 g. of petroleum ether (b.p. 30–60°) and 6.9 g. (0.045 mole) of benzyl nitrate was passed a slow stream of boron trifluoride. Within a few seconds the reaction mixture turned yellow, and after *ca.* 1.5 min. an exothermic reaction took place which was sufficient to reflux the mixture. Boron trifluoride was passed through for a total of *ca.* 20 min. The mixture was then made basic with 40% sodium hydroxide and extracted successively with 20 cc. of petroleum ether, two 20-cc. portions of ethyl ether, 20 cc. of benzene, and two 20-cc. portions of ether, the extracts being combined and evaporated to *ca.* 25% of the volume. The residue was cooled and 50 cc. of saturated sodium bisulfite solution was added and the precipitate filtered, washed with ether, and dried. Liberation of the aldehyde and formation of the 2,4-dinitrophenylhydrazone yielded 3.83 g. (30%) of derivative. Acidification of the base solution precipitated 1.0 g. (18%) of benzoic acid to bring the total yield of products to 48%.

Reaction of boron trifluoride with triphenylmethyl nitrate. Into a solution of 1.5 g. (0.0051 mole) of triphenylmethyl nitrate was passed a slow stream of boron trifluoride for *ca.* 20 min. To the mixture was added *ca.* 25 cc. of ether. A reaction took place with apparently some evolution of nitrogen dioxide. The suspended solid was filtered to yield 0.26 g. of yellow powder, m.p. 145–155°. The melting point increased to 159–160° after washing with water, and the melting point of this latter material was unchanged when mixed with an authentic sample of triphenylcarbinol.

Evaporation of the ether solution left darkly colored crystals which were redissolved in ether and twice decolorized with Norit to yield 0.36 g. (29%) of material, m.p. 90–92°, mixed m.p., taken with an authentic sample of triphenylmethane, 91–92.5°.

Isopropyl nitrate. Isopropyl nitrate was prepared by the method of Silva[8] from isopropyl iodide and powdered silver nitrate in 69% yield, n_D^{20} 1.3897, b.p. 23–24° (27 mm.).

Reaction of isopropyl nitrate with boron trifluoride in petroleum ether. Isopropyl nitrate, 10.0 g. (0.0952 mole), was dissolved in 14 g. of petroleum ether (b.p. 40–60°). The mixture, in a round-bottomed flask fitted with an ice-water-cooled reflux condenser, was cooled in Dry Ice, and a slow stream of boron trifluoride was passed through for 20 min., at which time the solution was colored and appeared to contain some solid matter. The solution was allowed to warm to room temperature very slowly. Shortly after the mixture had reached room temperature, it effervesced and finally reacted very violently, with some volatile material escaping through the reflux condenser. After this violent reaction subsided, two phases were present, a nearly colorless upper phase and a dark brown lower phase. The layers were separated, and the lower phase washed with petroleum ether, the washings being added to the upper layer. Addition of a sample of 2,4-dinitrophenylhydrazine reagent to the petroleum ether extract precipitated 0.15 g. of acetone dinitrophenylhydrazone, m.p. 119–122°. Huntress and Mulliken[9] reported m.p. 126°.

The dark lower phase was connected to a vacuum pump through a Dry Ice trap, and the liquid distillate in the trap was treated with 2,4-dinitrophenylhydrazine to yield an additional 0.20 g. of derivative, m.p. 122–125° to give a total of 0.35 g. of acetone 2,4-dinitrophenylhydrazone.

China Lake, Calif.

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[CONTRIBUTION NO. 604 FROM THE CENTRAL RESEARCH DEPARTMENT, EXPERIMENTAL STATION, E. I. DU PONT DE NEMOURS AND CO.]

Synthesis of Fluorides by Metathesis with Sodium Fluoride

C. W. TULLOCK AND D. D. COFFMAN

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Sodium fluoride suspended in nonaqueous tetramethylene sulfone, acetonitrile, or dimethylformamide has been found to exchange halogen readily with carboxylic acid chlorides, α-chloro ethers, trichloromethanesulfenyl chloride, thiocarbonyl chloride, selenium oxychloride, phosphorus oxychlorides, phosphorus thiochlorides, and phosphonitrilic chlorides. The conversion to fluorides was usually accomplished by heating the reactants at temperatures ranging up to 250° at atmospheric pressure.

Syntheses of aliphatic[1-5] and aromatic[6] fluorides by metathesis of organic halides with metallic fluorides have generally avoided sodium fluoride which has been considered a poor reagent for halogen exchange. However, sodium fluorosilicate has been used in exchange reactions with acyl chlorides and chloroalkanes.[7a] More recently, sodium fluoride has served auspiciously in the synthesis of sulfur tetrafluoride in 90% yield by reaction with sulfur dichloride in acetonitrile at 80°.[7b] This result has led to an exploration of sodium fluoride as a fluorination agent in exchange reactions with chlorine-containing compounds in a nonaqueous polar medium.[6,8,9]

Compounds containing reactive chlorine bonded to carbon, sulfur, or phosphorus have now been converted to the corresponding fluorides by reaction with sodium fluoride in tetramethylene sulfone, acetonitrile, or dimethylformamide.

Synthesis of carbon fluorides. Members of three classes of compounds, namely, acid chlorides, α-chloro ethers, and carbon chlorides bonded to sulfur, were found to exchange readily with sodium fluoride. Thus, oxalyl fluoride, acetyl fluoride, benzoyl fluoride, methyl fluoroformate, cyanuric fluoride, monofluorodimethyl ether, 1,2-difluoro-1,4-dioxane, and trifluoromethanesulfenyl chloride were prepared from the corresponding chlorides. Trifluoromethanesulfenyl chloride was obtained along with bis(trifluoromethyl) disulfide in 47% combined yield in a 3:2 weight ratio by reaction of trichloromethanesulfenyl chloride with sodium fluoride in tetramethylene sulfone at 170–250°. Similar treatment of thiocarbonyl chloride at 85–245° gave bis(trifluoromethyl) disulfide in 37% conversion.

In an interesting modification of the metathesis, fluorocarbonyl cyanide, FCOCN, was obtained in 14% conversion by reaction of phosgene at room temperature with sodium fluoride in hydrogen cyanide which served both as a medium and as a reactant. The chief product was carbonyl fluoride. Fluorocarbonyl cyanide was also prepared directly from carbonyl fluoride and hydrogen cyanide using sodium fluoride as hydrogen fluoride acceptor.

Conditions under which the foregoing reactions were carried out are summarized in Table I.

Synthesis of sulfur and selenium oxyfluorides. Sulfuryl fluoride, sulfuryl chlorofluoride, and thionyl fluoride were prepared from the corresponding chloro compounds in good conversions through reactions with sodium fluoride at atmospheric pressure, and selenium oxyfluoride was obtained from the oxychloride (see Table II). In these syntheses tetramethylene sulfone, acetonitrile, and dimethylformamide were apparently interchangeable as reaction media. The synthesis of the oxyfluorides of sulfur and selenium as reported in the literature[10-14] usually requires reactions under pressure with such reagents as silver (I) fluoride, antimony or arsenic trifluorides, zinc fluoride, hydrogen fluoride, or even elemental fluorine. Sulfuryl fluoride has been prepared in low conversions by the reaction of sodium fluoride with sulfuryl chloride at 400°.[13]

Synthesis of phosphorus fluorides. Sodium fluoride suspended in tetramethylene sulfone has also exchanged fluorine for chlorine bonded to phos-

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phorus in the tri- and pentavalent phosphorus compounds listed in Table III. Two new compounds, phenylphosphonic difluoride, $C_6H_5POF_2$, and phenylphosphonothioic difluoride, $C_6H_5PSF_2$, were prepared from the corresponding chlorides. The phosphonitrilic fluorides, $(PNF_2)_{3,4}$, previously obtained from the corresponding chlorides and potassium fluosulfinate,[15] have also been prepared by metathesis with sodium fluoride.

Although sodium fluoride has been used in isolated instances to prepare phosphorus fluorides[16–18], arsenic trifluoride, lead difluoride, zinc difluoride, or antimony trifluoride have been employed more commonly in such syntheses.[19–21]

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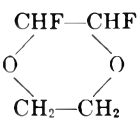
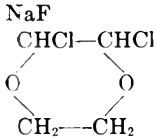
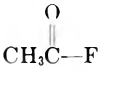
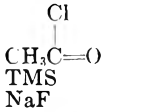
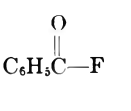
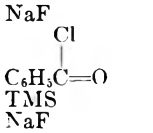
EXPERIMENTAL

With the exception of a few reactions in a sealed vessel under autogenous pressure, the syntheses (Tables I–III) were carried out at atmospheric pressure in Pyrex glass equipment. In most instances the product was distilled from

TABLE I

SYNTHESIS OF CARBON FLUORIDES

Products	Reactants	(Moles)	Reaction Conditions	% Conversion of Chloride to Fluoride	Properties
CF_3SSCF_2	$CSCl_2$	(1.03)	33–89°/1.0 hr.	37	b.p. 31–35°[a]
CS_2	TMS	(2.18)	89–122°/3.0 hr.		
	NaF	(2.62)	122–224°/0.6 hr.		
			224–245°/0.2 hr.		
CF_3SCl	CCl_3SCl	(1.09)	34–107°/0.5 hr.	47	CF_3SCl, b.p. −4° to +2°[b]
CF_3SSCF_3	TMS	(3.16)	107–209°/1.3 hr.		CF_3SSCF_3, b.p. 27–37°[a,b]
(3:2 by wt.)	NaF	(4.76)	209–240°/2.75 hr.		
$(CNF)_3$	$(CNCl)_3$	(0.67)	43–134°0.2 hr.	74	b.p. 72.5–73.5°[c]
	TMS	(1.85)	134–193°/0.4 hr.		
	NaF	(2.50)	193–248°/0.2 hr.		
FCH_2OCH_3	$ClCH_2OCH_3$	(1.29)	33–100°/1.5 hr.	47	b.p. 8–11.5°[d]
	TMS	(1.33)	100–145°/1.0 hr.		
	NaF	(1.90)	145–168°/0.7 hr.		
					
		(0.50)	32–93°/0.7 hr.	42	b.p. 28–30°/21 mm.[e]
	TMS	(1.33)	93–143°/1.0 hr.		
	NaF	(1.50)	143–173°/0.75 hr.		
FCO_2CH_3	$ClCO_2CH_3$	(1.00)	33–81°/0.7 hr.	33	b.p. 35–37°[f]
	TMS	(1.33)	81–119°/1.4 hr.		
	NaF	(2.00)	119–140°/1.5 hr.		
$(COF)_2$	$(COCl)_2$	(0.50)	59–89°/1.5 hr.	60	b.p. 0° to 2°[g]
COF_2	TMS	(1.33)	89–122°/2.0 hr.		
	NaF	(2.00)			
					
		(1.02)	41–60°/1.5 hr.	48	b.p. 19–20.5°[h]
	TMS	(1.33)	60–95°/2.4 hr.		
	NaF	(2.00)			
					
		(1.00)	29–128°/0.4 hr.	62	b.p. 157–159°[i]
	TMS	(1.33)	128–188°/0.5 hr.		
	NaF	(1.50)	188–226°/0.6 hr.		
			226–250°/0.4 hr.		

[a] CF_3SSCF_3, b.p. 34°, has been obtained (1) by the fluorination of carbon disulfide with mercuric fluoride [E. L. Muetterties, U. S. Patent **2,729,663** (1954); (2) by the fluorination of carbon disulfide with IF_5 [R. N. Haszeldine and J. M. Kidd, *J. Chem. Soc.*, 3223 (1953)]; and (3) by the present method [C. W. Tullock, U. S. Patent **2,884,453** (1959)]; infrared analysis showed the product to contain 70 mole % CF_3SSCF_3 and 25 mole % CS_2. [b] The products were identified by infrared analysis. CF_3SCl, b.p. −1°, has been prepared by the chlorination of CF_3SSCF_3 and of $(CF_3S)_2Hg$ [R. N. Haszeldine and J. M. Kidd, *J. Chem. Soc.*, 3219–23 (1953)]. [c] The fluorine NMR spectrum was consistent for $(CNF)_3$. The literature reports a b.p. of 74° [D. W. Grisley, Jr., E. W. Gluesencamp, and S. A. Heininger, *J. Org. Chem.*, **23**, 1802 (1958)]. The product was distilled from the flask as it formed. [d] Fluorine and proton NMR spectra were consistent for FCH_2OCH_3. The literature reports a b.p. of about 19°. The compound was prepared by reacting $ClCH_2OCH_3$ with mercuric fluoride [C. T. Masen and C. C. Allain, *J. Am. Chem. Soc.*, **78**, 1682 (1956)]. [e] The product was separated from the reaction mixture by heating at 163–187°/107 mm. *Anal.* Calcd. for $C_4H_6O_2F_2$: F, 30.60. Found: F, 29.26; Cl, 1.64. This compound was recently synthesized from 2,3-dichloro-*p*-dioxane and mercuric fluoride [C. T. Masen, Southeastern Regional ACS Meeting, Gainsville, Fla., December 1958].

(*Continued on page 2018*)

TABLE I (*Continued*)

Products	Reactants	(Moles)	Reaction Conditions	% Conversion of Chloride to Fluoride	Properties
O ‖ FC—CN COF_2	$COCl_2$	(2.00)	25°/20 hr. in 1-l. reactor at autogenous pressure	14	b.p. −20° to −18°[j]
	HCN	(2.04)			
	NaF	(9.52)			
O ‖ FC—CN	COF_2	(1.00)	150°/3 hr. in 1-l. reactor at autogenous pressure; mixture was then transferred to evacuated pressure reactor containing NaF and stored at 25° for 24 hr.	22.5	b.p. −22° to −19°[k]
	HCN	(1.00)			
	CH_3CO_2H (3 drops)				

TMS = tetramethylene sulfone; the compound darkens with partial decomposition above 220°.

[f] The literature reports a b.p. of 40°. The product was obtained by treating $ClCO_2CH_3$ with TlF or potassium fluoride [H. C. Goswami and P. B. Sarkar, *J. Indian Chem. Soc.*, **10**, 537 (1933); G. Olah and S. Huhn, *J. Org. Chem.*, **21**, 1319 (1956)]. In our experiment CH_3Cl was obtained in a 20% conversion. [g] The product was characterized by infrared analysis. The literature reports a b.p. of +26° [N. Fukuhara and L. A. Bigelew, *J. Am. Chem. Soc.*, **63**, 788 (1941)]. The amount of COF_2 produced was not determined. [h] The product was characterized by infrared analysis. The literature reports a b.p. 21–22°. The product has been obtained from NaF and $CH_3C(=O)Cl$ [A. I. Mashentsev, *J. Applied Chem.* (*U.S.S.R.*), **20**, 854–63 (1947)].

[i] The product was distilled from the mixture as formed. The literature reports a b.p. of 156°. This product has been obtained by heating benzoyl chloride and NaF in the absence of a medium [A. T. Dann, W. Davies, A. N. Hambly, R. E. Paud, and G. Semmens, *J. Chem. Soc.*, 18 (1933)]. [j] The volatile products from three experiments were combined and distilled. The amount of COF_2 formed was not determined. C. W. Tullock, U. S. Patent **2,816,131** (1957) describes the preparation of FCOCN. [k] Appreciable reaction probably occurred after the reactants had been stored over sodium fluoride. *Anal.* Calcd. for C_2FNO: Mol. Wt. 73. Found: Mol. Wt. 72.4. Mass spectrometric and infrared analyses were satisfactory for FC(=O)—CN; the product was further characterized by reaction with aniline to obtain diphenylurea.

TABLE II

SYNTHESIS OF SULFUR AND SELENIUM OXYFLUORIDES

Products	Reactants	(Moles)	Reaction Conditions	% Conversion of Chloride to Fluoride	Properties
SOF_2	$SOCl_2$	(0.50)	43–69°/0.4 hr.	77	b.p. −43° to −36°[a]
	NaF	(2.00)	69–80°/1.6 hr.		
	CH_3CN	(2.88)			
SOF_2	$SOCl_2$	(0.50)	44–70°/0.5 hr.	52	b.p. −39° to −36°[a]
	NaF	(2.00)	70–78°/2.0 hr.		
	TMS	(1.58)			
SO_2FCl	SO_2Cl_2	(0.50)	80°/3.5 hr.	64	b.p. 3–7°[a]
	NaF	(2.48)			
	CH_3CN	(3.24)			
SO_2F_2/SO_2FCl (1:2 by wt.)	SO_2Cl_2	(0.50)	52–80°/1.1 hr.	55	SO_2F_2, b.p. −49° to −48°[a] SO_2ClF, b.p. 3–6°[a]
	NaF	(2.00)	80°/1.1 hr.		
	DMF	(1.93)			
SO_2F_2	SO_2Cl_2	(1.00)	60°/1 hr.; 80°/1 hr.; 100°/1 hr.; 125°/1 hr.; 150°/2 hr.	85	b.p. −49° to −48°[b]
	NaF	(4.00)			
	TMS	(2.50)	1-l. reactor at autogenous pressure		
$SeOF_2$	$SeOCl_2$	(0.64)	60–100°/0.8 hr.	28	b.p. 30–32°/6 mm.[c]
	NaF	(1.78)	100–115°/0.5 hr.		
	TMS	(1.32)			

TMS = tetramethylene sulfone
DMF = dimethylformamide

[a] The reported b.p. are: SOF_2, −43.8°; SO_2FCl, 7.1°; SO_2F_2, −55.4° (J. H. Simons, *Fluorine Chemistry*, Academic Press, Inc., New York, 1950, Vol. 1, p. 94). These products were identified by infrared analysis. [b] This experiment was carried out by Dr. R. D. Cramer. [c] The product was removed from the reaction mixture by heating at 120–167°/2 mm. for 1.6 hr. The reported b.p. for $SeOF_2$ is 124 ±3° (see J. H. Simons, *Fluorine Chemistry*, Academic Press, Inc., New York, 1950, Vol. 1, p. 95; E. Anysley, R. Peacock, and P. Robinson, *J. Chem. Soc.*, 1231–4 (1952).
Anal. Calcd. for F_2OSe: F, 28.57; Se, 59.40. Found: F, 29.57; Se, 58.73.

TABLE III

SYNTHESIS OF PHOSPHORUS FLUORIDES

Products	Reactants	(Moles)	Reaction Conditions	% Conversion of Chloride to Fluoride	Properties
POF_3	$POCl_3$	(0.49)	48–80°/0.4 hr.	43	b.p. −44° to −40°[a]
	NaF	(2.00)	80–96°/2.8 hr.		
	TMS	(1.33)	96–168°/0.5 hr.		
			168–215°/0.5 hr.		
			215–228°/0.2 hr.		
$C_6H_5POF_2$	$C_6H_5POCl_2$	(0.50)		65	b.p. 44°/2.5 mm.[d]
	NaF	(1.50)	75–120°/1.8 hr.		
	TMS	(1.33)			
PSF_3	$PSCl_3$	(0.50)		53	b.p. −52° to −48°[a]
	NaF	(2.00)	37–140°/0.6 hr.		
	TMS	(1.33)	140–170°/2.7 hr.		
$C_6H_5PSF_2$	$C_6H_5PSCl_2$	(0.50)		73	b.p. 47–49°/3 mm.[e]
	NaF	(1.50)	25–89°/0.4 hr.		
	TMS	(1.33)	89–107°/1.8 hr.		
$(PNF_2)_{3,4}$	$(PNCl_2)_{3,4,5,6}$	(4.31)	80°/20 hr.	54	$(PNF_2)_3$, b.p. 51–2°[b]; n_D^{32} = 1.3183[c]; m.p. 29–31°
	NaF	(32.14)			$(PNF_2)_4$, b.p. 89–89.5°[b]; n_D^{32} = 1.3449; m.p. 30°
	CH_3CN	(34.39)			
PF_3	PCl_3	(0.73)	47–52°/1.0 hr.	18	[g]
	NaF	(2.74)	52–75°/0.6 hr.		
	TMS	(1.85)	75–109°/2.5 hr.		
$ClCH_2POF_2$	$ClCH_2POCl_2$	(0.50)	60–175°/0.6 hr.	76	b.p. 112–113°[f]
	NaF	(2.00)	175–194°/0.9 hr.		
	TMS	(1.33)	194–230°/0.5 hr.		

TMS = tetramethylene sulfone; the compound darkens with partial decomposition above 220°.

[a] The reported b.p. for POF_3 is −39.4° and for PSF_3 is −52.3° (J. H. Simons, *Fluorine Chemistry*, Academic Press, Inc., New York, 1950, Vol. 1, p. 100). PSF_3 inflamed on contact with air. The products were further characterized by infrared analysis. [b] The reported b.p. are: $(PNF_2)_3$, 51.8°; $(PNF_2)_4$, 89.7° (F. Seel and J. Langer, *Angew. Chem.*, 68, 461 (1956). [c] This experiment was carried out by Dr. C. M. Langkammerer. A mixture of phosphonitrilic chlorides was employed; it was obobtained by treating 280 g. ammonium chloride, with 900 g. phosphorus pentachloride in 3000 ml. sym.-tetrachloroethane as reflux with stirring and then removing the solvent by distillation under 0.5–2.0 mm. pressure. The value of 4.31 moles $(PNCl_2)_{3,4,5,6}$ is based on $PNCl_2$ monomer. After reaction with sodium fluoride, the $(PNF_2)_3$, b.p. 50–62°, was distilled directly from the stirred reaction mixture; the $(PNF_2)_4$ codistilled with acetonitrile, b.p. 73–80°. Pure $(PNF_2)_4$ was isolated by washing out the acetonitrile with water, drying, and redistilling.

Anal. Calcd. for $(P_3N_3F_6)$: P, 37.38; Mol. Wt., 236. Found: P, 37.43; Mol. Wt., 236, 255. Mass spectrometric analysis satisfactory for $(PNF_2)_3$.

Anal. Calcd. for $P_4N_4F_8$: N, 16.87. Found: N, 16.69. Mass spectrometric analysis was satisfactory for $(PNF_2)_4$.

[d] The product was removed by heating the reaction mixture to 80–100°/2–3 mm. *Anal.* Calcd. for $C_6H_5F_2PO$: F, 23.42. Found: F, 23.24. [e] The product was removed by heating the reaction mixture to 80–100°/2–3 mm. *Anal.* Calcd. for $C_6H_5F_2PS$: F, 21.35. Found: F, 21.47. [f] The product was removed from the reaction mixture by heating to 80–100°/2–3 mm. for 30–40 min.

Anal. Calcd. for CH_2ClF_2OP: F, 28.25. Found: F, 28.84. [g] Infrared showed the samples to contain 35 mole % PF_3 and 20 mole % HCl.

the reaction mixture as formed and was collected in glass traps cooled in solid carbon dioxide and acetone. When the product was too high boiling to be removed in this way, it was isolated by warming the reaction mixture under reduced pressure. Gaseous products were purified by distillation at low temperature and were identified by boiling point and infrared spectra. Liquids were fractionally distilled through a spinning band column or a 10-inch Vigreux column.

The tetramethylene sulfone, acetonitrile, and dimethylformamide used as reaction medium were purified by distillation. The sodium fluoride employed was dry and finely divided. It was presumed that small particle size was beneficial. Commercial product as supplied by the Mallinckrodt Chemical Works or Baker and Adamson was satisfactory.

The usual procedure was to employ a volume of medium (ml.) numerically equal to the sum of the weights (g.) of sodium fluoride and chloro compound employed. The chloro compound was introduced slowly into the stirred suspension of sodium fluoride at such a rate that the reaction temperature was less than 100°. In many cases the chloro compound could be added in less than 5 min. without an appreciable rise in temperature. Heating was begun only after all the reactants had been added.

WILMINGTON, DEL.

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

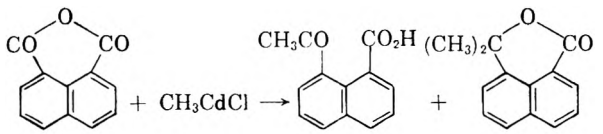
Organocadmium Reagents. II. Evidence for a Displacement Reaction Effected by the Methylcadmium Reagent[1,2]

PAUL R. JONES AND ANDRÉ A. LAVIGNE

Received May 11, 1960

Naphthalic anhydride reacts with methylcadmium chloride to form 3,3-dimethylnaphthalide, as well as the normal product, 8-acetyl-1-naphthoic acid. Formation of the lactone can be formulated as the result of a direct displacement by the cadmium reagent, and this idea is supported by the observation that a series of 3-substituted phthalides are converted to 3-methylphthalides when subjected to the same conditions.

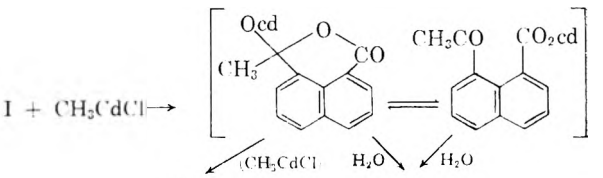
In connection with our previous observations[2] on the formation of both *o*-acetylbenzoic acid and 3,3-dimethylphthalide from phthalic anhydride and the methylcadmium reagent, it was of great interest to determine the behavior of the six-membered ring in naphthalic anhydride (I) under the same conditions. If it were similarly reactive, then the expected products with methylcadmium reagent would be 8-acetyl-1-naphthoic acid (II) and 3,3-dimethylnaphthalide (III). We have found that both II and III are formed from I, although the extent of reaction is considerably lower than



I II III

that in the case of phthalic anhydride. Even the reaction of I with the methyl Grignard reagent led to II and III in low yields. In both instances, the anhydride was recovered in substantial amount. While this difference in the reactivities of phthalic and naphthalic anhydrides toward the methylcadmium reagent might be ascribed to the difference in size of the anhydride rings, it is most likely a result of the lower solubility of I in diethyl ether. It has been shown previously[3] that I will react extensively with both cadmium and Grignard reagents when toluene is used as solvent. We have found that the yield of II with methylmagnesium iodide can be increased three-fold by using benzene-ether as solvent.

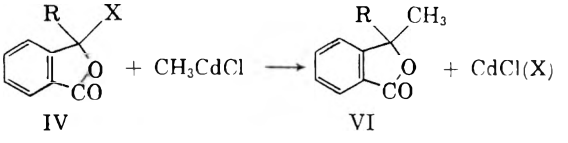
In order to explain the unexpected formation of lactone with the cadmium reagent, we suggested it might arise by a direct displacement reaction on the initial adduct (a cyclic tautomer) by additional reagent. The alternative explanation—that the lactone was formed by reaction of methylcadmium reagent at the ketone function of *o*-acetylbenzoic acid—was rejected because it was found that the latter acid was extremely unreactive under comparable conditions. Similar reasoning to rationalize the formation from I of III, an "abnormal product," as well as the normal product II, may be represented as follows.



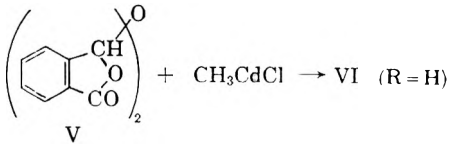
("cd" = ½Cd or its equivalent)

Chemical evidence for this series of transformations comes from the observation that II, like *o*-acetylbenzoic acid, is not converted to lactone under the usual reaction conditions. Only a trace of III could be isolated, and II was recovered to the extent of 88%.

The validity of this explanation was, of course, highly questionable because it necessitated postulation of an unusual displacement of some oxycadmium species by the alkylcadmium reagent. We have tested the feasibility of such a displacement by subjecting a series of 3-substituted phthalides (IV. R = H, CH_3; X = Br, OH, OCH_3, OC_2H_5, $OCOCH_3$) and di-3-phthalidyl ether (V) to the action of excess methylcadmium chloride. If reaction were to proceed by the proposed displacement pathway, the expected products would be 3-methylphthalides (VI).



IV VI



V

Indeed, under the relatively mild conditions of the cadmium reaction previously employed with phthalic and naphthalic anhydrides, all but one of

(1) This work was generously supported by a Frederick Gardner Cottrell grant from the Research Corporation of New York.

(2) Part I: P. R. Jones and S. L. Congdon, *J. Am. Chem. Soc.*, 81, 4291 (1959).

(3) D. V. Nightingale, W. S. Wagner, and R. H. Wise, *J. Am. Chem. Soc.*, 75, 4701 (1953).

the substrates were converted to the corresponding lactones. The yields of VI under standard conditions, which are a rough measure of the relative reactivities, vary considerably with the structure of IV. With 3-bromophthalide, for example, the displacement product, 3-methylphthalide, was isolated in 90% yield, while the same product was formed in only 9% yield from either 3-methoxy- or 3-ethoxyphthalide. When the substituent was hydroxyl (3-hydroxyphthalide, the cyclic tautomer of *o*-phthalaldehydic acid),[4] the conversion to lactone was found to be only 31%, the starting material being recovered to the extent of 46%. Perhaps most surprising was the extremely low reactivity of 3-acetoxyphthalide, which failed to yield any isolable lactonic product. By contrast, di-3-phthalidyl ether (V), in which the group being displaced is the phthalaldehydic acid radical, was converted to VI in quantitative yield (based on formation of two moles of lactone per mole of ether). This remarkable reactivity implies that a facile displacement on the ether occurs, and this is followed by a second reaction of methylcadmium chloride with the phthalaldehydic acid radical that has been displaced.

If this unusual displacement were considered to be nucleophilic in nature, one would expect the relative reactivities of IV to vary in accord with Swain's scale of nucleophilicity.[5] Thus, acetoxyl, one of the poorest nucleophiles, should undergo displacement most readily, and a bromo substituent should be somewhat less reactive. Since the predicted order is not observed, there is no justification for classifying this reaction as another example of nucleophilic displacement. It is interesting to note, however, that the 3-methoxy- and 3-ethoxy- derivatives react only slightly, according to expectation. The extent of displacement is apparently sensitive to structural features other than the leaving group, as evidenced by the observation that 3-methyl-3-acetoxyphthalide reacts to the extent of 44%, although 3-acetoxyphthalide failed to react at all.

It is presumed that 3-substituted naphthalides would undergo a similar displacement, but this series was not investigated because of the difficulty in preparing derivatives. The reaction may be of broad scope and, indeed, can be utilized to rationalize some previously reported abnormal products formed from cadmium reagents. For example, the formation of 3,3-diphenylphthalide from phthaloyl chloride[6] and of 3-phenyl-3-ethylnaphthalide from the acid chloride of 8-benzoyl-1-naphthoic acid[3] might be the result of direct displacement of a chloro substituent in the corresponding pseudo acid chlorides.

(4) Our previous suggestion that phthalaldehydic acid be assigned the open chain tautomeric structure in the solid state was based on infrared data (See Refs. 2 and 10). Because it reacts considerably more readily with cadmium reagent than either *o*-acetylbenzoic acid or 8-acetyl-1-naphthoic acid, however, there is justification for assuming the existence of some ring tautomeric form in ether solution. It is clearly indicated that neither infrared absorption nor reactivity with the methylcadmium reagent is an unequivocal criterion for assigning ring or chain tautomeric structures to compounds of this type.

(5) C. G. Swain and C. B. Scott, *J. Am. Chem. Soc.*, **75**, 141 (1953).

EXPERIMENTAL[7]

1,8-Naphthalic anhydride. Crude anhydride, obtained from Koppers Co., Inc., was purified in one of two ways: solution in 10% sodium hydroxide, decolorization with charcoal, and precipitation with mineral acid; or adsorption chromatography on a Florisil column eluted successively with benzene, ether, and 95% ethanol. The recovery of pure anhydride by these two methods was, respectively, 44% (m.p. 259–262°) and 9% (m.p. 260–263°).

Action of methylcadmium reagent on 1,8-naphthalic anhydride. The cadmium reagent was prepared as previously described[2] from 3.1 g. (0.13 mole) of magnesium, 20.4 g. (0.14 mole) of methyl iodide, 27.5 g. (0.15 mole) of cadmium chloride, and 180 ml. of ether. To this mixture, cooled in an ice-bath, was added 8.5 g. (0.043 mole) of solid 1,8-naphthalic anhydride, with stirring, in 10 min. Stirring and heating under reflux were maintained for 75 min.; then the flask was surrounded by an ice-bath and the mixture decomposed with dilute sulfuric acid. The solid was removed by filtration, taken up in base, and the alkaline mixture filtered. By acidification of the filtrate with dilute hydrochloric acid, 2.1 g. (25%) of 1,8-naphthalic anhydride was recovered, m.p. 257–261°. The ether layer from the original filtrate was separated and combined with ether washings of the water layer. The organic phase was washed with 0.06 mole of potassium carbonate, and the alkaline solution added to dilute sulfuric acid. The precipitated 8-acetyl-1-naphthoic acid, recrystallized from aqueous ethanol, separated as tiny clusters of needles, m.p. 171–173°, yield 2.1 g. (23%). After two more recrystallizations the melting point was 173–174°.

Anal. Calcd. for $C_{13}H_{10}O_3$: C, 72.89; H, 4.71. Found: C, 73.14; H, 4.71.

The infrared spectrum (Nujol) contains strong, broad bands at 3410 and 1690 cm.$^{-1}$

All attempts to prepare the oxime, phenylhydrazone, and semicarbazone of 8-acetyl-1-naphthoic acid by standard methods[8] were unsuccessful, as were attempts to prepare the cyclic acetyl derivative by the method previously described.[2]

By concentration of the remaining ether solution, crystalline 3,3-dimethylnaphthalide was collected and washed with ice-cold ether, m.p. 103–105°, yield 1.4 g. (17%). It was recrystallized several times from ether, m.p. 110.5–111.0°.

Anal. Calcd. for $C_{14}H_{12}O_2$: C, 79.24; H, 5.70. Found: C, 79.49; H, 5.82.

The infrared spectrum (Nujol) contains a carbonyl band at 1706 cm.$^{-1}$

Reaction of naphthalic anhydride with methylmagnesium iodide. An ethereal solution of methylmagnesium iodide was prepared (about 0.1 mole) and to this was added, with stirring, solid naphthalic anhydride during 30 min. The Grignard reagent was always used in excess. Reaction conditions

(6) R. C. Fuson, S. B. Speck, and W. R. Hatchard, *J. Org. Chem.*, **10**, 55 (1945).

(7) The infrared spectra were determined with a Perkin-Elmer Model 21 recording double-beam spectrophotometer with sodium chloride optics. Analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Melting points and boiling points are uncorrected.

(8) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *The Systematic Identification of Organic Compounds*, John Wiley and Sons, Inc., New York, 1957.

varied in several runs from 0.5 hr. at room temperature to 1.5 hr. at reflux, and products were isolated as described above. The yield of 8-acetyl-1-naphthoic acid ranged from 0–13%, that of 3,3-dimethylnaphthalide from 2–14%. Anhydride was recovered to the extent of 50–68%. When benzene was added to the reaction mixture before the reflux period of 1.5 hr., the yield of keto acid was 36%; and only a trace of lactone could be isolated.

Action of methylcadmium reagent on 8-acetyl-1-naphthoic acid. To the cadmium reagent, prepared from 0.47 g. (0.02 mole) of magnesium, 3.0 g. (0.021 mole) of methyl iodide, 4.1 g. (0.023 mole) of cadmium chloride, and 80 ml. of ether, was added, with stirring, 1.2 g. (0.006 mole) of 8-acetyl-1-naphthoic acid during 30 min. When the mixture had been heated under reflux for 1.5 hr. and was worked up as described above, 1.05 g. (88%) of the keto acid was recovered. Only a trace of 3,3-dimethylnaphthalide, m.p. 108–110°, was obtained by concentration of the ether layer.

3-Acetoxyphthalide. Phthalaldehydic acid was converted to the acetyl derivative in 63% yield by the method previously described[2] for *o*-acetylbenzoic acid. The lactol acetate was recrystallized from *n*-hexane, m.p. 64–67°.

Anal. Calcd. for $C_{10}H_8O_4$: C, 62.50; H, 4.20. Found: C, 62.69; H, 4.36.

The infrared spectrum (Nujol) contains strong carbonyl bands at 1777 and 1760 cm.$^{-1}$ but none attributable to a hydroxyl group.

The displacement by methylcadmium reagent of 3-substituted phthalides. The following description for phthalaldehydic acid is typical of the reaction conditions for the displacement of various 3-substituted phthalides, including 3-methoxy-,[9] 3-ethoxy-,[10] 3-bromo-,[11] 3-acetoxy-,[10] 3-methyl-3-acetoxyphthalide,[2] and di-3-phthalidyl ether.[12] The reaction time was held constant throughout; and the cadmium reagent, always in excess, was that prepared from approximately equimolar amounts of magnesium and cadmium chloride. All samples of 3-methylphthalide exhibited identical infrared spectra (film, strong carbonyl band at 1760 cm.$^{-1}$); and the 3,3-dimethylphthalide was compared by mixture melting point and infrared spectrum with an authentic sample.[2] The results are tabulated below.

The methylcadmium reagent, prepared from 2.2 g. (0.09 mole) of magnesium, 15.0 g. (0.12 mole) of methyl iodide, 19.6 g. (0.12 mole) of cadmium chloride, and 150 ml. of ether, was cooled in an ice bath; 7.5 g. (0.05 mole) of phthalaldehydic acid was added with stirring, in 30 min. The mixture was heated under reflux for 1.5 hr., cooled, and decomposed with dilute sulfuric acid. The ether layer was separated and combined with ether washings of the water layer. This organic phase was washed with four 60-ml. portions of 10% potassium carbonate. From the ether layer, which was dried and distilled, was obtained 2.4 g. (32%) of 3-methylphthalide, b.p. (aspirator) 170–175°. When the product was heated at atmospheric pressure to its reported boiling point,[13] it decomposed.

Anal. Calcd. for $C_9H_8O_2$: C,72.96; H,5.44. Found: C, 72.73; H, 5.57.

SUMMARY OF RESULTS

Phthalide	Product	Yield, %
3-Hydroxy-(IV; R = H, X = OH)	VI (R = H)	31[a]
3-Methoxy-(IV; R = H, X = OCH_3)	VI (R = H)	9
3-Ethoxy-(IV; R = H, X = OC_2H_5)	VI (R = H)	9
3-Bromo-(IV; R = H, X = Br)	VI (R = H)	90
3-Acetoxy-(IV; R = H, X = $OCOCH_3$)	—	—[b]
3-Acetoxy-3-methyl-(IV; R = CH_3, H = $OCOCH_3$)	VI (R = CH_3)	44
Di-3-phthalidyl ether-(V)	VI (R = H)	100[c]

[a] Starting material recovered, 46%. [b] Starting material recovered, 59%. [c] Based on formation of two moles of lactone from one mole of ether.

Acknowledgment. The authors are grateful to Dr. M. G. Sturrock, Koppers Company, for a generous sample of naphthalic anhydride.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF BAYLOR UNIVERSITY]

Hydrogenolysis by Metal Hydrides. II. Hydrogenolysis of Aryl Vinyl Ethers by Lithium Aluminum Hydride[1]

VIRGIL L. TWEEDIE AND BENNY G. BARRON[2a,b]

Received May 2, 1960

Aryl vinyl ethers have been hydrogenolyzed in good yields by lithium aluminum hydride to give phenols and hydrocarbons. The extent of hydrogenolysis, which was catalyzed by nickel (II) chloride and by Raney nickel, was significantly influenced by temperature and the solvent. Phenyl vinyl ether was cleaved more than 90% on treatment with excess lithium aluminum hydride and nickel chloride at 0° in bis(2-ethoxyethyl) ether, contrasted to 40% hydrogenolysis at 35° in ethyl ether. Substituents on the aromatic ring and on the vinyl group, in general, caused a decrease in the hydrogenolysis compared with phenyl vinyl ether.

INTRODUCTION

The ether linkage is generally considered stable in the presence of lithium aluminum hydride since ethers are the usual solvents for this reagent. Certain types of ethers, however, undergo hydrogenolysis readily with lithium aluminum hydride; for example, epoxides,[3] allyl aryl ethers,[4,5] and β-alkoxy- and β-aryloxypropionitriles[6] are cleaved in good yields under mild conditions. It is the purpose of this paper to report an investigation of the lithium aluminum hydride hydrogenolysis of aryl vinyl ethers.

This hydrogenolysis, which apparently has not been previously observed, has been applied to a series of nine aryl vinyl ethers by treating the ethers with a large excess of lithium aluminum hydride in a suitable solvent at reflux temperature or below and in the presence of nickel chloride. The alkyl-oxygen bond was preferentially cleaved to yield phenols and alkyl hydrocarbons. As in the various solvents the reaction was nearly complete in three hours or less, this time was arbitrarily chosen for comparative runs evaluating other variables. The extent of hydrogenolysis was measured by quantitative determination of the resultant phenol, and in general, the results were reproducible within ±3%.

The aryl vinyl ethers with the exception of β-chlorovinyl phenyl ether were obtained by dehydrohalogenation of the corresponding aryl β-haloethyl ethers, which in turn were generally prepared by the Williamson reaction. All were extensively purified to remove phenolic impurities. Several of the ethers were characterized completely with physical properties, ultraviolet spectra, and analysis for the first time.

DISCUSSION

Data presented in Table I show the effect of a variety of experimental conditions on the hydrogenolysis.

TABLE I

EFFECT OF REACTION CONDITIONS ON HYDROGENOLYSIS OF PHENYL VINYL ETHER

Solvent	Catalyst	Temp.	Time, hr.	Cleavage, %
Carb.[a]	$NiCl_2$	0°	3	93
Carb.	$NiCl_2$	35	3	61
Carb.	$NiCl_2$	35	24	61
Carb.	$NiCl_2$	65	3	52
Carb.	$NiCl_2$	100	3	47
Carb.	Raney Ni	0	3	97
Carb.	Raney Ni	35	3	80
Carb.	Black pwd.	0	3	62
THF[b]	$NiCl_2$	0	3	89
THF	$NiCl_2$	35	24	40
THF	Raney Ni	0	3	88
Dioxane	$NiCl_2$	35	3	77
Dioxane	$NiCl_2$	35	24	96
Dioxane	$NiCl_2$	65	3	61
Dioxane	$NiCl_2$	101	24	60
Ethyl ether	$NiCl_2$	35	24	38
THP[c]	$NiCl_2$	0	3	68
THP	$NiCl_2$	35	3	24
THP	$NiCl_2$	85	24	15

[a] Bis(2-ethoxyethyl) ether. [b] Tetrahydrofuran. [c] Tetrahydropyran.

The hydrogenolysis reaction was favored by low temperatures, all other variables being held constant. Using phenyl vinyl ether in bis(2-ethoxyethyl) ether at 0°, 35°, 65°, and 100°, the observed cleavages were 93%, 61%, 52%, and 47%, respectively. In dioxane the cleavage of phenyl ether was 96% at 35° but only 60% at reflux temperature. Similar results were obtained with tetrahydrofuran and tetrahydropyran as solvents. This unusual temperature effect suggests that the reaction is dependent on the formation of an intermediate complex which is stabilized at low tempera-

(1) Presented in part at the 129th meeting of the American Chemical Society, April, 1956, Dallas, Tex.

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tures and which is broken down into reaction products upon addition of water.

Nickel (II) chloride was used as a catalyst on the basis of its use in the hydrogenolysis of the allyl aryl ethers.[5] Lithium aluminum hydride effected 13% hydrogenolysis of phenyl vinyl ether in the absence of catalyst compared with 67% in the catalyzed reaction. The effective minimum amount of catalyst was about fifteen millimoles per mole of reactant ether; however, excessive amounts were undesirable and reduced the cleavage yield. In all cases the amount of catalyst was in excess of its solubility in the solvent.

The black color which characterized the catalyzed reactions suggested that the nickel chloride was reduced by the lithium aluminum hydride. When nickel chloride was added to a solution of lithium aluminum hydride in bis(2-ethoxyethyl) ether, an energetic reaction occurred and produced a finely divided black solid resembling Raney nickel. Similar reactions were observed using tetrahydrofuran, tetrahydropyran, and ethyl ether as solvents; however, the reaction was very slow in dioxane and required heating. In all the solvents except ethyl ether the suspended black material was only partially collected by centrifugation. Dilution of these solvents with ether caused coalescence and precipitation. After decantation of the solvents and repeated washing of the precipitate with ether to remove unchanged lithium aluminum hydride, the black material reacted vigorously with water, liberating a gas which was presumed to be hydrogen. Upon exposure to air the dried solid became hot and occasionally flamed. The solid was not identified but on the basis of x-ray analysis appeared to be a nickel hydride or more probably an active form of metallic nickel, with a large amount of adsorbed hydrogen.[7,8] Many metal halides are reported to be reduced by lithium aluminum hydride to the metal hydride or in some cases to the metal.[9] The preparation of a nickel hydride or nickel by this method apparently has not been reported.

The black solid when kept under organic solvents to avoid contact with moisture and air was as effective as nickel chloride in the catalysis of the hydrogenolysis. Because of the resemblance of the solid to Raney nickel, it seemed likely that Raney nickel would also catalyze the hydrogenolysis. Indeed, Raney nickel was as effective as nickel chloride.

The solvent had a marked effect on the extent of hydrogenolysis, all other conditions being constant. The decreasing order of effectiveness of solvents for the hydrogenolysis of phenyl vinyl ether at 35° was: dioxane > bis(2-ethoxyethyl) ether > tetrahydrofuran > ethyl ether > tetrahydropyran. This order is similar to the order of solvents for the hydrogenolysis of allyl phenyl ether,[5] except that the positions of tetrahydrofuran and dioxane are exchanged. Other workers[6,10] have observed varying solvent effects in lithium aluminum hydride reactions; however, the order of effectiveness of solvents appears to be characteristic for each reaction. Wiberg[11] has shown that highly ether soluble coordination compounds are formed between nucleophilic solvents and lithium aluminum hydride, and that the number of dentates increases as the temperature decreases. Thus the observed solvent effect might be interpreted in terms of the competition between the solvent and the aryl vinyl ether for coordination with the hydride.

A series of chloro- and methyl- substituted aryl vinyl ethers was subjected to hydrogenolysis as a means of determining the effect of ring-activating and ring-deactivating groups. The conditions used for these comparative runs were those which gave moderate cleavage of phenyl vinyl ether so that any increase or decrease in cleavage caused by the substituent could be detected. The data are presented in Table II. In a similar study with allyl aryl ethers[5] it was shown that hydrogenolysis was decreased by methyl- and increased by chloro-substituents on the ring compared with the unsubstituted ether. In the aryl vinyl ethers the effect of ring substituents was not clearly defined and appeared to be highly solvent-dependent. In dioxane all of the substituted ethers, especially chloro, were cleaved less than phenyl vinyl ether. In bis(2-ethoxyethyl) ether the chloro- and methyl-substituted compounds, with exception of the trichloro- and the trimethyl-, showed equal or greater cleavage than phenyl vinyl ether. The very sharp decrease in hydrogenolysis for both the mesityl vinyl and the 2,4,6-trichlorophenyl vinyl ethers suggests that steric factors are equally or more important than the kind of substituent on the ring.

Unsaturation in the alkyl moiety near the ether linkage has been shown an essential structural feature for significant hydrogenolysis by catalyzed lithium aluminum hydride. Negligible cleavage has been reported with phenyl propyl ether, 3-butenyl phenyl ether, β-chlorophenetole, and anisole at 65° in tetrahydrofuran[5]; phenetole and β-ethoxyphenetole were not cleaved in refluxing butyl ether.[12] Likewise, when the vinyl unsaturation was

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TABLE II

EFFECT OF STRUCTURE ON HYDROGENOLYSIS OF ARYL VINYL ETHERS[a]

Ether	Per Cent Hydrogenolysis	
	In dioxane	In carb.
Phenyl vinyl	77	67
p-Tolyl vinyl	55	89
o-Tolyl vinyl	60	69
p-Chlorophenyl vinyl	53	65
o-Chlorophenyl vinyl	31	80
Mesityl vinyl	29	28
2,4,6-Trichlorophenyl vinyl	12[b]	37
β-Chlorovinyl phenyl	41[c]	42
Phenyl	5	4

[a] Reaction time, 3 hr.; temperature, 35°; catalyst, nickel (II) chloride; lithium aluminum hydride, 100% mole excess. [b] Recovered 85% of 2,4,6-trichlorophenyl vinyl ether. [c] Hydrogenolysis of chlorine was 43.2% (Volhard).

made a part of an aromatic ring—as in phenyl ether—hydrogenolysis was negligible.

Substitution of chlorine in the vinyl group greatly reduced the hydrogenolysis. It is interesting that with β-chlorovinyl phenyl ether the carbon-halogen bond underwent hydrogenolysis to the same extent as the ether linkage. It is very unlikely that after the hydrogenolysis of the ether the halogen would be quantitatively cleaved from the resulting vinyl chloride or ethyl chloride; equally unlikely would be the removal of the chlorine from the chlorovinyl ether followed by the quantitative cleavage of the resulting phenyl vinyl ether. Thus, it is proposed that the carbon chlorine and the carbon oxygen hydrogenolyses occur simultaneously or in sequence in the transition complex. The final products of the reaction must be held as complexes until decomposition with water, as no gaseous products were liberated during the reaction.

To account for the observed effects of the solvent, the catalyst, temperature, the initially rapid reaction, and the reaction products, it is proposed that the aryl vinyl ethers form reversibly intermediate complexes with the solvent and/or the hydride which then undergo hydrogenolysis by excess hydride to yield product complexes from which the final products are liberated upon decomposition with water. The reversible first step would be favored by low temperatures and by certain solvents. The catalyst may stabilize the intermediate or may catalyze its hydrogenolysis by the excess hydride.

EXPERIMENTAL

Materials. The aryl β-haloethyl ethers, which were starting materials for the preparation of the aryl vinyl ethers, were either purchased or prepared by recognized methods. The β-chlorophenetole and phenyl ether (Eastman, white label) were used without further purification. β-Bromoethyl 2,4,6-trichlorophenyl ether and β-bromoethyl mesityl ether were prepared by the method of Peak and Watkins.[13] According to the method of Clemo and Perkin,[14] *o*- and *p*-cresol were treated in basic aqueous solution with β-chloroethyl *p*-toluenesulfonate to obtain the β-chloroethyl *o*- and *p*-tolyl ethers in yields above 50%. The β-bromoethyl *o*- and *p*-chlorophenyl ethers were prepared from the corresponding chlorophenols and ethylene bromide by the Williamson reaction.[15] The observed physical constants of these several ethers were in agreement with those reported in the literature.

The anhydrous nickel (II) chloride was prepared from the hexahydrate (Baker and Adamson, reagent grade) by heating at 125° for several hours. The solvents—ethyl ether, dioxane, tetrahydrofuran, tetrahydropyran, and bis(2-ethoxyethyl) ether—were purified by drying over sodium wire, filtering, and finally distilling from lithium aluminum hydride (Metal Hydrides, Inc., Beverly, Mass.).

Dehydrohalogenation. The β-chlorophenetole and the β-bromoethyl mesityl ether were dehydrohalogenated by heating slowly 0.32 mole of the haloether with 70 g. of powdered potassium hydroxide in a 500-ml. flask arranged for simple distillation of the aryl vinyl ether as it was formed. The crude product was dried in ether solution over anhydrous sodium sulfate and purified by fractionation. Phenyl vinyl ether: yield 35%; b.p. 155–157°, reported[16] 155–156°; ultraviolet spectrum λ_{max} 270 and 225 mμ, ε 1,113 and 14,480, respectively. Mesityl vinyl ether: yield 50%; b.p. 200–202°; d^{25} 0.9728, d^{30} 0.9686; n_D^{25} 1.5089, n_D^{30} 1.5072; ultraviolet spectrum λ_{max} 276 mμ, ε 312.

Anal. Calcd. for $C_{11}H_{14}O$: C, 81.30; H, 8.80. Found: C, 81.12; H, 8.90.

To a cooled solution of 80 g. potassium hydroxide in 50 g. of 2-ethoxyethanol was added 25 g. of aryl β-haloethyl ether. Upon heating dehydrohalogenation proceeded smoothly, and the aryl vinyl ether distilled. This procedure was used to dehydrohalogenate the β-chloroethyl *o*- and *p*-tolyl ethers and the β-bromoethyl *o*- and *p*-chlorophenyl ethers to the corresponding aryl vinyl ethers. *o*-Tolyl vinyl ether: yield 76%; b.p. 167–169°, reported[16] 167–168.5°; d^{25} 0.9531, d^{30} 0.9484; n_D^{25} 1.5072, n_D^{30} 1.5050; ultraviolet spectrum λ_{max} 276, 270.5, and 225.5 mμ, ε 769, 923 and 8,070, respectively. *p*-Tolyl vinyl ether: yield 50%; b.p. 177–178° reported,[17] b.p. 177–178°; d^{25} 0.9509, d^{30} 0.9461; n_D^{25} 1.5077, n_D^{30} 1.5057; ultraviolet spectrum λ_{max} 275 and 228 mμ, ε 1,290 and 13,720, respectively. *p*-Chlorophenyl vinyl ether: yield 36%; b.p. 198–202°, reported[18] 90° (20 mm.); d^{25} 1.1118, d^{30} 1.1130; n_D^{25} 1.5356, n_D^{30} 1.5330; ultraviolet spectrum λ_{max} 279 and 232 mμ, ε 1170 and 18,800, respectively. *o*-Chlorophenyl vinyl ether: yield 47%; b.p. 195–198°, reported[19] b.p. 192–195°; d^{25} 1.1300, d^{30} 1.1248; n_D^{25} 1.5336, n_D^{30} 1.5310; ultraviolet spectrum λ_{max} 280, 273.5 and 226 mμ, ε 1245, 1184, and 8780, respectively.

Anal. Calcd. for C_8H_7OCl: C, 59.00; H, 4.54. Found: C, 59.12; H, 4.40.

For dehydrohalogenation of β-bromoethyl 2,4,6-trichlorophenyl ether, 50 g. (0.116 mole) was dissolved in an alcoholic solution of sodium ethoxide (10 g. of sodium in 150 ml. of absolute ethanol) and warmed for 40 min. The cooled reaction mixture was diluted with four volumes of water and acidified with sulfuric acid. The red oil which separated was taken up in ethyl ether, washed with water, dried over anhydrous sodium sulfate, and distilled. The yield was 42% of

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2,4,6-trichlorophenyl vinyl ether, b.p. 230–235°, reported[19] b.p. 135–40° (21 mm.); d^{25} 1.350, d^{30}1.339; n_D^{25} 1.5494, n_D^{30} 1.5474; ultraviolet spectrum λ_{max} 288 and 279.5 mμ, ε 652 and 627, respectively.

Anal. Calcd. for $C_8H_5OCl_3$: C, 43.00; H, 2.25. Found: C, 43.17; H, 2.41.

β-Chlorovinyl phenyl ether. To 350 ml. of absolute methanol was added 120 g. (0.9 mole) of powdered potassium phenoxide[20] and 110 g. (1.13 moles) of 1,2-dichloroethene. The solution was heated in an autoclave so that a temperature of 110° was reached in 6 hrs. and maintained for an additional 12 hrs. When cooled to room temperature, the reaction mixture was removed and steam distilled. Upon diluting the alcoholic distillate with water, the crude β-chlorovinyl phenyl ether separated as an oil and was taken up in ethyl ether for washing with 20% potassium hydroxide solution and finally with water. After drying over anhydrous calcium sulfate, the drying agent and excess ethyl ether were removed. Vacuum distillation gave 28 g. (0.18 mole) of β-chlorovinyl phenyl ether, b.p. 74–75° (5 mm.); d^{25} 1.147, d^{30} 1.141; n_D^{25} 1.5444, n_D^{30} 1.5420; ultraviolet spectrum λ_{max} 268 and 226 mμ, ε 1,062 and 13,560, resp.

Anal. Calcd. for C_8H_7OCl: C, 59.00; H, 4.54. Found: C, 59.16; H, 4.42.

Procedure for ether hydrogenolysis. For a typical hydrogenolysis run 100 ml. of solvent, 43–76 mg. ($3.3–5.8 \times 10^{-4}$ moles) anhydrous nickel (II) chloride, and 3 g. (0.08 mole) of finely divided lithium aluminum hydride were mixed in a 250-ml. three necked flask equipped with a dropping funnel and a reflux condenser with drying tube protection. A weighed quantity (usually about 0.03 mole) of the phenol-free aryl vinyl ether in a small amount of solvent was added. The mixture was refluxed 3 hrs., after which time it was cooled below room temperature, and the excess lithium aluminum hydride was destroyed by the slow addition of 30 ml. of water. The inorganic solids were dissolved by addition of hydrochloric acid (18%), and the organic constituents were extracted with ether to a negative Folin[21] test on the aqueous layer. The phenolic content of the ether extract was determined quantitatively by the methods used by Tweedie and Cuscurida. For reactions run at temperatures lower than the reflux temperature of the solvent, a constant temperature bath was used and the reaction mixture was agitated.

In the hydrogenolysis of β-chlorovinyl phenyl ether the reaction mixture was acidified with sulfuric acid instead of hydrochloric, and the extracted aqueous residue was analyzed for chloride by the Volhard Method.[22] A chloride blank on a reaction mixture without β-chlorovinyl phenyl ether present was used to correct for the nickel chloride catalyst and the trace of chloride in the lithium aluminum hydride.

Waco, Tex.

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Notes

A department for short papers of immediate interest.

Reduction of Conjugated 1,4-Diketones with Tin Amalgam

JOHN P. SCHAEFER

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A kinetic study of the oxidation of 1,4-diketones in which we are currently engaged has necessitated the synthesis of a series of these compounds. Since the unsaturated 1,4-diketones are readily available, reduction of the olefinic linkage offers a convenient route to these substances.

The usual reducing agent for effecting this conversion is zinc in acetic acid; however, this reduction is often accompanied by serious side reactions which make it useless as a synthetic tool. In studies on the reduction of 1,4-diphenyl-2-butene-1,4-dione (I) Lutz[1,2] has reported the isolation of five different bimolecular reduction products along with the desired saturated diketone. In an effort to develop a reliable system for converting 1,4-enediones to 1,4-diones a more specific reducing agent was sought.

We have found that amalgamated tin and acid will rapidly reduce unsaturated 1,4-diketones to the saturated derivative in high yield without any detectable side reactions in the cases studied. Reduction of I with tin amalgam and hydrochloric acid in ethanol gave 1,4-diphenylbutane-1,4-dione (II) in 90% yield. 1,4-*p*-Chlorophenyl-2-butene-1,4-dione (III) reacted in an analogous manner to give similar results.

Utilizing the same procedure β-norcholest-4-ene-3,6-dione (IV) was quantitatively reduced to β-norcoprostane-3,6-dione[3] and quinone (V) to hydroquinone. Substitution of acetic acid for hydrochloric acid was attempted in the cases I and V and also worked well, although reaction times were considerably longer and the reaction mixtures were usually lightly colored. Typical experimental procedures are illustrated below.

EXPERIMENTAL

Tin amalgam. To a flask containing 15 g. of mercuric chloride and 100 ml. of water was added 100 g. of 30-mesh tin metal. The flask was stoppered and shaken for a few minutes until all of the tin appeared to have a shiny coating of mercury on the surface. The tin amalgam was then washed repeatedly with water until the washings were clear, and stored under distilled water.

Reduction of 1,4-diphenyl-2-butene-1,4-dione. To 5.0 g. of 1,4-diphenyl-2-butene-1,4-dione and 10 g. of tin amalgam was added 150 ml. of ethanol. The solution was heated to reflux and 20 ml. of concd. hydrochloric acid was added cautiously. After 5 min. the solution was colorless. The solution was filtered and cooled to give 4.5 g. (90%) of crystalline product, m.p. 142–143°.

Reduction of quinone. To 5.7 g. of quinone was added 10 g. of tin amalgam and 50 ml. of glacial acetic acid. The mixture was heated on a steam bath and after 3 min. lustrous green crystals separated (quinhydrone). The crystals soon dissolved to give a light yellow solution. After 0.5 hr. the solution was filtered and the solvent removed *in vacuo*. Recrystallization of the hydroquinone from benzene-acetone gave 5.0 g. (88%) of product, m.p. 169–170°.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF CALIFORNIA
BERKELEY 4, CALIF.

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The Stereochemistry of Some Hydrophenanthrones[1]

ERNEST WENKERT AND JAMES W. CHAMBERLIN

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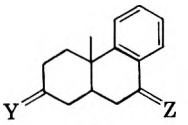
The recent synthesis of hydrophenanthrones Ia by three new routes[2] has made available compounds which can serve as the backbone for tricarbocyclic diterpenes. A partial use of Ia for the synthesis of the latter has been illustrated already,[3] while further work in this connection is continuing. Since any rational synthesis of the natural products was dependent, among other things, on the stereochemistry of the two isomers of Ia every effort had to be made to determine their configuration. Thus, a correlation of *cis*- and *trans*-Ia with substances of known constitution was sought, even though a large body of stereochemical evidence had been accumulated already.[2,3]



I

a, Y = O, Z = H_2
b, Y = Z = H_2
c, Y = H_2, Z = O

(1) This work was aided by research grant NSF-G6226. The authors are grateful to the National Science Foundation for this support.

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A few years ago the stereoisomeric hydrocarbons Ib were converted *via* their ketones Ic to dibasic acids of known configuration.[4] As a consequence the saturated ketones Ia were transformed into their aromatic counterparts Ic by Wolff-Kishner reduction followed by chromic acid oxidation and the 2,4-dinitrophenylhydrazones of the latter compared with authentic samples.[5] These experiments were in full accord with the previous stereochemical assignment[2,3] of the isomers of Ia.

EXPERIMENTAL

Hydrocarbons Ib. A mixture of 350 mg. of *cis*-Ia and 0.7 ml. of hydrazine hydrate in 12 ml. of diethylene glycol was heated at 190° for 1 hr. After cooling to 70°, a solution of 700 mg. of sodium in 10 ml. of diethylene glycol was added and the mixture heated at 215–220° for 6 hr. Thereupon the mixture was cooled, poured into 100 ml. of saturated brine solution, and extracted with benzene. The extract was washed with water, dried, and its solvent removed, leaving 265 mg. of an oil. Chromatography of the latter on 25 g. of alumina and elution with petroleum ether (b.p. 30–60°) gave 204 mg. of colorless oil, which was used directly in the chromic acid oxidation.

A similar operation on 150 mg. of *trans*-Ia yielded 105 mg. of crude product which on chromatography on 9 g. of alumina led to 88 mg. of colorless hydrocarbon. The latter also was used for oxidation without further purification.

Ketones Ic. A solution of 50 mg. of chromic oxide in 0.1 ml. of water and 0.4 ml. of glacial acetic acid was added dropwise with stirring to a solution of 52 mg. of *cis*-Ib in 0.5 ml. of glacial acetic acid. The mixture was allowed to stand at room temperature for 6.5 hr. and then was diluted with 15 ml. of saturated brine solution and extracted with chloroform. The extract was washed three times with 10% sodium hydroxide solution and once with saturated brine solution, dried over anhydrous sodium sulfate, and evaporated. The resulting 30 mg. of residual neutral oil was chromatographed on 5 g. of alumina, yielding 9 mg. of colorless liquid ketone, infrared spectrum (chloroform): C=O 5.88(s)μ, C=C 6.26 (m)μ, by 9:1 petroleum ether–ether elution.

A similar operation on 126 mg. of *trans*-Ib, however for 11 hr. reaction time,[6] led to 105 mg. of neutral oil which on chromatography on 10 g. of alumina and 9:1 petroleum ether–ether elution gave 31 mg. of colorless liquid ketone, infrared spectrum (chloroform): C=O 5.88(s)μ, C=C 6.26(m)μ.

2,4-Dinitrophenylhydrazones. The derivative of *cis*-Ic melted at 182–183°, m.m.p. 179–183° with authentic sample[4] (m.p. 182.5–184°), identical infrared spectrum with that of an authentic sample.

The derivative of *trans*-Ic melted at 208–210.5°, m.m.p. 207°–210° with an authentic specimen[4] (m.p. 209.5–210.5°), identical infrared spectrum with that of an authentic specimen.

DEPARTMENT OF CHEMISTRY
IOWA STATE UNIVERSITY
AMES, IOWA

(4) R. A. Barnes and M. T. Beacham, *J. Am. Chem. Soc.*, **77**, 5388 (1955) and preceding papers.

(5) The authors wish to express their gratitude to Professor Barnes for his gift of comparison samples.

(6) The *trans* hydrocarbon is over-oxidized more slowly than its *cis* isomer [*cf.* E. Wenkert and B. G. Jackson, *J. Am. Chem. Soc.*, **80**, 211 (1958)].

A Reinvestigation of the Action of Formaldehyde on 1,2- and 1,3-Hydroxyamines in the Pyrrolidine and Piperidine Series

RICHARD K. HILL AND LARRY J. LOEFFLER

Received March 21, 1960

In 1913, Hess reported[1] a remarkable synthesis of the coca alkaloid hygrine (V) by heating the amino alcohol I with formaldehyde in acidic solution. Although direct comparison of his product with the natural base was not made at the time, the empirical formula and the close correspondence of the physical and chemical properties of the base and its derivatives[2] all supported his conclusion that a disproportionation reaction had occurred which resulted in simultaneous methylation of the nitrogen and oxidation of the secondary hydroxyl. Continued investigation showed that the reaction was apparently a general one for 1,2- and 1,3-hydroxyamines, and over a dozen examples were reported.[4,5]

It must be noted that except in two cases (those which gave hygrine and the isomeric ketone VI, both of which were reported to yield oximes) no experimental evidence was offered for the presence of either the *N*-methyl or the carbonyl group in the products. The structures were proposed solely on the empirical formulas of their picrates and the analogy to the initial reaction which had afforded hygrine. The only chemical behavior reported was first, that many of the reaction products gave a positive silver mirror test, and second, that with the exception of the two cases already mentioned, every effort to prepare carbonyl derivatives yielded only the corresponding derivative of formaldehyde plus the original hydroxyamine.

It is not surprising, in the face of this tenuous evidence, that it soon became apparent that some of Hess' products were incorrectly formulated. It was pointed out by both Kohn[6] and Rolfes[7] that the products from the reactions of aldehydes with diacetone alcohol amine were more likely tetrahydro 1,3-oxazines. In two other cases,[8,9]

(1) K. Hess, *Ber.*, **46**, 4104 (1913).

(2) The picrate of the synthetic base was first reported to melt at 174°, although hygrine picrate melts at 149–150°; Hess regarded this discrepancy as due to differences in purity of the two samples. Some years later,[3] he reported that the original sample of the synthetic picrate now melted at 149–150°, and did not depress the melting point of authentic hygrine picrate.

(3) K. Hess and H. Fink, *Ber.*, **53**, 781 (1920).

(4) K. Hess, F. Merck, and C. Uibrig, *Ber.*, **48**, 1886 (1915).

(5) K. Hess and C. Uibrig, *Ber.*, **48**, 1974 (1915).

(6) M. Kohn, *Ber.*, **49**, 250 (1916).

(7) H. Rolfes, *Ber.*, **53**, 2203 (1920).

(8) K. Hess and A. Eichel, *Ber.*, **50**, 1407 (1917).

(9) K. Hess and W. Corleis, *Ber.*, **54**, 3010 (1921).

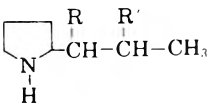
including the closely related piperidine alcohol III, Hess found that the supposed aminoketones were different from genuine samples prepared by other routes, and was forced to assign tetrahydrooxazine and oxazolidine structures to them, too.

While it is surprising that the reaction should take different courses with compounds of such similar structure, there seemed to be no doubt about the constitution of the ketones from I and II, as both reportedly formed oximes of the expected composition. Hess' work is still widely cited in texts as the first synthesis of hygrine. It appeared worthwhile to reinvestigate these reactions to confirm their authenticity and with a view to studying the mechanism.

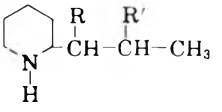
The reaction of the pyrrolidine alcohols I and II with formaldehyde in aqueous acid was carried out in sealed tubes exactly as described by Hess. Basic products were isolated whose empirical formulas and physical properties agreed with those reported. The infrared spectra quickly revealed, however, the complete absence of absorption in the carbonyl region. As the spectra were also devoid of N—H and O—H absorption, the only plausible structures for the products are the tetrahydrooxazine VII and the oxazolidine IX, respectively. A closer examination of the spectra showed the presence of the triplet in the 1080–1200 cm.$^{-1}$ region characteristic of cyclic compounds containing the —N—C—O— grouping.[10] Also consistent with this formulation was the liberation of formaldehyde, identified as its dimedone derivative, on mild hydrolysis with dilute hydrochloric acid. Even when the initial reaction mixture was made alkaline and extracted with ether, no trace of carbonyl absorption could be found in the infrared spectra of the total extracts, and consequently it must be concluded that *N*-methyl aminoketones are not formed in detectable amounts in these reactions.[11] We are unable to account for the reported formation of oximes from these two bases, since in our hands, the reaction of VII with hydroxylamine following Hess' procedure gave no solid product.

We have also carried out the reaction with compounds III and IV, the corresponding alcohols of the piperidine series. The mixture of diastereoisomers of formula III was first reported[4] to yield an *N*-methyl aminoketone, but later[8] the structure was changed to a tetrahydrooxazine and the isolation of a second product containing an additional carbon was claimed. We were able to isolate only the base VIII, with an analysis corresponding to $C_9H_{17}NO$; the tetrahydrooxazine structure is again supported by the infrared spectrum[12] and the hydrolysis to formaldehyde. In this case, the starting amino alcohol was also isolated from the hydrolysis.

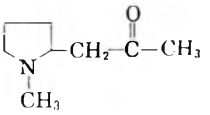
Finally, in the case of *d,l*-conhydrine (IV), the starting material was available as a single isomer of known configuration.[13] Once again, the product from formaldehyde treatment was shown to be the oxazolidine (X) by its infrared spectrum and hydrolysis to formaldehyde.



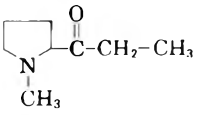
I. R = H, R′ = OH
II. R = OH, R′ = H



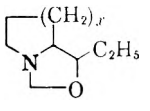
III. R = H, R′ = OH
IV. R = OH, R′ = H



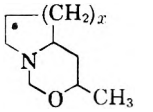
V



VI



IX. $x = 1$
X. $x = 2$



VII. $x = 1$
VIII. $x = 2$

EXPERIMENTAL

Preparation of starting amino alcohols. 1-α-Pyrrolidyl-2-propanol (I), prepared by the method of Hess,[14] distilled at 115–125° (16 mm.), lit. b.p. 115–120° (15 mm.).

1-α-Pyrrolidyl-1-propanol (II). 1-α-Pyrryl-1-propanone was prepared by a modification of Oddo's method[15]; steam distillation of the acidified Grignard reaction mixture gave directly the pure ketone, m.p. 52–53°, lit. m.p. 52.5°, in 12–14% yields. Reduction with sodium and ethanol, according to Hess,[14] followed by vacuum sublimation, gave hygroscopic needles of II, m.p. 45–52°, lit. m.p. 50°. The picrate, after three recrystallizations from ethanol, melted at 125–127°.

Anal. Calcd. for $C_{13}H_{18}N_4O_8$: C, 43.57; H, 5.06; N, 15.64: Found: C, 43.41; H, 5.17; N, 15.78.

1-α-Piperidyl-2-propanol (III) was prepared by hydrogenation of 1-α-pyridyl-2-propanol[16] in 85–90% yields. The mixture of stereoisomers obtained melted at 52–59°; reported[17] melting points are 75° and 70–71° for the two pure isomers, 45–55° for the mixture obtained by hydrogenation.

1-α-Piperidyl-1-propanol (*d,l-conhydrine*) (IV), m.p. 99.5–100°, was synthesized as described previously.[13]

(10) E. D. Bergmann, *Chem. Rev.*, **53**, 309 (1953).

(11) After this work had been completed, the same conclusion was announced by Lukeš and co-workers; R. Lukeš, J. Kloubek, J. Kovář, and K. Bláha, *Coll. Czech. Chem. Comm.*, **24**, 2433 (1959).

(12) The crude basic product showed weak but reproducible absorption at 5.82 and 5.95 μ, but the grouping responsible for this absorption could not be identified. No pure material containing either band could be isolated, a 2,4-dinitrophenylhydrazone could not be formed from the crude product, and the picrate of the crude base showed no absorption in this region.

(13) R. K. Hill, *J. Am. Chem. Soc.*, **80**, 1609 (1958).

(14) K. Hess, *Ber.*, **46**, 3113 (1913).

(15) B. Oddo, *Ber.*, **43**, 1012 (1910).

(16) L. A. Walter, *Org. Syntheses*, Coll. Vol. II, 757.

(17) H. C. Beyerman, J. Eenshuistra, W. Eveleens, and A. Zweistra, *Rec. trav. chim.*, **78**, 43 (1959).

Reaction of I *with formaldehyde.* A solution of 2.0 g. of 1-α-pyrrolidyl-2-propanol in 5 ml. of water was acidified with concd. hydrochloric acid and treated with 6 ml. of 40% formalin solution. The resulting mixture was heated in a sealed pyrex tube at 117° (refluxing 1-butanol) for 4 hr. The dark brown contents of the tubes were cooled, made alkaline with 50% potassium hydroxide solution, and the base extracted with ether and dried over magnesium sulfate. Vacuum distillation gave 1.5 g. of a colorless liquid, b.p. 83–84° (21 mm.), lit.[1] b.p. 89–92° (22 mm.). The picrate melted at 174–175°, lit.[2] m.p. 174°.

Anal. Calcd. for $C_{14}H_{18}N_4O_8$: C, 45.40; H, 4.90; N, 15.15. Found: C, 45.33; H, 4.93; N, 15.44.

In an attempt to prepare the reported oxime, 1.4 g. of VII, 0.7 g. of hydroxylamine hydrochloride and 0.6 g. of potassium hydroxide were warmed on the steam bath in 20 ml. of water for 2 hr. Working up the mixture in the manner described by Hess[1] gave no solid products.

Hydrolysis of VII. A solution of 0.25 g. of VII in 5 ml. of ethanol, 5 ml. of 1*N* hydrochloric acid, and 5 ml. of a 10% alcoholic solution of dimedone was refluxed for 2 hr., neutralized with potassium hydroxide and concentrated on the steam bath. Chilling gave a crude solid, which was recrystallized from ethanol to yield 50 mg. of the dimedone derivative of formaldehyde, m.p. and mixed m.p. 188–191.5°.

Reaction of II *with formaldehyde.* The base (1.66 g.) isolated by vacuum distillation of the product from reaction of 2.0 g. of II with formaldehyde, as described above, gave a picrate, needles from ethanol, melting at 101–103°, lit.[1] m.p. 103°.

Anal. Calcd. for $C_{14}H_{18}N_4O_8$: C, 45.40; H, 4.90; N, 15.15. Found: C, 45.35; H, 5.03; N, 15.38.

Hydrolysis of the base in the presence of dimedone, as described above, gave the crystalline derivative of formaldehyde.

Reaction of III *with formaldehyde.* A solution of 10 g. of III in 17.5 ml. of water was acidified with 8.2 ml. of concd. hydrochloric acid, treated with 10.5 ml. of 40% formalin solution, and heated at 117° for 4 hr. The mixture was worked up as described above, affording 9.1 g. of colorless liquid, b.p. 110–113° (14 mm.), 70–72° (6 mm.), lit.[3] b.p. 108–111° (28 mm.).

Anal. Calcd. for $C_9H_{17}NO$: C, 69.70; H, 11.04; N, 9.03. Found: C, 69.31; H, 11.06; N, 9.08.

The picrate, twice recrystallized from ethanol, melted at 140.5–144°, lit. m.p. 162–163°.

Anal. Calcd. for $C_{15}H_{20}N_4O_8$: C, 46.87; H, 5.24; N, 14.58. Found: C, 46.89; H, 5.31; N, 14.71.

Hydrolysis of the base in the presence of dimedone again afforded the dimedone derivative of formaldehyde. The starting amino alcohol (III) was also recovered by crystallization and identified by its infrared spectrum.

Reaction of IV *with formaldehyde.* The reaction of 1.70 g. of IV with formaldehyde was carried out as described above, and yielded 1.50 g. of colorless product. The picrate was recrystallized twice from ethanol, and melted at 142–144°.

Anal. Calcd. for $C_{16}H_{20}N_4O_8$: 46.87; H, 5.24; N, 14.58. Found: C, 47.06; H, 5.11; N, 14.85.

Formaldehyde was isolated as the dimedone derivative when the base was hydrolyzed as described above.

FRICK CHEMICAL LABORATORY
PRINCETON UNIVERSITY
PRINCETON, N. J.

The Dinitration of *m*-Toluic Acid

A. H. BLATT

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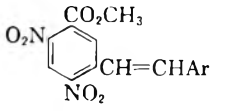
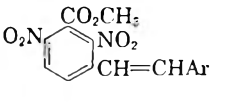
The first report of the dinitration of *m*-toluic acid is that of van Scherpenzeel[1a] who nitrated the acid in one- to two-gram quantities with 100% nitric acid and obtained in an unspecified, low yield a dinitro acid (m.p. 173°) which he formulated as 2,6-dinitro-*m*-toluic acid.[1b] From methyl *m*-toluate by the same procedure he obtained, again in an unspecified, low yield, a methyl ester (m.p. 104°) which he considered to be methyl 2,6-dinitro-*m*-toluate because it could be hydrolyzed with hydrochloric acid to the dinitro-*m*-toluic acid he had already prepared. No direct comparison was made of the two samples of the dinitro acid and no comment was made about the ready hydrolysis of a di-*ortho* substituted benzoic ester.

In the second report of the dinitration of *m*-toluic acid, Hargreaves and McGookin[2] described the use of mixed acid to furnish in 60% yield a dinitro-*m*-toluic acid which they considered to be identical with the acid obtained by van Scherpenzeel. They converted the acid to the acid chloride with thionyl chloride. From the crude acid chloride with methanol they obtained a methyl ester, m.p. 104°, which confirms the identity of their acid and van Scherpenzeel's, and a second unidentified product, m.p. 67°, which casts doubt on the homogeneity of their acid.

Since the nitration of *m*-toluic acid with 100% nitric acid was so unpromising and inconvenient, we used mixed acid and obtained consistent yields of 85% of a crude product which is a mixture containing 2,6-dinitro- and 4,6-dinitro-*m*-toluic acid in approximately equal amounts. The two acids can be separated and structures may be assigned to them from the behavior of the crude product on heating with methanol containing sulfuric acid: 4,6-dinitro-*m*-toluic acid is converted to the methyl ester (m.p. 104°) while 2,6-dinitro-*m*-toluic acid is unaffected. The two reactions, nitration and treatment with methanol and sulfuric acid, show that the earlier workers actually had in hand an impure 4,6-dinitro-*m*-toluic acid rather than the 2,6-dinitro acid as they believed. It also follows from these two experiments that 2,6-dinitro-*m*-toluic acid and its esters have not hitherto been prepared, that the description of these compounds in the literature are erroneous, and that the substituted stilbenes prepared by Hargreaves and McGookin[2] from aromatic aldehydes and the 104° methyl ester have structure I rather than the structure II that was assigned to them.



I



II

(1a) L. van Scherpenzeel, *Rec. trav. chim.*, 20, 149–182 (1901).

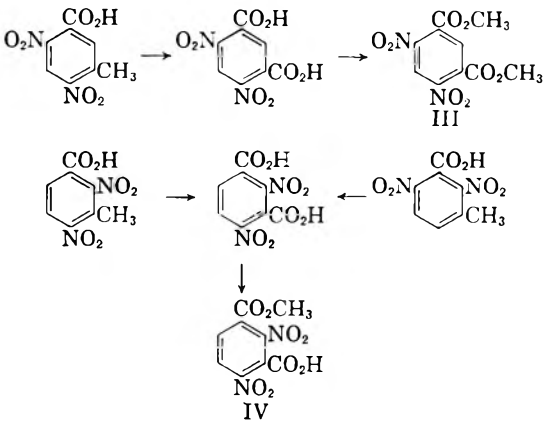
(1b) In *m*-toluic acid and its substitution products the carboxyl group and the methyl group are assigned positions 1 and 3, respectively.

(2) K. R. Hargreaves and A. McGookin, *J. Soc. Chem. Ind. (London)*, 69, 190 (1950).

We next nitrated methyl *m*-toluate by the same procedure we had used to nitrate the acid. This furnished in quantitative yield a product that is obviously identical with the unidentified esterification product described earlier by Hargreaves and McGookin. We first thought that this product, most samples of which melt fairly sharply in the neighborhood of 65°, might be methyl 2,6-dinitro-*m*-toluate. Actually it is a mixture that contains methyl 2,6-dinitro-*m*-toluate and methyl 4,6-dinitro-*m*-toluate in about a 5 to 4 ratio. On heating with concentrated hydrochloric acid, the crude ester mixture furnishes 4,6-dinitro-*m*-toluic acid and unattacked methyl 2,6-dinitro-*m*-toluate. Nitration of methyl *m*-toluate followed by heating with hydrochloric acid is therefore a route to the 4,6-dinitro acid and the methyl ester of the 2,6-dinitro acid, which complements the nitration and esterification described in the previous paragraph both as a preparative procedure and as a basis for assigning structure.

The structure of 2,6-dinitro-*m*-toluic acid and its methyl ester are adequately established by their resistance to esterification and hydrolysis, respectively. We have considered the isomeric dinitro acid to be the 4,6- rather than the 2,4-dinitro derivative because of the identity in melting point (104°) of the methyl ester prepared by (a) esterification of the acid in question, (b) dinitration of methyl *m*-toluate, and (c) esterification of the acid obtained by the partial oxidation of 4,6-dinitro-1,3-dimethylbenzene.[3] Direct comparison of the methyl ester prepared by routes (a) and (b) has been made, but no direct comparison has been made between these samples and the ester made by route (c). Instead of preparing the ester by route (c) and comparing it with our samples, we chose to confirm its structure by the following method which is independent of the orientation of 4,6-dinitro-1,3-dimethylbenzene.

Oxidation of 4,6-dinitro-*m*-toluic acid would yield 4,6-dinitroisophthalic acid, which should esterify to the neutral dimethyl ester III. Oxidation of 2,4-dinitro-*m*-toluic acid would yield 2,4-dinitroisophthalic acid, which should esterify to the acid monomethyl ester IV. On oxidation, our presumed 4,6-dinitro-*m*-toluic acid furnished a dinitroisophthalic acid which esterified to a dimethyl ester, thus establishing the correctness of the structure of the dinitro-*m*-toluic acid as the 4,6-isomer and confirming the orientation of 4,6-



dinitro-*m*-xylene and 4,6-dinitroisophthalic acid.[4] For completeness we also oxidized 2,6-dinitro-*n*-toluic acid and found, as we expected, that the resulting hitherto unknown 2,4-dinitroisophthalic acid esterifies only to the acid methyl ester IV.

The material in the preceding paragraphs provides new and somewhat different examples of the high *ortho-para* ratio in the nitration products of aromatic compounds containing a *meta*-directing group. The phenomenon and possible explanations for it have been discussed earlier[4a] so that it is necessary here only to mention by way of illustration that the nitration of benzonitrile furnishes, in addition to the principal product *m*-nitrobenzonitrile, the *ortho* and *para* nitrobenzonitriles in a ratio greater than 3:1. On statistical grounds a 2:1 ratio would be expected and steric effects should lower this ratio. *m*-Toluic acid and its methyl ester differ from the monosubstituted benzenes hitherto studied in that the 2-, 4-, and 6-positions would be activated. Statistically one would expect equal amounts of the 2,4-, 4,6-, and 2,6-dinitro derivatives, while steric factors would favor the 4,6-isomer at the expense of both the 2,4- and 2,6-isomers. One finds that all of the dinitration products are substituted in the 6-position, and that the ratio of 2-substitution to 4-substitution is about 1:1 with the acid and about 5:4 with the methyl ester. Since these ratios are based on products isolated (64% of the material was accounted for in the nitration of the acid and 80% in the nitration of the ester) we cannot say that none of the 2,4-dinitration product was formed. It is clear, however, that activation *ortho* to the nitro group is occurring and that it is sufficient to offset the considerable hindrance to substitution in the 2-position. Although our results constitute additional evidence of *ortho* activation, they do not enable us to add to or distinguish between the explanations already advanced.

Two other items should be mentioned. The first is the extraordinary solubility in water of 2,6-dinitro-*m*-toluic acid: 1 g. of the acid will dissolve

(3) R. D. Haworth and P. R. Jeffries, *J. Chem. Soc.*, 2069 (1951).

(4) T. Nozoe, Y. Kitahara, K. Yamane, and K. Yamaki, *Proc. Japan Acad.*, **26**, No. 8, 14–18 (1950) [*Chem. Abstr.*, **45**, 7097 (1951)] reported that nitration of hinokitiol followed by oxidation furnished 4,6-dinitroisophthalic acid, m.p. 240–241°. The acid, which was crystallized from boiling water, gave a dimethyl ester, m.p. 141°. The properties of this acid and its dimethyl ester do not agree with those of 4,6-dinitroisophthalic acid and dimethyl 4,6-dinitroisophthalate. See the Experimental section.

(4a) Pertinent references are to be found in an article by George S. Hammond and Katharine J. Douglas, *J. Am. Chem. Soc.*, **81**, 1184 (1959).

in less than 5 ml. of hot water. Presumably, the crowding and resulting nonplanarity of the four adjacent substituents prevents close packing in the crystals and favors solvation at the carboxyl group. Similar striking solubility relations are observed with the dinitroisophthalic acids. The second is that the dinitro acids and their derivatives described in this paper show the yellow color that is characteristic of dinitro aromatic compounds in acetone solution in the presence of iodide ion.[5]

EXPERIMENTAL

We are indebted to the Hercules Powder Co. for the *m*-toluic acid and methyl *m*-toluate used in these experiments.

Melting points are uncorrected.

Nitration of m-toluic acid. Isolation of 2,6-dinitro-m-toluic acid and methyl 4,6-dinitro-m-toluate. Nitrating acid was prepared from 89 ml. of chilled fuming nitric acid (*d.* 1.5) and an equal volume of chilled fuming sulfuric acid (30% sulfur trioxide) in a 500-ml., three-necked, round-bottomed flask that was fitted with a mechanical stirrer and thermometer and was surrounded by an ice-water bath. The temperature of the nitrating acid was kept between 25 and 30° during its preparation and during the subsequent nitration.

Stirring and cooling were continued while 27.2 g. (0.2 mole) of *m*-toluic acid was added in portions. As soon as the addition was complete—about 50 min. was required—the cooling bath was removed. Stirring was continued for 90 min., then the reaction mixture, which usually contained a considerable amount of precipitate, was drowned on 400 g. of ice. The solid was filtered, washed with 75 ml. of water, stirred for a few minutes with 100 ml. of water, filtered, and dried. The yield of crude product, an almost white solid that turns superficially yellow on prolonged exposure to light, averaged 38.5 g. (85%). On heating, the product begins to soften at about 155° and melts from 162 to 170°. If larger amounts of ice are used to decompose the reaction mixture or more water is used to wash the product, the yield decreases.

In order to separate the reaction products, 22.6 g. (0.1 mole) of the crude dinitro-*m*-toluic acids was dissolved in 226 ml. of cold absolute methanol and 22.6 ml. of cold concd. sulfuric acid was added. The solution, protected from moisture, was heated under reflux for 16 hr. and then chilled. The precipitate of methyl 4,6-dinitro-*m*-toluate was filtered, and the filtrate was diluted with 400 ml. of ether and shaken with one 300-ml. and two 150-ml. portions of water. The ether was then extracted with 1% aqueous sodium carbonate and dried over sodium sulfate. Evaporation of the ether left methyl 4,6-dinitro-*m*-toluate.

The sodium carbonate extract was freed of ether by a current of air, filtered if necessary, acidified with hydrochloric acid, and extracted with an equal volume of ether divided in two portions. The combined ether extracts were washed with water, dried over sodium sulfate, and evaporated to leave a residue of 2,6-dinitro-*m*-toluic acid as an off-white solid.

The average recovery in a series of these separations was 7.7 g. of crude ester (32%) m.p. 94–98°, and 7.5 g. of acid (33%) m.p. 174–178°. After it had been established that the two isomeric dinitro-*m*-toluic acids were present in approximately equal amounts in the crude dinitration product, a single separation was carried out with half the amounts of methanol and sulfuric acid called for above. This gave a 75%, instead of a 65%, recovery with a small but not significant increase in the relative amount of the 2,6- acid.

It should be possible to separate the mixture of dinitro-*m*-toluic acids without going through the esterification just described, for the 2,6-dinitro acid is far more soluble in hot water than is the 4,6-dinitro acid. (See below.) We have not attempted to work out a procedure for such a separation.

Nitration of methyl m-toluate. Isolation of 4,6-dinitro-m-toluic acid and methyl 2,6-dinitro-m-toluate. The nitrating mixture was prepared from 110 ml. of fuming nitric acid and 110 ml. of fuming sulfuric acid as described for the preceding nitration. To the stirred mixed acid, whose temperature was held between 20° and 30° by an ice-water bath, was added dropwise 30 g. (0.20 mole) of methyl *m*-toluate during 20 min. The ice bath was removed and the clear yellow solution was stirred for an hour, then poured onto 450 g. of ice. The precipitate was filtered, washed with water, and dried to yield 48 g. (quant.) of a pale yellow solid. The crude product usually melts over less than a 2° range, *e.g.*, 63–65°, with some preliminary softening.

In order to separate the nitration products, 24 g. (0.1 mole) of the crude ester mixture was suspended in 400 ml. of concd. hydrochloric acid and heated under reflux for 24 hr. during which time a slow stream of nitrogen was bubbled through the reaction mixture to reduce oxidative discoloration and to remove methanol and methyl chloride. The reaction mixture was cooled and ether was added to dissolve the dark yellow oil and admixed crystals. Water was added, the aqueous acid layer was discarded, and the ether was washed three times with water. The ether was then extracted with 1% aqueous sodium carbonate, washed with water, and dried over sodium sulfate. On evaporation, the ether left methyl 2,6-dinitro-*m*-toluate, m.p. 80–83°. The sodium carbonate extract was freed of dissolved ether by an air stream, filtered if necessary, and acidified with hydrochloric acid which precipitated 4,6-dinitro-*m*-toluic acid as an off-white solid, m.p. 166–170°.

The average recovery in a number of these separations was 12 g. of methyl 2,6-dinitro-*m*-toluate (50%) and 7 g. of 4,6-dinitro-*m*-toluic acid (30%). By extracting with ether the acidified sodium carbonate extract from which the 4,6-dinitro acid had precipitated, it was possible to increase the recovery of that acid to about 40%, but the additional material obtained in this way was of such poor quality that the extra operation was not worthwhile.

By crystallizing the crude dinitro ester mixture from methanol one can obtain reasonable amounts of methyl 4,6-dinitro-*m*-toluate, the less soluble of the two esters, and by a laborious and inefficient fractional crystallization from the same solvent one can isolate identifiable amounts of methyl 2,6-dinitro-*m*-toluate. We have not, however, been able to work out a satisfactory procedure for separating the ester mixture into its components by crystallization.

4,6-Dinitro-*m*-toluic acid is an almost colorless solid with a faint yellow cast. On exposure to direct sunlight the material turns superficially bright yellow. The acid is exceedingly soluble in the common organic solvents except ligroin or benzene. It can be crystallized from benzene (*ca.* 40 ml./g.) or water (*ca.* 50 ml./g.) with a 75% recovery. The pure acid, obtained in this way as very fine transparent crystals, melts at 178–179°.

The acid is esterified only slowly with methanol or ethanol and sulfuric acid. When 1 g. of the acid is heated under reflux with 10 ml. of methanol or ethanol and 1 ml. of concd. sulfuric acid, 16 hr. is required for complete esterification. *Methyl 4,6-dinitro-m-toluate*, obtained by esterification of the acid or by nitration of methyl-*m*-toluate, is very soluble in hot benzene, methanol, acetone, dioxane, tetrahydrofuran, dimethylformamide, or pyridine and is only very sparingly soluble in the same solvents cold. It is very slightly soluble in ether. The ester can be purified conveniently by crystallization from methanol (*ca.* 10 ml./g.; recovery, 85%). The pure ester is obtained as small pale yellow crystals that melt at 103–104°. The ester is hydrolyzed slowly by aqueous hydrochloric acid: 1.2 g. of ester heated under reflux with 20 ml. of concd. hydrochloric acid requires 16 hr. for complete hydrolysis.

(5) A. H. Blatt and Norma Gross, *J. Org. Chem.*, **22**, 1046 (1957).

Ethyl 4,6-dinitro-m-toluate can be prepared by esterifying the acid with ethanol as described above for the methyl ester. It can also be prepared by heating the acid, suspended in benzene, with excess thionyl chloride until the solid goes into solution (*ca.* 4 hr.), adding excess absolute ethanol, heating for a short time, and then evaporating the solvents. Both procedures give better than 90% yields. The ester is purified by dissolving it in ethanol at 35° and cooling the solution slowly. The pure ester, pale yellow crystals, melts at 47–48°.

Anal. Calcd. for $C_{10}H_{10}N_2O_6$: C, 47.24; H, 3.93. Found: C, 47.17; H, 4.11.

This ester has previously been prepared by esterification of the acid obtained by the partial oxidation of 4,6-dinitro-1,3-dimethylbenzene. It was described[6] as brown prisms, m.p. 61–62°. We have no explanation for the difference in color and melting point between the earlier sample and ours.

Oxidation of 4,6-dinitro-m-toluic acid to 4,6-dinitroisophthalic acid. The procedure was taken from that of Ruggli and Schmid for the oxidation of 4,6-dinitro-1,3-dimethylbenzene.[7] A solution of 4.6 g. of 4,6-dinitro-*m*-toluic acid in 60 ml. of concd. sulfuric acid was stirred and chilled in an ice-salt bath to −7°, then a solution of 4.6 g. of chromium trioxide in 6.5 ml. of water was added dropwise slowly enough to permit the temperature of the reaction mixture to be held below 20°. Stirring was continued until the temperature dropped to 5°, when the reaction mixture was poured onto 300 g. of ice. The precipitate of unoxidized acid, 1.2 g., identified by melting point and mixed melting point, was removed by filtration and the filtrate was extracted with 120 ml. and then 60 ml. of ether. The ether, after washing, drying, and evaporating, left 3 g. of crude dinitroisophthalic acid, which melted at 241–243° after it had been digested with hot benzene. The pure acid, crystallized by solution in nitrobenzene at 160°, was obtained as sandy transparent crystals, m.p. 246–247° dec.

Since our material melted higher than the material prepared by Ruggli and Schmid by the oxidation of 4,6-dinitro-1,3-dimethylbenzene (246° *vs.* 234°), we esterified our product not only with methanol but also with ethanol so as to be able to compare the melting point of the diethyl ester with that reported by Ruggli and Schmid.

A solution of 1.28 g. of 4,6-dinitroisophthalic acid in 22.6 ml. of absolute methanol and 2.26 ml. of concd. sulfuric acid was heated under reflux for 16 hr. during which time a large precipitate of glistening white crystals formed in the hot solution. The precipitate was filtered, the filtrate was diluted with ether, washed with water, and extracted with 10 ml. of 1% aqueous sodium carbonate. On evaporation the ether left 0.3 g. of product which, with the original precipitate, made a total yield of 1.25 g. or 88%. The strongly alkaline carbonate extract on acidification furnished a small precipitate which was rejected since the ester already obtained accounted for 88% of the starting material.

The dimethyl ester was purified for analysis by crystallization from methanol and by solution in acetone followed by addition of methanol and heating to expel most of the acetone. The pure ester, obtained as colorless glistening crystals which are moderately soluble in hot acetone and very sparingly soluble in hot methanol, melts at 162–163°.

Anal. Calcd. for $C_{10}H_8N_2O_8$: C, 42.25; H, 2.8; OCH_3, 21.8. Found: C, 42.71; H, 2.83; OCH_3, 21.35.

The diethyl ester, prepared in 86% yield in the same way as its lower homolog, melted at 126°, in satisfactory agreement with the melting point of 124° given by Ruggli and Schmid for a sample prepared from the silver salt of the acid and ethyl iodide.[7]

(6) G. Errera and R. Maltese, *Gazz. chim. ital.*, **33**, II, 277 (1903).

(7) P. Ruggli and O. Schmid, *Helv. Chim. Acta*, **18**, 247 (1935).

Anal. Calcd. for $C_{12}H_{12}N_2O_8$: C_2H_5O, 28.84. Found C_2H_5O, 28.45, 29.48.

2,6-Dinitro-m-toluic acid is an almost colorless solid with a faint yellow cast. It is very soluble in the common organic solvents except ligroin or benzene and is remarkably soluble in hot water: 1.0 g. requires less than 5 ml. of water for solution on the steam bath and about 0.75 g. crystallizes on cooling the solution. Benzene is the most satisfactory solvent for purification: 1.0 g. of the acid dissolves in about 50 ml. of benzene and 0.75 g. can be recovered on cooling. The pure acid, obtained in large transparent chunky crystals from benzene and in very small crystals from water, melts at 182–183° with considerable sublimation.

Anal. Calcd. for $C_8H_6N_2O_6$: C, 42.48; H, 2.67. Found: C, 42.74; H, 2.81.

The hindrance to esterification of the 2,6-dinitro acid is pronounced. When 1.0 g. of the acid in 10 ml. of absolute methanol and 1 ml. of concd. sulfuric acid was heated under reflux for 16 hr.—conditions under which the isomeric 4,6-dinitro acid is quantitatively esterified—only enough of the methyl ester was formed to permit identification by melting point and mixed melting point.

Methyl 2,6-dinitro-m-toluate can be prepared by the nitration of methyl *m*-toluate (see above) and in quantitative yield from the acid by conversion to the acid chloride with thionyl chloride followed by reaction of the crude acid chloride with methanol. The ester crystallizes as large chunky pale yellow lozenges that melt at 83–84°. Its solubility is similar to but greater than that of the isomeric 4,6-dinitro ester. It is conveniently purified by crystallization from methanol (*ca.* 5 ml./g.) with an 80–85% recovery.

Anal. Calcd. for $C_9H_8N_2O_6$: C, 45.0; H, 3.33. Found: C, 45.67; H, 3.40.

The ester is resistant to hydrolysis. A suspension of 1.2 g. of the ester in 20 ml. of concd. hydrochloric acid was heated under reflux for 24 hr. in a nitrogen stream. The material solidified on cooling. It was dissolved in ether and the ether shaken out with 1% aqueous sodium carbonate. The carbonate extract on acidification gave no precipitate and an ether extract of the acidified carbonate solution yielded only about 0.06 g. of the 2,6-dinitro acid, which corresponds to about 5% hydrolysis. (The isomeric 4,6-dinitro ester is completely hydrolyzed in 16 hr. under the same conditions.) The original ether solution that had been shaken out with sodium carbonate left unhydrolyzed ester on evaporation.

Ethyl 2,6-dinitro-m-toluate was prepared by converting the acid to the acid chloride with thionyl chloride in the presence of benzene as a solvent and heating the crude acid chloride with absolute ethanol. The yield of crude ester left on evaporation of the solvents at room temperature was quantitative. The ester was purified by dissolving it in ethanol at 35°, filtering, and cooling the filtrate slowly. A second crystallization from a larger volume of ethanol diluted with a little water after filtering did not change the melting point, 58–59°. The pure ester is colorless.

Anal. Calcd. for $C_{10}H_{10}N_2O_6$: C, 47.24; H, 3.93. Found: C, 47.33; H, 3.99.

2,6-Dinitro-*m*-toluic acid was oxidized to 2,4-dinitroisophthalic acid by the procedure described above for the oxidation of 4,6-dinitro-*m*-toluic acid. The amount of unoxidized 2,6-dinitro-*m*-toluic acid that precipitated on pouring the reaction mixture into water was small: 2,6-dinitro-*m*-toluic acid is quite soluble in water. Evaporation of the ether extract gave 2.1–2.3 g. of crude product which was purified for analysis by crystallization from nitrobenzene and then from ether–petroleum ether (b.p. 60–90°). The pure acid melts at 246–247°, as does the isomeric 4,6-dinitroisophthalic acid. Mixtures of the two acids melt from 215 to 225°.

Anal. Calcd. for $C_9H_4N_2O_8$: C, 38.28; H, 1.56. Found: C, 38.22; H, 1.86.

2,4-Dinitroisophthalic acid was esterified with methanol and sulfuric acid following the procedure described above

for the preparation of dimethyl 4,6-dinitroisophthalate. No precipitate formed on cooling the reaction mixture so the solution was diluted with ether and shaken out three times with water to remove sulfuric acid and most of the methanol. The ether was then shaken out with 1% aqueous sodium carbonate; 20 ml. was required. The carbonate extract freed of ether was acidified and furnished the crude acid methyl ester IV in 43% yield. The poor yield is probably a result of the high solubility of the acid ester. No attempt was made to obtain more of the acid ester from the water washings or the acidified carbonate extract. The ether solution that had been extracted with sodium carbonate left no residue on evaporation showing that no neutral ester had been formed. The acid methyl ester is too soluble in aqueous methanol to permit crystallization from that solvent. For analysis, the material was crystallized from ether–petroleum ether (b.p. 60–90°). The pure methyl acid ester IV melts at 184–185°.

Anal. Calcd. for $C_9H_6N_2O_8$: CH_3O, 11.1. Found: CH_3O, 11.44.

DEPARTMENT OF CHEMISTRY
QUEENS COLLEGE
FLUSHING, N. Y.

Reaction of Hydrogen Bromide with Conjugated Dienols[1]

R. L. LOHMAR, C. R. SMITH, JR., AND T. L. WILSON

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Dimorphecolic acid, the major fatty acid of *Dimorphotheca aurantiaca* seed oil, rapidly consumes essentially one molar equivalent of hydrogen bromide in the Durbetaki titration for oxirane oxygen.[2] Formulation of this acid as 9-hydroxy-*trans*,*trans*-10,12-octadecadienoic acid indicated no grouping known to consume hydrogen bromide in this manner. We report here a comparison of the behavior of dimorphecolic acid with that of two model compounds, 2,4-hexadiene-1-ol (sorbyl alcohol) and 4,6-octadiene-3-ol, when treated with hydrogen bromide in nonaqueous media.

Although several aliphatic compounds with a secondary hydroxyl group in α-position to a conjugated diene are known, their behavior toward hydrogen bromide has not been examined. Kuhn and Grundmann[3] showed that 4,6-octadiene-3-ol is readily dehydrated by *p*-toluenesulfonic acid to 2,4,6-octatriene. Heilbron and co-workers,[4] as well as Braude and co-workers,[5] examined the effect of acid catalysts on related unsaturated alcohols. They found that compounds containing the system —CH=CH—CHOH—CH=CH— showed a pronounced tendency to rearrange to secondary conjugated dienols (—CHOH—CH=CH—CH=CH—) which were readily dehydrated to trienes. Heilbron examined the action of hydrochloric acid on the closely related hex-4-ene-1-yne-3-ol and similar compounds. Rearrangement similar to that of the dienols was observed, accompanied by replacement of hydroxyl by chlorine. However, the action of hydrobromic acid led to "unstable heterogeneous products."

2,4-Hexadiene-1-ol does not consume hydrogen bromide under the conditions of the Durbetaki[6,7] titration, but 4,6-octadiene-3-ol behaves in a manner analogous to that of dimorphecolic acid. It rapidly consumes a like amount of hydrogen bromide. Ultraviolet absorption studies indicate that essentially all the dienoid absorption is preserved immediately after titration, but triene is then formed at a slower rate. Appearance of triene is accompanied by disappearance of diene, suggesting that an initially formed bromodiene is dehydrobrominated. Similar results are obtained when a chloroform solution of hydrogen bromide is used rather than an acetic acid solution. Hydrogen chloride in acetic acid is not consumed rapidly.[8] Treatment of the octadienol with two thirds the titrimetric amount of hydrogen bromide results in eventual turning of the indicator. This observation supports the interpretation of replacement followed by elimination. The presence of free acid in mixtures that had stood some time after Durbetaki titration was confirmed by the rapid neutralization of sodium carbonate dissolved in acetic acid.

Although consumption of hydrogen bromide appears to be stoichiometric or nearly so, formation of triene is not. Diene and triene are in equilibrium (Fig. 1). The molar sum of conjugated diene and triene is 75–80% of that expected. The fate of the remainder is not known, but a possibility exists that in the equilibrium reaction some of the hydrogen bromide is added to yield a nonconjugated bromodiene that would not be estimated by the spectral method used. Conversion of diene to triene is reminiscent of the results Bergström and Hansson[9] obtained by treating linoleate with *N*-bromosuccinimide. The initially formed conjugated dienoid bromide lost hydrogen bromide to form a conjugated triene. They also observed that about 30% of the bromide was not eliminated, even after prolonged refluxing.

The mechanism sequence may resemble that proposed by DeWolfe and Young[10] for the reaction of

(1) This is a contribution from the laboratory of the Northern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture. Article not copyrighted.

(2) C. R. Smith, Jr., T. L. Wilson, E. H. Melvin, and I. A. Wolff, *J. Am. Chem. Soc.*, **82**, 1417 (1960).

(3) R. Kuhn and C. Grundmann, *Ber.*, **71**, 442 (1938).

(4) I. M. Heilbron, J. T. McCombie, and B. C. L. Weedon, *J. Chem. Soc.*, **1945**, 84, and preceding papers.

(5) E. A. Braude and J. A. Coles, *J. Chem. Soc.*, **1951**, 2085, and preceding papers.

(6) A. Durbetaki, *Anal. Chem.*, **28**, 2000 (1956).

(7) American Oil Chemists' Society, "Official and Tentative Methods," 2nd ed. (1958 revision), Method Cd 9-57.

(8) Miss Glenda Geisinger carried out this experiment.

(9) S. Bergström and G. Hansson, *Acta Chem. Scand.*, **4**, 435 (1950).

(10) R. H. DeWolfe and W. G. Young, *Chem. Revs.*, **56**, 753 (1956).

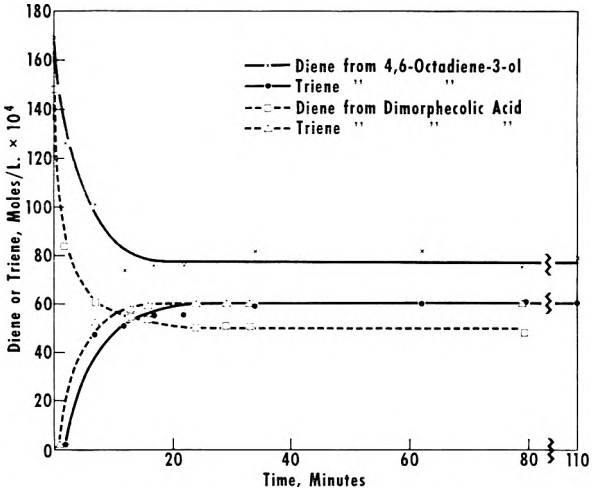

Fig. 1. Effect of hydrogen bromide on 4,6-octadiene-3-ol and on dimorphecolic acid

monoethenoid allylic alcohols with hydrogen bromide, followed by elimination to form triene. Interpretation of the initial substitution as an S_N2 mechanism is favored by the similar uptake of hydrogen bromide in either acetic acid or chloroform solution, by the slower uptake of the more weakly nucleophilic hydrogen chloride, and by the appearance of triene only after the uptake of hydrogen bromide, rather than concurrently as would occur from a carbonium ion intermediate in an S_N1 scheme. However, an S_N1 route is strongly supported by the lack of uptake of hydrogen bromide by the primary alcohol, 2,4-hexadiene-1-ol, which should have a lesser tendency toward carbonium ion formation than the secondary dienols.[11]

EXPERIMENTAL

Dimorphecolic acid. An analytically pure sample was prepared by chromatographing acid isolated by solvent partitioning of mixed acids from *Dimorphotheca aurantiaca* seed oil.[12] A benzene solution of acid (0.5 g.) was added to a silica gel column (5 g.) pretreated with 80% aqueous methanol:-hexane (1:1). The pure acid (0.22 g.) was eluted by benzene under nitrogen. It was a semisolid at room temperature. $\lambda_{max}^{C_2H_5OH}$ 231, ϵ 28,800.

Anal. Calcd. for $C_{18}H_{32}O_3$: C, 73.0; H, 10.8. Found: C, 73.3; H, 10.9.

Trans,trans-2,4-hexadiene-1-ol. Ethyl sorbate was reduced by lithium aluminum hydride by a slight modification of the method of Nystrom and Brown.[13] The alcohol was obtained as a colorless mobile liquid. Its 3,5-dinitrobenzoate, prepared according to Reichstein and co-workers,[14] melted at 82–84° (Fisher-Johns[15] block) (lit. m.p., 85°).

Trans,trans-4,6-octadiene-3-ol. Technical grade hexadienal[16] was purified by distillation at 65.5–66°/18 mm., $\lambda_{max}^{C_2H_5OH}$ 271, ϵ 28,700. Hausser, *et al.*[17] reported ϵ 26,500. The distilled hexadienal was condensed with ethylmagnesium bromide according to Kuhn and Grun lmann[3] to give the octadienol (78%) $\lambda_{max}^{C_2H_5OH}$ 229, ϵ 24,2)). Distillation at 77–79°/20 mm. gave a product having $\lambda_{max}^{C_2H_5OH}$ 229. ϵ 28,400, n_D^{18} 1.4895 (lit., 1.4892).

Hydrogen bromide consumption. Uptake of hydrogen bromide by the unsaturated alcohols was determined by Durbetaki titration[6,7] in benzene–acetic acid solution. For spectral studies, acetic acid only was used as solvent. This solvent change reduced the molar hydrogen bromide uptake to 0.77 (from 0.9 or higher).

Hydrogen bromide reactions. The unsaturated alcohols (0.15–0.2 mmole) were dissolved in 5–10 ml. of glacial acetic acid and were treated with a volume of 0.03–0.05*N* hydrogen bromide in acetic acid found, by prior titration, to be rapidly consumed. At intervals, 0.1-ml. aliquots were removed and diluted to 100 ml. with absolute ethanol. Conjugated diene was determined in 1-cm. cells in a Beckman Model DU spectrophotometer, using the experimentally determined extinction coefficients given above. A molecular extinction of 59,200 at 264 mμ[18] was used for conjugated triene. Data in Fig. 1 are from one of several similar experiments.

NORTHERN REGIONAL RESEARCH LABORATORY
PEORIA, ILL.

(11) E. R. Alexander, *Principles of Ionic Organic Reactions*, John Wiley & Sons, New York, 1950, p. 41.

(12) C. R. Smith, Jr., M. C. Burnett, T. L. Wilson, R. L. Lohmar, and I. A. Wolff, *J. Am. Oil Chemists' Soc.*, 37, 320 (1960).

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(15) Mention of firm names or trade products does not imply that they are endorsed or recommended by the U. S. Department of Agriculture over other firms or similar products not mentioned.

(16) Generously supplied by Union Carbide Chemicals Co.

(17) K. W. Hausser, R. Kuhn, A. Smakula, and M. Hoffer, *Z. physik. Chem.*, B29, 371 (1935).

(18) American Oil Chemists' Society, "Official and Tentative Methods," 2nd ed. (1958 revision), Method Cd 7-58.

Specificity of the Phenolic Component for Sakaguchi Reaction[1]

KSHIROD R. BHATTACHARYA, JYOTIRINDRA DATTA, AND DURLAV K. ROY

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In 1925, Sakaguchi observed that an intense red color was produced when arginine was treated in alkaline solution with 1-naphthol and hypohalite[2]; it was found later that the reaction was specific for a class of monosubstituted guanidines.[2,3] The specificity of the phenolic component for this reaction has not, however, been studied adequately

(1) (a) This constitutes Paper V in a series *Studies on Sakaguchi Reaction;* for Paper IV, see K. R. Bhattacharya, *Ann. Biochem. Exptl. Med.*, 20, 57 (1960). (b) Presented in part by K. R. Bhattacharya and J. Datta before the 46th session of the Indian Science Congress Association, Delhi, January 21–28, 1959.

(2) S. Sakaguchi, *J. Biochem. (Tokyo)*, 5, 25 (1925). See for review R. J. Block and D. Bolling, *The Amino Acid Composition of Proteins and Foods*, 2nd Ed., Charles C. Thomas, Springfield, Ill., 1951, p. 47.

(3) (a) C. J. Weber, *J. Biol. Chem.*, 86, 217 (1930). (b) J. D. Mold, J. M. Ladino, and E. J. Schantz, *J. Am. Chem Soc.*, 75, 6321 (1953).

so far, although a few aromatic hydroxy compounds other than 1-naphthol have been employed from time to time in analytical work as useful substitutes for the latter.[4] Color response of various substituted phenols to this reaction was therefore studied in detail. It was hoped that apart from throwing useful light on the mechanism of the reaction, this might also indicate the point of coupling between the guanidine and the phenolic residues in the colored reaction product.[9]

In Table I are listed a few of the results obtained with arginine. That all the indicated positive tests were in response to specific Sakaguchi reactions was shown by the fact that no other amino acid nor creatine could replace arginine in these color reactions, but glycocyamine[2,3a] reacted positively like arginine. It is clear from these results that the Sakaguchi reaction is actually a general reaction of phenolic compounds but that a free *para* position in the phenol is specifically required for participation in it. The positive response of a few (though not all) *p*-halophenols (also observed earlier[4]) is admittedly at variance with the latter requirement, but such occasional exceptional behavior of some *p*-halophenols is not without precedent. Thus although the Gibbs indophenol reaction[11a] is in general specific for *para*-unsubstituted phenols, *p*-chlorophenol is able to give the same reaction.[11b] Similarly, in the indophenol reaction between *p*-aminodimethylaniline and phenols in presence of hypohalite, *p*-cresol gives no reaction but *p*-chlorophenol does (although trichlorophenol, as in the present work, does not).[12] This behavior thus appears to be a property inherent in a phenolic *p*-halogen substituent itself which, under the conditions of these reactions, is apparently sufficiently activated to be eliminated or migrated to another position.

TABLE I

COLOR PRODUCTION BY VARIOUS PHENOLIC COMPOUNDS BY SAKAGUCHI REACTION WITH ARGININE

Compound	Color Produced[a]	Relative Intensity of Color[b]
Phenol	LY	++
p-Phenylphenol	—	...
o-Cresol	Y	+++
m-Cresol	GY	++++
p-Cresol	—	...
Thymol	GY	++++
Salicylic acid	Y	++
p-Hydroxybenzoic acid	—	...
o-Aminophenol	LY	±
p-Aminophenol	—	...
Resorcinol	Y	±
Hydroquinone	—	...
o-Chlorophenol	LY	++
p-Chlorophenol	LY	++
2,4-Dichlorophenol	LY	±
2,4,6-Trichlorophenol	—	...
1-Naphthol-8-sulfonic acid	R	++++
1-Naphthol-4-sulfonic acid	—	...
1,4-Naphthoquinone	—	...
5-Quinolinol	RS	++++
2-Methyl-4-quinolinol	—	...
2-Naphthol	B	++
2-Naphthol-6-sulfonic acid	B	+
1-Nitroso-2-naphthol	—	...

[a] Y = Yellow; LY = lemon yellow; GY = golden yellow; R = red; B = brown; RS = reddish saffron;— = none. These refer to the color in alkaline soln. In acid,[10] the color varied from very faint (in the case of a benzene ring) to fairly strong (naphthalene or quinoline ring) yellow. [b] The intensities are based on visual comparison. The larger the number of plus signs, the higher is the color intensity. The sign ± indicates very feeble coloration.

The overall nature of the Sakaguchi reaction would thus place it in the general class of the coupling-type reactions of phenols, the point of coupling being limited here to the carbon atom at position *para* with respect to the phenolic hydroxyl.[13] More specifically, however, the great similarity in the circumstances of reaction and in the nature and specificity of the reactants involved (including the singular reactivity of some *p*-halophenols) suggest in particular that there is probably a good deal of similarity between the mechanism of Sakaguchi reaction and those of the two indophenol reactions noted above (and probably other indophenol and indamine reactions as well). This view is further strengthened by our recent finding[9b] that the colored product of this reaction also, like the indophenols, behaves as a typical redox system. Another very similar indophenol reaction is that between ammonia and phenol mediated by hy-

(4) The following compounds have been used: 8-quinolinol,[5] 7-chloro-8-quinolinol, and 5,7-dichloro-8-quinolinol,[5b] 1-naphthol-8-sulfonic acid,[6] 2,4-dichloro-1-naphthol,[7] and 2-naphthol.[8]

(5) (a) S. Sakaguchi, *J. Biochem.* (*Tokyo*), **37**, 231 (1950). (b) J. W. Janus, *Nature*, **177**, 529 (1956).

(6) H. Kraut, E. von Schrader-Beielstein, and M. Weber, *Z. physiol. Chem.*, **286**, 248 (1950). Cited in *Chem. Abstr.*, **47**, 5977-a (1953).

(7) J. McLeish and H. S. A. Sherratt, *Exptl. Cell Research*, **14**, 625 (1958).

(8) P. M. Strocchi and P. Drago, *Ann. chim.* (*Rome*), **44**, 836 (1954). Cited in *Chem. Abstr.*, **49**, 6035-d (1955).

(9) See discussion in (a) K. R. Bhattacharya, J. Datta, and D. K. Roy, *Arch. Biochem. Biophys.*, **77**, 297 (1958); (b) K. R. Bhattacharya, *Nature*, **184**, 53 (1959).

(10) See K. R. Bhattacharya, J. Datta, and D. K. Roy, *Arch. Biochem. Biophys.*, **84**, 377 (1959), for the effect of pH on color in the case of 1-naphthol.

(11) (a) H. D. Gibbs, *J. Biol. Chem.*, **72**, 649 (1927). See for review F. D. Snell and C. T. Snell, *Colorimetric Methods of Analysis*, Vol. III, 3rd Ed., D. Van Nostrand Company, Inc., New York, N. Y., 1953. pp. 106, 118. (b) M. B. Ettinger and C. C. Ruchhoft, *Anal. Chem.*, **20**, 1191 (1948).

(12) G. U. Houghton and R. G. Pelly, *Analyst*, **62**, 117 (1937).

(13) As neither *para*-substituted phenols nor a simple derivative of 4-quinolinol could participate in the reaction, any linkage through the aromatic hydroxyl group itself[2] or through positions *ortho* or *meta* to it can be safely ruled out. Similarly, the nonparticipation of hydroquinone or 1,4-naphthoquinone would show that the linkage is also not through the 2-position of a preformed *p*-quinone. With 2-naphthol, the linkage is apparently at position 1.

pohalite.[14] The only apparent difference between these two types of reaction is that, whereas in one the phenol is condensed with a simple amine (or ammonia) under the influence of hypohalite,[15] it is condensed with a guanido group in the other. It may thus be speculated that perhaps their products also parallel each other in structure, although it must be remembered that the indophenols and indamines as a class (blue, green or purple) differ appreciably from the products of Sakaguchi reaction (yellow to red) in being more intensely colored.

Incidentally, thymol, 5-quinolinol and 5-chloro-7-iodo-8-quinolinol (the latter in ethyl acetate solution), besides 8-quinolinol, gave sufficiently intense color to be of possible use as substitutes for 1-naphthol in the estimation of arginine by Sakaguchi reaction; 1-naphthol is known to have several disadvantages in this respect.[5b,6,10] With thymol, moreover, blank coloration was practically absent.

EXPERIMENTAL

Arginine and glycocyamine[2,3a] were employed as the guanidine compounds. Because of the advantage of a clear contrast between the color of the spot and that of the surrounding areas, the reactions were carried out on filter paper[9a] rather than in solution. Briefly, spots of arginine (or glycocyamine) were treated first with 2.5% potassium hydroxide in ethanol, then with a 0.1–0.2% solution of the phenol[16] in a suitable solvent, and finally with aqueous hypobromite solution (0.1–2 g. % bromine in 1*N* potassium hydroxide).

Note added in proof: After this note went to the press, a copy of the paper of Kraut *et al.*[6] has been procured. It has been noted that these workers, while selecting a suitable naphtholsulfonic acid for the method, found 1-naphthol-4-sulfonic acid to be ineffective in producing color by this reaction and so concluded that a free 4-position in 1-naphthol was apparently essential for Sakaguchi reaction.

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(14) A. P. Orr, *Biochem. J.*, **18**, 806 (1924); J. A. Russell, *J. Biol. Chem.*, **156**, 457 (1944).

(15) It is noteworthy that the 2,6-dibromoquinonechlorimine of Gibbs is itself prepared by the action of hypochlorite on 2,6-dibromo-*p*-aminophenol.[11a]

(16) We wish to express our appreciation to Prof. B. D. Tilak of the Department of Chemical Technology, University of Bombay, for generous gifts of 1-naphthol-4-sulfonic acid and 2-naphthol-6-sulfonic acid.

Isolation and Characterization of a Phenol Half-Salt

A. T. SHULGIN AND H. O. KERLINGER

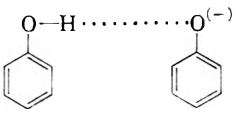
Received April 1, 1960

Many observations have been made of anomalous behavior at or near the half neutralization point in the nonaqueous titration of weak acids. In conductometric titration[1] conductivity maxima have frequently been recorded, whereas in potentiometric titration[2] there have been observed corresponding inflections or distortions in the titration curve.

These anomalies have been explained[2a] by the generation, during titration, of an association species in which the generated anion (of either a

$$R{-}O{-}H \ldots\ldots O^{-}{-}R$$

carboxylic acid or a phenol) protects an equivalent amount of acid, the association being stoichiometric at the half-titration point. This new species is then the acidic participant for the remainder of the titration. The evidence for such a material has been entirely physical and predominately spectroscopic. Pool[3] and Kaufman[4] have presented cryoscopic evidence for the formation of a solid compound composed of one molecule of a base and two molecules of a carboxylic acid, the latter preparing several half-salts between fatty acids and tertiary amines. Analysis of the infrared spectra of dilute solutions of carboxylic acids and tertiary amines[5] has yielded support for this same 2:1 relationship. Recently the alkali half-salts of several carboxylic peptide precursors have been described.[6] In the case of phenols, the evidence for this relationship with bases has been heretofore titrimetric The structural requirements of an unhindered —OH group,[1b,2a,b] and for the exclusion of appreciable amounts of polar solvents (as hydrogen bonding competitors)[1b] imply that the acid-anion structure is a dimer as shown:



We have found that the inclusion of a sterically hindered formamido group *para* to the phenolic —OH group greatly increases the stability of these half-salts, permitting their isolation and manipulation as discrete chemical substances.

When a solution of 4-formamido-3,5-xylenol in methyl isobutyl ketone is titrated with tetrabutylammonium hydroxide in solution in a mixture of methanol and isopropanol, there is obtained a titration curve typical of those described earlier.[2a] In addition, however, there is the generation of a

(1) (a) A. A. Maryott, *Journ. of Res. Nat. Bureau. Standards*, **38**, 527 (1947). (b) D. B. Bruss and G. A. Harlow, *Anal. Chem.*, **30**, 1836 (1958).

(2) (a) G. A. Harlow, and D. B. Bruss, *Anal. Chem.*, **30**, 1833 (1958). (b) H. B. van der Heijde, *Anal. Chem. Acta*, **16**, 392 (1957).

(3) W. O. Pool, H. J. Harwood, and A. W. Ralston, *J. Am. Chem. Soc.*, **67**, 775 (1945).

(4) S. Kaufman, and C. R. Singleterry, *J. Phys. Chem.*, **56**, 604 (1952).

(5) G. M. Barrow, *et al.*, *J. Am. Chem. Soc.*, **76**, 5211 (1954). *J. Am. Chem. Soc.* **77**, 4475 (1955). *J. Am. Chem. Soc.*, **78**, 5802 (1956).

(6) M. Goodman, and K. C. Stueben, *J. Org. Chem.*, **24**, 112 (1959).

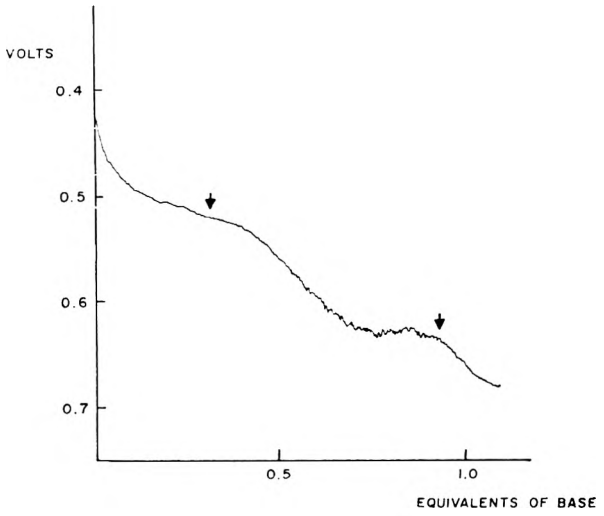


Fig. 1. Titration curve of 4-formamido-3,5-xylenol with tetrabutylammonium hydroxide. The arrows indicate the point of first appearance and of final disappearance of the crystalline half-salt

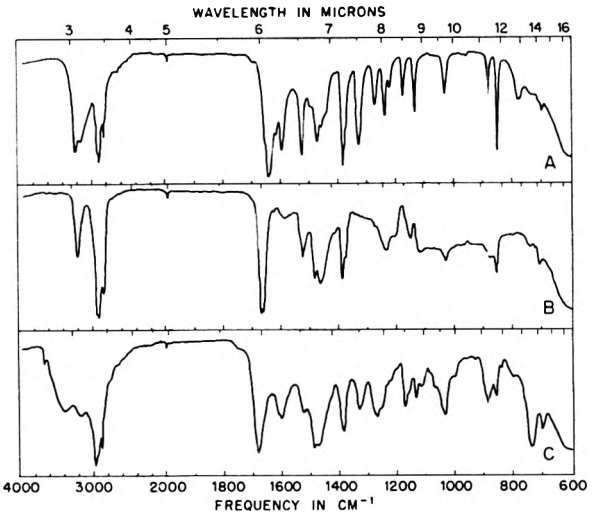


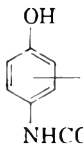
Fig. 2. Spectra of: a) 4-Formamido xylenol (mineral oil mull). b) 4-formamido xylenol·tetrabutylammonium 4-formamido xylenate (mineral oil mull). c) Tetrabutylammonium 4-formamido xylenate (smear). All from a Beckman prism-grating IR-7 spectrophotometer

crystalline product prior to the half-neutralization point, which redissolves prior to the final endpoint (see Fig. 1).

This material may be filtered free of the solvent and recrystallized as required. If the titration is continued to the full 1:1 endpoint, the normal salt is formed (in solution) from which the half-salt may be regenerated by the introduction of an additional mole of phenol. The normal salt cannot be isolated from this ketone medium, however.

As to the structural requirements permitting formation of an isolatable half-salt under these conditions, it appears that both a hindered formamido group and an unhindered —OH group are necessary. The acetamido homolog yielded no such precipitate.

The following table summarizes the structural requirements permitting the formation of a stable, insoluble half-salt with tetrabutylammonium hydroxide under the experimental conditions mentioned below.



R_1	R_2	Formulation of Half-Salt
H	H	−
2,6-CH_3	H	−
3,5 CH_3	H	+
3 CH_3,5 C_2H_5	H	+
3,5-C_2H_5	H	+
2,3,5-CH_3	H	+
2,3,5,6-CH_3	H	−
3,5-CH_3	CH_3	−

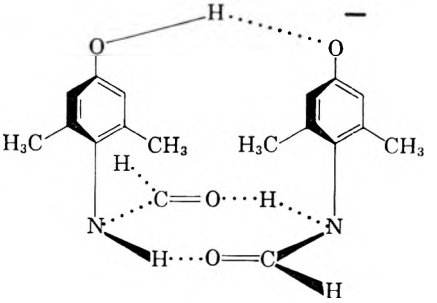
The solvent employed in the titration is not critical. Various diethers of ethylene glycol and diethylene glycol all yielded an insoluble half-salt and a redissolved normal salt. However, dioxane yielded a dark solution at the endpoint and lower ketones (acetone) were unsatisfactory.

When the tetrabutyl ammonium hydroxide was in water solution, apparently any solvent may be used in which both the phenol and water are soluble. Dimethyl formamide and diethylene glycol dimethyl ether were satisfactory.

The only other base employed was trimethylbenzylammonium hydroxide in methanol (with the phenol in methyl isobutyl ketone). The half-salt was a gummy solid, and was not further pursued.

Structure of the half-salt. Infrared spectra of the free phenol, the half-salt, and the normal salt of 4-formamido-3,5-xylenol and tetrabutylammonium hydroxide are shown in Fig. 2.

The unexpected stability of this half-salt, demonstrated by its formation in water and its insolubility, suggests a more strongly bonded dimer than one associated by the phenolic —OH alone. In the structure below these arguments are



achieved. Infrared spectra of dilute solutions (saturated in methylene chloride solution, 1 cm. cells) show no unbonded —OH in the half-salt, whereas the free phenol contains such an —OH (at 3595 cm.$^{-1}$).[7] Any attempt to provide a quinone-like structure for the anionic portion of the half-

salt must allow for the complete absence of color in all the half-salts observed so far.

EXPERIMENTAL

Acylamido phenols. All formulations and acetylations were performed as described by Smith, *et al.*[8] for the formation of 4-formamido-2,3,5-trimethylphenol from the aminophenol. It was desirable, however, to employ boiling water or a water–formic acid mixture as a recrystallization solvent, after prior treatment of the crude reaction product with charcoal.

4-Formamido phenol melted at 137.5–139° (from water).

4-Formamido-2,6-xylenol melted at 159–160° (from water).

4-Formamido-3,5-xylenol melted at 233° (from water).

5-Ethyl-4-formamido-m-cresol melted at 185–186° (from formic acid-water).

3,5-Diethyl-4-formamido phenol melted at 208–209° (from formic acid–water).

4-Formamido-2,3,5-trimethylphenol melted at 215° (from water).

4-Formamido-2,3,5,6-tetramethylphenol melted at 298° dec. (from formic acid–water).

4-Acetamido-3,5-xylenol was obtained as the monohydrate from water; m.p., 179–180.5°, with sintering at 90°. The anhydrous form may be obtained by dehydration with boiling benzene and recrystallization from ether-pentane.

4-Formamido-3,5-xylenol tetrabutylammonium 4-formamido-3,5-xylenate. Preparation in nonaqueous medium. A solution of 1.0 g. of 4-formamido-3,5-xylenol in a minimum amount of methyl isobutyl ketone was titrated to its normal endpoint with a full equivalent of 0.2*M* tetrabutylammonium hydroxide[2a] in isopropyl alcohol methanol (5:1 V/V). To this solution of the normal salt was then added an additional 1.0 g. of the parent phenol in a minimum amount of solvent. The mixture was stirred for 2 hr. during which time the half-salt was deposited as a white, crystalline solid. It was removed by filtration and washed sparingly with methyl isobutyl ketone. Recrystallization from acetonitrile yielded 2.5 g. (72%) of a fine, white microcrystalline product; m.p. 189° dec.

Anal. Calcd. for $C_{34}H_{57}N_3O_4$: C, 71.41%; H, 10.05%; N, 7.35%; neut. equiv. ($HClO_4$) 571. Found: C, 71.08%; H, 9.96%; N, 7.28%; neut. equiv. 560.

Preparation in aqueous medium. To a solution of 4-formamido-3,5-xylenol in three times its weight of dimethylformamide there was added exactly 0.5 equivalent to a 1*M* solution of tetrabutylammonium hydroxide in water (Southwestern Analytical Chemical Co.). Crystallization of the half-salt started immediately and was essentially complete in 10 min. Filtration and recrystallization yielded a product identical with that formed in preparation in nonaqueous medium, above.

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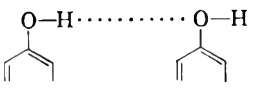
(7) This does not exclude a dimeric form for the free phenol, as a normal —OH group would still be expected for the unbonded form, and the bonded —OH may well lie outside of the narrow, transparent region available in methylene chloride.



Unfortunately, neither the free phenol nor the half-salt was sufficiently soluble in carbon tetrachloride or carbon disulfide to permit their use as solvents.

(8) L. I. Smith, H. H. Hoehn, and A. G. Whitney, *J. Am. Chem. Soc.*, **62**, 1867 (1940).

The Preparation of Tetrahydro-3,3,5,5-tetrakis(hydroxymethyl)pyran

THOMAS J. PROSSER

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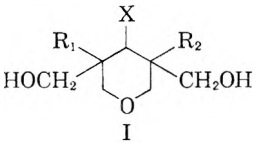
Limited evidence found in the literature indicates that the base catalyzed, exhaustive hydroxymethylation of ketones in which the carbonyl group is flanked by methylene groups gives rise to substituted tetrahydropyran-4-ols. Thus, the reaction of acetone and formaldehyde gives anhydroenneaheptitol (Ia),[1] whereas methyl ethyl ketone and diethyl ketone are reported to give tetra-

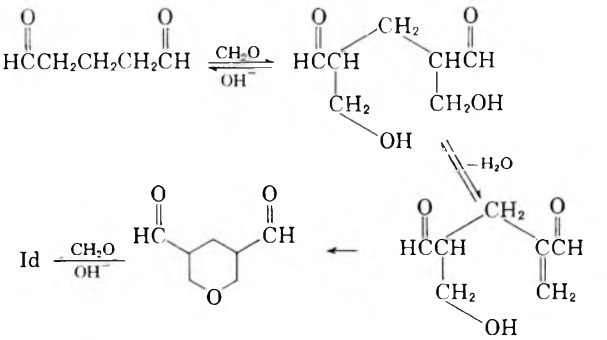


I

a) $R_1 = R_2 = CH_2OH$; X = OH
b) $R_1 = CH_2OH$; $R_2 = CH_3$; X = OH
c) $R_1 = R_2 = CH_3$; X = OH
d) $R_1 = R_2 = CH_2OH$; X = H

hydro-3,3,5-tris(hydroxymethyl)-5-methylpyran-4-ol (Ib) and tetrahydro-3,5-bis(hydroxymethyl)-3,5-dimethylpyran-4-ol (Ic), respectively.[2]

It has now been found that a similar reaction takes place in a 1,3-bis(methylene) system activated by terminal aldehyde groups rather than by a central ketone function. The exhaustive hydroxymethylation of glutaraldehyde gives the previously unreported tetrahydro-3,3,5,5-tetrakis(hydroxymethyl)pyran (Id). A general reaction mechanism would seem to apply to all of the above cases. The following scheme is proposed for the glutaraldehyde-formaldehyde reaction and is analogous to that suggested for the formation of dipentaerythritol in the preparation of pentaerythritol from acetaldehyde and formaldehyde.[3]



The tetraacetate, dibenzylidene acetal, and diisopropylidene ketal derivatives of Id were prepared.

(1) M. Apel and B. Tollens, *Ber.*, **27**, 1089 (1894), *Ann.*, **289**, 46 (1896); C. Mannich and W. Brose, *Ber.*, **55**, 3155 (1922).

(2) I. R. Roach, H. Wittcoff, and S. E. Miller, *J. Am. Chem. Soc.*, **69**, 2651 (1947).

(3) S. Wawzonek and D. A. Rees, *J. Am. Chem. Soc.*, **70**, 2433 (1948).

EXPERIMENTAL[4]

Tetrahydro-3,3,5,5-tetrakis(hydroxymethyl)pyran (Id). To 236 g. (3.30 moles) of 42% aqueous formaldehyde solution adjusted to *p*H 11.0 by addition of 50% sodium hydroxide solution was added 200 g. (0.50 mole) of 25% aqueous glutaraldehyde (Union Carbide Chemicals Co.) at 40–45° over a 1-hr. period. Thereafter, the temperature of the mixture was held at 50, 60, and 70° for 4, 3, and 2 hr., respectively. A *p*H of 11.0 was maintained throughout by intermittent addition of base. Theoretical base consumption was observed following the complete heating period. Deionization of the total crude reaction solution by passage through columns of Dowex 50 and Dowex 1 exchange resin, in that order, gave 60.6 g. of crystalline to semicrystalline product in the initial portions of effluent. Further rinsing gave an additional 10.3 g. of oily by-product considered to represent lower condensation products. The major portion of the latter material was absorbed by the exchange resin and not recovered. The main product contained 55.5% Id (32.6% yield) as determined by quantitative isolation of its dibenzylidene derivative. Preparation of an analytical sample of Id by water recrystallization gave a white crystalline solid; m.p. 176.5°.

Anal. Calcd. for $C_9H_{18}O_5$: C, 52.41; H, 8.80; OH, 32.99; mol. wt., 206.23. Found: C, 52.64, 52.51; H, 8.80, 8.96; OH (acetylation), 32.3, 31.9; mol. wt. (cryoscopic in ethanol), 206, 206.

Derivatives of tetrahydro-3,3,5,5-tetrakis(hydroxymethyl)-pyran (Id). (1) *Tetraacetate.* A mixture of 10 g. (0.049 mole) of Id, 40 g. (0.39 mole) of acetic anhydride, and 4 ml. of glacial acetic acid was heated under reflux for 1 hr., allowed to stand overnight, and then poured into 100 ml. of water. The crystalline, white solid which separated amounted to 7.8 g. (43% yield), m.p. 91–95°, recrystallized from *n*-hexane, 94°.

Anal. Calcd. for $C_{17}H_{26}O_9$: C, 54.54; H, 7.00; mol. wt., 374.38; Sapon. No., 599.48. Found: C, 54.81, 55.00; H, 7.09, 7.17; mol. wt. (Rast), 386, 381; Sapon. No., 604.

(2) *Dibenzylidene acetal.* A mixture of 5.0 g. (0.024 mole) of impure Id, 25 ml. of water, 25 ml. of methanol, and 5 ml. of concd. hydrochloric acid was reacted with 10 ml. of benzaldehyde for 45 min. at steam bath temperature. There was obtained 8.14 g. (89% yield) of crude, white solid which upon recrystallization from butyl acetate melted at 232–234°.

Anal. Calcd. for $C_{23}H_{26}O_5$: C, 72.22; H 6.85; mol. wt., 382.43. Found: C, 72.37, 72.47; H, 7.01, 7.02; mol. wt. (Rast), 388, 403.

Tests with pure Id showed the dibenzylidene reaction to be quantitative and applicable to the determination of Id in mixtures, or compounds hydrolyzed under the reaction conditions.

(3) *Diisopropylidene ketal.* A mixture of 10 g. (0.048 mole) of Id, 150 ml. of acetone, 5 drops of concd. sulfuric acid, and 15 g. of 2,2-dimethoxypropane (Dow Chemical Co.) was heated under reflux overnight. Concentration of the reaction mixture gave 11.6 g. (91.4% yield) of white crystals. Recrystallization from acetone gave a melting point of 201–205°.

Anal. Calcd. for $C_{15}H_{26}O_5$: C, 62.91; H, 9.15. Found: C, 63.27, 63.25; H, 9.39, 9.29.

The Id content of the recrystallized product was determined by conversion to its dibenzylidene derivative: calcd., 72.02; found, 71.2. Various samples of Id diisopropylidene ketal melted over a range of 153–206°, suggesting the presence of allotropic crystalline forms.

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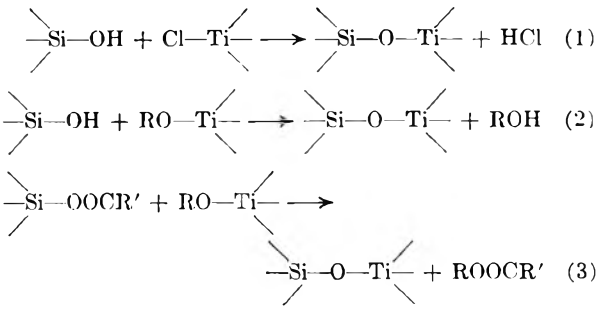
(4) All melting points are uncorrected.

Reaction of Trimethylacetoxysilane with Tetraisopropoxytitanium[1]

J. B. RUST, H. H. TAKIMOTO, AND G. C. DENAULT[2]

Received April 25, 1960

The preparations of organotitanium derivatives containing the silicon-oxygen-titanium linkage have been reported by several investigators.[3–9] These compounds have been prepared by any one of the following methods:



$$\text{—Si—OH} + \text{Cl—Ti—} \longrightarrow \text{—Si—O—Ti—} + \text{HCl} \quad (1)$$

$$\text{—Si—OH} + \text{RO—Ti—} \longrightarrow \text{—Si—O—Ti—} + \text{ROH} \quad (2)$$

$$\text{—Si—OOCR}' + \text{RO—Ti—} \longrightarrow \text{—Si—O—Ti—} + \text{ROOCR}' \quad (3)$$

Although these three methods have been utilized in the synthesis of the tetrasubstituted triorganosiloxy titanium derivatives, only Danforth[8] has reported the preparation of monomeric, partially substituted trimethylsiloxy titanium esters. He studied the reaction of trimethylsilanol with tetraisopropoxytitanium. The reaction was reported to proceed as follows:

$$n(CH_3)_3SiOH + Ti(OC_3H_7)_4 \longrightarrow [(CH_3)_3Si{:}O]_nTi(OC_3H_7)_{4-n} + nC_3H_7OH \quad (4)$$

where n is 1, 2, or 4. The extent of the substitution may be controlled by the stoichiometry of the reactants used.

The condensation reaction of trimethylacetoxysilane with tetrabutoxytitanium as reported by Andrianov and Ganina[10] results not in the desired tetrakis(trimethylsiloxy)titanium but rather in

(1) This work was supported in part by the Office of Naval Research under Contract No. Nonr 2540(00).

(2) Hughes Research Laboratories, A Division of Hughes Aircraft Company, Malibu, Calif.

(3) W. D. English and L. H. Sommer, *J. Am. Chem. Soc.*, **77**, 170 (1955).

(4) V. A. Zeitler and C. A. Brown, *J. Am. Chem. Soc.*, **79**, 4616 (1957).

(5) D. N. Dolgov and N. F. Orlov, *Izvest. Akad. Nauk. S.S.S.R., Otdel. Khim Nauk*, 1395 (1957), *Doklady Akad. Nauk S.S.S.R.*, **117**, 617 (1957).

(6) K. A. Andrianov, A. A. Zhdanov, N. A. Kurasheva, and V. G. Dulova, *Doklady Akad. Nauk. S.S.S.R.*, **112**, 1050 (1957).

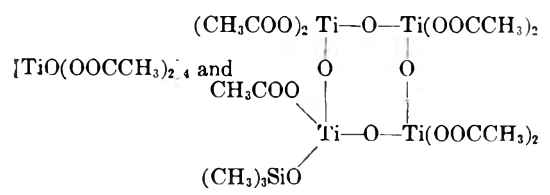
(7) D. C. Bradley and I. M. Thomas, *Chem. and Ind.*, **17** (1958).

(8) J. D. Danforth, *J. Am. Chem. Soc.*, **80**, 2585 (1958).

(9) E. H. Takimoto and G. C. Denault, *Reactions of Acetoxysilanes with Tetraisopropyl Titanate*, Pacific Southwest Regional Meeting of the American Chemical Society, Redlands, Calif., October 1958.

(10) K. A. Andrianov and T. N. Ganina, *Z. Obschei Khimii S.S.S.R.*, **29**, 605 (1959).

solid infusible substances. Among the products characterized and reported were



These authors concluded that the basic reaction between trimethylacetoxysilane and tetrabutoxytitanium resulted in the substitution of the butoxy group by acetoxy groups with the formation of cyclic structures.

Bradley and Thomas,[11] on the other hand, obtained a 95% yield of the tetrakis(trimethylsiloxy)titanium by the reaction of trimethylacetoxysilane with tetraisopropoxytitanium; furthermore, they also found that the treatment of tetrakis(trimethylsiloxy)titanium with trimethylacetoxy silane resulted in a solid product containing acetoxy groups. Thus, the following reaction appears to take place readily:

$$\equiv Ti{-}OSi(CH_3)_3 + (CH_3)_3SiOOCCH_3 \longrightarrow \equiv Ti{-}OOCCH_3 + [(CH_3)_3Si]_2O \quad (5)$$

It is apparent from this work that the use of an excess of the acetoxysilane would result in the destruction of the trimethylsiloxy titanium derivative formed initially in the condensation reaction.

The apparent anomaly of the ester-interchange reaction reported by Andrianov and Ganina becomes clear upon the re-examination of their experimental procedures. These workers used a six to one molar ratio of trimethylacetoxysilane to tetrabutoxytitanium, whereas stoichiometry would require a ratio of four to one. In addition, the titanium orthoester was added to the acyloxysilane, and consequently the latter compound was in considerable excess at all times. Under these reaction conditions, then, it is expected that the formation of $Ti{-}OOCCH_3$ compounds would be favored to the point of exclusion of tetrakis(trimethylsiloxy)titanium.

In the present study the findings of Bradley and Thomas have been confirmed. Under proper reaction conditions, the condensation of trimethylacetoxysilane with tetraisopropoxytitanium proceeds smoothly to yield trimethylsiloxy titanium derivatives. By the control of the stoichiometry of the reaction as well as of the order of addition, the mono-, di-, tri-, and tetrasubstituted trimethylsiloxy titanium esters have been produced in good yields.

$$n(CH_3)_3SiOOCCH_3 + Ti(OC_3H_7)_4 \longrightarrow [(CH_3)_3SiO]_nTi(OC_3H_7)_{4-n} + nC_3H_7OOCCH_3 \quad (6)$$

To obtain a high yield of the desired product, the purity of the starting materials is very important. Strict care must be taken to exclude moisture from the reaction mixture, as both the acyloxysilane and the titanium esters are readily hydrolyzed. In our later work on the synthesis of tetrakis(trimethylsiloxy)titanium, we found that cooling of the reaction mixture during the slow addition of the trimethylacetoxysilane and minimizing the subsequent period of heating resulted in an improved yield. The use of this modified procedure would probably give higher yields of the partially substituted trimethylsiloxy titanium esters than that reported here.

In analogy to the reaction of tetrakis(trimethylsiloxy)titanium with trimethylacetoxy silane as reported by Bradley and Thomas, the treatment of the former compound with acetic anhydride was investigated. The use of acetic anhydride was of interest in our work on metalloxane polymers. Trimethylacetoxysilane was liberated with the formation of a white, solid product containing acetoxy groups. The reaction may be written as

$$\equiv Ti{-}OSi(CH_3)_3 + (CH_3CO)_2O \longrightarrow \equiv Ti{-}OOCCH_3 + CH_3COOSi(CH_3)_3 \quad (7)$$

and is analogous to the acetylation of $(CH_3)_3SiO{-}Ti$ with trimethylacetoxysilane.

EXPERIMENTAL

Materials. Trimethylacetoxysilane was prepared by the method of Schuyten[12] using freshly distilled trimethylchlorosilane. A commercially available tetraisopropoxytitanium was distilled and the product, boiling at 89–91°/3–4 mm., n_D^{25} 1.4608, was used.

Trimethylsiloxytriisopropoxytitanium. Trimethylacetoxysilane (13.2 g., 0.10 mole) was slowly added to 28.4 g. (0.10 mole) of tetraisopropoxytitanium (n_D^{25} 1.4630) in a flask equipped with a stirrer and an addition funnel. Drying tubes were used to protect the mixture from moisture. The addition of acetoxysilane caused the temperature of the mixture to rise. The contents of the flask were stirred for 1.5 hr. and the condensation by-product, isopropyl acetate, was then removed.

Fractionation of the residual material was carried out at reduced pressure to give 26.10 g. (93.1% yield) of product boiling at 91°/5 mm., n_D^{25} 1.4509.

Anal. Calcd. for $C_{12}H_{30}O_4SiTi$: C, 45.85; H, 9.62. Found: C, 45.80, H, 9.56.

Bis(trimethylsiloxy)diisopropoxytitanium. Trimethylacetoxysilane (132.0 g., 1.00 mole) was slowly added to 142.0 g. (0.50 mole) of tetraisopropoxytitanium. A considerable amount of heat was evolved upon addition of the acetoxysilane. The reaction mixture was stirred for 2 hr. and the isopropyl acetate was removed. The product (131.6 g., 76% yield) distilling at 103°/9 mm., n_D^{25} 1.4378 was collected.

Anal. Calcd. for $C_{12}H_{32}O_4Si_2Ti$: C, 41.85; H, 9.37. Found: C, 41.66; H, 9.22.

(11) D. C. Bradley and I. M. Thomas, *J. Chem. Soc.*, 3404 (1959).

(12) H. A. Schuyten, J. W. Weaver, and J. D. Reid, *J. Chem. Soc.*, **69**, 2110 (1947).

Tris(trimethylsiloxy)isopropoxytitanium. Trimethylacetoxysilane (26.4 g., 0.20 mole) was treated with 19.0 g. (0.067 mole) of tetraisopropoxytitanium as described previously. Isopropyl acetate was removed. Fractionation of the residual material yielded 16.3 g. (65.3% yield) of product boiling at 107°/8 mm., n_D^{25} 1.4321.

Anal. Calcd. for $C_{12}H_{34}O_4Si_3Ti$: C, 38.49; H, 9.15. Found: C, 38.48; H, 9.08.

Tetrakis(trimethylsiloxy)titanium. This compound was prepared by the addition of 26.4 g. (0.20 mole) of trimethylacetoxysilane to 14.3 g. (0.05 mole) of tetraisopropoxytitanium. After isopropyl acetate was removed, fractionation of the reaction mixture gave 16.6 g. 82.5% yield of product distilling at 125°/8 mm., n_D^{25} 1.4283.

Anal. Calcd. for $C_{12}H_{36}O_4Si_4Ti$: C, 35.62; H, 8.98. Found: C, 35.42, H, 8.73.

Reaction of tetrakis(trimethylsiloxy)titanium with acetic anhydride. Acetic anhydride (5.1 g., 0.05 mole) was added over a period of 10 min. to 10.1 g., (0.025 mole) of tetrakis(trimethylsiloxy)titanium. The temperature of the reaction mixture rose from 28° to 51° during the addition, and a low boiling material was observed refluxing on the wall of the flask. The contents of the flask became increasingly cloudy and a viscous, opaque gel appeared after 15 min. After 30 min. the gel turned into a white solid. The reaction mixture was heated for 30 min. At this time the mixture consisted of two phases, a clear fluid and a white solid. Distillation of the volatile material yielded 9.4 g. of the product boiling at 102°, n_D^{25} 1.3810. The infrared spectrum taken on the volatile product was similar to that of trimethylacetoxysilane. The white solid pot residue weighed 4.5 g. (Si, 10.7%; Ti, 13.8%).

HUGHES RESEARCH LABORATORIES
HUGHES AIRCRAFT CO.
CULVER CITY, CALIF.

The Preparation of *i*-Propyl Cyanomethyl Fumarate

PAUL G. CAMPBELL AND CHARLES H. SCHRAMM

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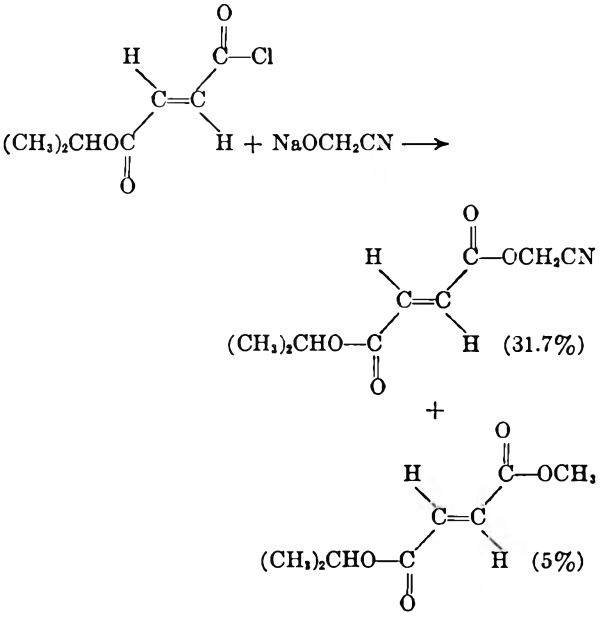
In the course of the preparation of new vinyl monomers, a convenient synthesis for alkyl fumaryl chlorides was developed. These acid chlorides served as intermediates for the preparation of various thiolfumarate esters and alkyl aryl fumarates *via* the Schotten-Baumann reaction.[1] As there are numerous examples of the synthesis and polymerization of cyanomethyl esters of α,β-unsaturated acids reported in the literature,[2] it was thought that alkyl cyanomethyl fumarates might also have useful properties.

Generally, the cyanomethyl esters of α,β-unsaturated acids have been prepared by alcoholysis of methyl or ethyl acrylates,[2d] the esterification reaction between an acyl halide and glycolonitrile,[2a,b,c,f] dehydrochlorination of the appropriate ester with quinoline,[2c] and the reaction of an acyl halide, formaldehyde, and an alkali metal cyanide.[2a,c] While Mowry was able to prepare a series of cyanomethyl esters by essentially a Schotten-Baumann reaction involving sodium cyanide and an appropriate acyl halide, these derivatives of dibasic acid halides, including fumaryl chloride, were formed in insignificant yield by this method. Instead biscyanomethyl fumarate was prepared from fumaryl chloride and glycolonitrile in the presence of a tertiary amine. However, as previously mentioned, the Schotten-Baumann reaction had been used successfully with various alkyl fumaryl chlorides, and the reaction between *i*-propyl fumaryl chloride, formaldehyde, and sodium cyanide was undertaken. The yield of



i-propyl cyanomethyl fumarate obtained was 31.7%. However, material of the empirical formula $C_8H_{12}O_4$ was also formed. This was shown to be methyl *i*-propyl fumarate by comparison with an authentic sample prepared from *i*-propyl fumaryl chloride and methanol in the presence of pyridine. The probable explanation for the presence of this by-product is the formation of methanol by the Cannizzaro reaction involving formaldehyde in the alkaline sodium cyanide solution. The methanol could then compete for the available acyl halide.

EXPERIMENTAL

Boiling points are uncorrected. Unless otherwise indicated, distillations were carried out through an 80-cm. Podbielniak-type column.

i-Propyl fumaryl chloride. A sample of crude *i*-propyl hydrogen maleate was prepared by warming a mixture of 0.5 mole each of maleic anhydride and *i*-propyl alcohol on the steam bath until a sirupy liquid resulted. To this

(1) P. G. Campbell, G. Sumrell, and C. H. Schramm, to be published.

(2a) D. T. Mowry, *J. Am. Chem. Soc.*, **66**, 371 (1944); (b) J. Harmon and C. J. Mighton, U. S. Patent **2,379,297** [*Chem. Abstr.*, **39**, 5128 (1945)]; (c) D. T. Mowry, U. S. Patents **2,380,061** and **2,380,062** [*Chem. Abstr.*, **40**, 91 (1946)]; (d) C. E. Rehberg, M. B. Dixon, and W. A. Faucette, *J. Am. Chem. Soc.*, **72**, 5199 (1950); (e) G. F. D'Alelio, U. S. Patent **2,583,062** [*Chem. Abstr.*, **48**, 11806 (1954)]; (f) C. S. Marvel, *et al.*, *Ind. Eng. Chem.*, **47**, 344 (1955).

mixture was added dropwise and with stirring, 0.6 mole of thionyl chloride. After the addition was complete, the mixture was gradually heated to 100°, in *ca.* 2 hr., and maintained at this temperature for an additional 4 hr. The amber colored mixture was fractionally distilled, yielding 41.2 g. (46.8%) of product at 87–89° (12 mm.), n_D^{25} 1.4539.

Anal. Calcd. for $C_7H_9ClO_4$: C, 47.60; H, 5.14; Cl, 20.08. Found: C, 47.69; H, 5.30; Cl, 20.23.

i-Propyl cyanomethyl fumarate. This compound was prepared by essentially the method of Mowry.[2a] A mixture of 13.9 g. (0.17 mole as a 37% aqueous solution) of formaldehyde, 8.4 g. (0.17 mole) of sodium cyanide, and 100 ml. of water was cooled to 5–10°. *i*-Propyl fumaryl chloride, 26.5 g. (0.15 mole) was added dropwise and the mixture was allowed to stir overnight. The solution was extracted with ether and the combined ether extracts were washed with dilute sodium carbonate, dilute hydrochloric acid, and finally with water. After drying over Drierite, the material was distilled through a 15-cm. Vigreux column. The bulk of the distillate, 9.4 g., b.p. 112–113° (1.1 mm.), n_D^{25} 1.4534, represented a 31.7% yield of the desired product.

Anal. Calcd. for $C_9H_{11}NO_4$: C, 54.82; H, 5.62; N, 7.10. Found: C, 54.80; H, 5.75; N, 6.82.

However, in the forerun, there was obtained 1.3 g. of material of b.p. 40° (0.2 mm.), n_D^{25} 1.4364.

Anal. Calcd. for $C_8H_{12}O_4$: C, 55.80; H, 7.03. Found: C, 55.65; H, 7.15; N, 0.26.

Methyl i-propyl fumarate. A mixture of 6 g. (0.18 mole) of methanol and 50 ml. of pyridine was cooled to 0°, 12.4 g. (0.07 mole) of *i*-propyl fumaryl chloride was added dropwise and the mixture was allowed to stir overnight. The solution was poured into ice water with stirring. The aqueous solution was extracted with ether and the combined ether extracts were washed with dilute hydrochloric acid and water. The material was fractionally distilled and 7.0 g. (63.4%) of product at 98° (10 mm.), n_D^{25} 1.4354 was obtained.

Anal. Calcd. for $C_8H_{12}O_4$: C, 55.80; H, 7.03. Found: C, 55.91; H, 7.12.

The infrared spectra of this material and the above-mentioned forerun were identical.

Acknowledgment. The authors wish to thank Alfred Foulds for the microanalyses, N. Kerschner for the infrared spectra, and C. F. Hartman for technical assistance in this work.

J. T. Baker Chemical Co.
Phillipsburg, N. J.

New Synthesis of Dibenzo[a,i]pyrene[1]

Guido H. Daub and Margaret A. Smith

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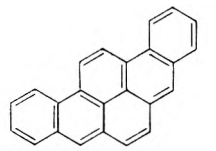
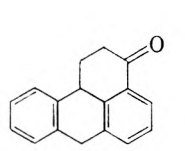
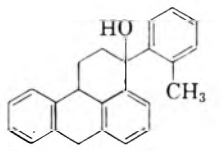
Recently Buu-Hoï and Lavit reported a five-step synthesis of dibenzo[a,i]pyrene (I) from benzo[a]pyrene in approximately 1% over-all yield.[2] Previously, the synthesis of I has been reported by several workers by the reduction of dibenzo[a,i]pyrene-5,8-quinone.[3–5]

A new synthesis of I has been accomplished in 7% over-all yield in this laboratory *via* 3-keto-1,2,3,11b-tetrahydro-7H-*meso*-benzanthracene (II), an intermediate readily available from previously reported research.[6,7] The ketone II was treated with *o*-tolylmagnesium bromide and the resulting carbinol, III, was dehydrated with Lucas reagent and chromatographed on alumina. The red, oily 3-(*o*-tolyl)-1,11b-dihydro-7H-*meso*-benzanthracene (IV) (or isomers thereof) thus obtained was cyclodehydrogenated with palladium on charcoal to dibenzo[a,i]pyrene (I).

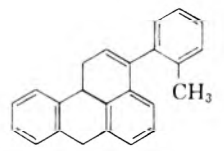

I



II



III



IV

EXPERIMENTAL

3-Hydroxy-3-(o-tolyl)-1,2,3,11b-tetrahydro-7H-meso-benzanthracene (III). A solution of 4.68 g. (0.02 mole) of 3-keto-1,2,3,11b-tetrahydro-7H-*meso*-benzanthracene (II) in 75 ml. of dry benzene was added dropwise over a period of 30 min. to a stirred ether solution of *o*-tolylmagnesium bromide prepared from 4.28 g. (0.025 mole) of *o*-bromotoluene. After refluxing for 1 hr. the reaction mixture was hydrolyzed with 50 ml. of 10% hydrochloric acid. The organic layer was washed with water and dried over anhydrous sodium sulfate. Removal of the solvent left 3-hydroxy-3-(*o*-tolyl)-1,2,3,11b-tetrahydro-7H-*meso*-benzanthracene (III) as a viscous brown oil which failed to crystallize.

3-(o-Tolyl)-1,11b-dihydro-7H-meso-benzanthracene (IV). The crude carbinol, III, was dissolved in anhydrous benzene and refluxed for 90 min. with 30 ml. of Lucas reagent. The organic layer was washed with water and saturated sodium carbonate solution, dried over anhydrous sodium sulfate, and chromatographed on alumina. Removal of the solvent yielded 5.2 g. of the hydrocarbon IV as a light red oil.

Dibenzo[a,i]pyrene (I). The hydrocarbon IV was cyclodehydrogenated by heating with 0.78 g. of 10% palladium on charcoal at 320–400° for 30 min. The crude hydrocarbon was sublimed from the reaction mixture at 275° and 0.05 mm. A toluene solution of the sublimate was chromatographed on alumina and concentration of the eluants yielded 0.42 g. (7% over-all yield from II) of dibenzo[a,i]pyrene (I) as small yellow plates, m.p. 281.5–282.5° uncorr.

Department of Chemistry
University of New Mexico
Albuquerque, N. M.

(1) This investigation was supported in part by a research grant (C-1595) from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service.

(2) N. P. Buu-Hoï and D. Lavit, *Tetrahedron*, 8, 1 (1960).

(3) R. Scholl and H. Neumann, *Ber.*, 55, 118 (1922).

(4) E. Clar, *Ber.*, 72, 1645 (1939).

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(6) G. H. Daub and W. C. Doyle, *J. Am. Chem. Soc.*, 74, 4449 (1952).

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A Convenient Synthesis of Crystalline L-Threonolactone

JAMES M. PEREL AND PETER G. DAYTON

Received March 28, 1960

Many attempts to obtain L-threonolactone have resulted in poor yields of crude, syrupy material which had to be characterized by derivatives.[1,2] Reichstein, Grüssner, and Bosshard[2] isolated L-threonolactone as the brucine and quinine salts, using acetone L-ascorbic acid as a starting material. Gätzi and Reichstein[3] synthesized for the first time crystalline L-threonolactone directly from L-ascorbic acid in 32% yield. Subsequently, Gätzi and Reichstein,[4] in degradation studies of 3,5:4,6-di-*O*-ethylidene-L-glucitol, obtained very small yields of crystalline L-threonolactone. Later, Lucas and Baumgarten,[5] upon reduction of L-threuronic acid, were unable to obtain crystalline L-threonolactone by the Gätzi and Reichstein[3] isolation procedure and had to characterize it as the brucine salt. Also, Micheel and Peschke,[6] starting from L-threaric acid, obtained a poor yield of a syrup which, upon several months of standing, crystallized and was characterized as L-threonolactone. Hardegger *et al.*[7] obtained crystalline L-threonolactone by direct oxygenation of L-ascorbic acid; in this and one other publication,[8] no yields were given.

The original method of Reichstein, *et al.*[2] has now been simplified, and crystalline material of purity higher than reported[3,7] has been consistently obtained in better yield. L-Threonolactone was needed, in order to continue studies of the metabolism of L-ascorbic acid.[9]

EXPERIMENTAL

5,6-O-Isopropylidene-L-ascorbic acid was prepared from L-ascorbic acid and dry acetone in the presence of anhydrous cupric sulfate, m.p. 218–220°; yields of 95% can be obtained.[10]

Potassium 3,4-O-isopropylidene-L-threonate was prepared by a twenty-fold enlargement of the method of Reichstein, *et al.*[2] The 5,6-*O*-isopropylidene-L-ascorbic acid (86 g., 0.37 mole) was dissolved in 2000 ml. of carbon dioxide-saturated water and was cooled to 0°, causing part of the sugar compound to precipitate. To the resulting suspension, a solution of potassium permanganate (84 g., 0.53 mole) and potassium carbonate (70 g., 0.51 mole) in 2400 ml. of water was added dropwise during 2–3 hr., with constant mixing, the reaction mixture being kept at 0–5°. After reaction was complete (as noticed by lack of decolorization of the permanganate solution), the mixture was heated to 50° to coagulate manganese dioxide, which was filtered off. Two milliliters of ethanol were added and the solution was again filtered. The filtrate was evaporated to dryness with a rotary evaporator at 40°. The residue was extracted three to four times with 100-ml. portions of hot absolute ethanol, and solutions were pooled and evaporated *in vacuo* to about 25 ml. Crystallization was induced by the addition of 3 ml. of cold acetone and, upon evaporation of the solvents, 62 g. (0.29 mole, 78% yield) of a pale yellow solid was obtained. For this synthesis, it was not necessary to recrystallize the crude compound, which melted at 148–150° (m.p. recrystallized material 158°).

L-Threonolactone. A solution of 62 g. (0.29 mole) of the above potassium salt in 175 ml. of distilled water was passed through a 250 g. column of Amberlite IR-120(H), resin, analytical grade. The effluent and 300 ml. water wash were pooled, and the solution (*p*H 3–4) was evaporated to dryness *in vacuo* at 50°. The residue was dissolved in 200 ml. of hot absolute ethanol, and treated twice with 2.5 g. of activated carbon. Upon evaporation to dryness, 35 g. of a pale yellow syrup was obtained which was distilled as described by Gätzi and Reichstein.[3] The first fraction, 8 g. of yellow, nonviscous syrup, distilled at 100–130° (0.8 mm.); it had a sweet odor, and $[\alpha]_D^{21}$ + 10.3° (methanol, *c* 1.90). The main fraction distilled at 145–150° (0.25 mm.) (some decomposition towards the end), and consisted of 18 g. (0.15 mole, 52% yield) of a pale yellow syrup which rapidly solidified into a white crystalline material. The low boiling fraction, suspected to be the acetone derivative of L-threonic acid, when dissolved in 50 ml. of water, refluxed for 1 hr., and treated as above, gave about 4 g. of additional crystalline L-threonolactone. This increased the yield to 65%. Upon recrystallizing from dry ethyl acetate and washing with anhydrous ether,[3] 16 g. of L-threonolactone melting at 66–71° was obtained[11]; phenylhydrazide, m.p. 160–161°, $[\alpha]_D^{21}$ + 52.5° (methanol, *c* 0.73); brucine salt, m.p. 209–210° dec., $[\alpha]_D^{21}$ −19.7° (H_2O *c* 1.92).

A small portion of the lactone, recrystallized three more times, melted at 74–75°, $[\alpha]_D^{19}$ + 51.2 (methanol, c 1.54). Infrared (potassium bromide): 1775 cm.$^{-1}$ (γ-lactone), 3380 cm.$^{-1}$ (OH).

Anal. Calcd. for $C_4H_6O_5$: C, 40.63; H, 5.16. Found: C, 40.74; H, 5.37.

The compound gave a quantitative hydroxamic acid as-

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(3) K. Gätzi and T. Reichstein, *Helv. Chim. Acta*, **20**, 1298 (1937).

(4) K. Gätzi and T. Reichstein, *Helv. Chim. Acta*, **21**, 186 (1938).

(5) H. J. Lucas and W. Baumgarten, *J. Am. Chem. Soc.*, **63**, 1653 (1941).

(6) F. Micheel and W. Peschke, *Ber.*, **75B**, 1603 (1942).

(7) E. Hardegger, K. Kreis, and H. El. Khaden, *Helv. Chim. Acta*, **34**, 2343 (1951).

(8) R. Pasternack and R. A. Patelski, *U.S. Patent* **2,308,385** (1943).

(9) H. H. Horowitz and C. G. King, *J. Biol. Chem.*, **200**, 125 (1953). J. J. Burns, J. Kanfer, and P. G. Dayton, *J. Biol. Chem.*, **232**, 107 (1958). P. G. Dayton, F. Eisenberg, and J. J. Burns, *Arch. Biochem. Biophys.*, **81**, 111 (1959).

(10) L. Von Vargha, *Nature*, **130**, 847 (1933). F. Micheel, and K. Hasse, *Ber.*, **69B**, 879 (1936).

(11) About 2 to 3 g. of additional crystalline L-threonolactone can be obtained by distillation of the mother liquor.

say for a glyconic acid lactone.[12] The best physical constants previously reported are: L-threonolactone, m.p. 74–76°,[8] $[\alpha]_D^{20}$ + 47.0° (methanol)[3]; phenylhydrazide, m.p. 161–161.5°, $[\alpha]_D^{21}$ + 48.6° (methanol)[3]; brucine salt, m.p. 209–210° dec., $[\alpha]_D^{22}$ −19.3° (H_2O).[3] Despite the high melting point given by Hardegger, *et al.*,[7] these authors report $[\alpha]_D$ −27.0° (H_2O) for the brucine salt, indicating the presence of optically active impurities: this suggests that the lower melting (65–68°) material obtained by Gätzi and Reichstein[3] was purer.

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THE RESEARCH SERVICE
THIRD (NEW YORK UNIVERSITY) MEDICAL DIVISION
GOLDWATER MEMORIAL HOSPITAL
NEW YORK 17, N.Y.

THE LABORATORY OF CHEMICAL PHARMACOLOGY
NATIONAL HEART INSTITUTE
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MD.

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Strong Analgesics. Some Ethyl 1-Alkyl-4-phenylpiperidine-4-carboxylates

BILL ELPERN,[1] PHILIP M. CARABATEAS, ALBERT E. SORIA, AND LEONARD GRUMBACH

Received May 5, 1960

Some time ago, it was shown,[2] that when the *N*-methyl substituent of meperidine, ethyl 1-methyl-4-phenylpiperidine-4-carboxylate hydrochloride, was replaced by lower alkyl groups the analgesic potency remained relatively constant although the toxicity gradually increased.

Recently it was reported[3] that replacement of the *N*-methyl substituent of meperidine by aralkyl groups other than benzyl gave compounds having significantly higher analgesic potency. It seemed of interest to us to see if relatively long alkyl groups would effect the same enhancement of analgesic potency.

Accordingly, analogs were prepared wherein the *N*-methyl substituent was replaced by various relatively long chain alkyl groups, both straight and branched.

The alkylation of ethyl 4-phenylpiperidine-4-carboxylate was accomplished using either alkyl halides or toluenesulfonates.

The pharmacological evaluation of these compounds for analgesic potency by the Bass, Vander Brook modification[4] of the D'Amour, Smith rat thermal stimulus method[5] will be reported more fully elsewhere, but a brief summary can be given here. It is apparent that the substituent on the nitrogen of meperidine can be extended to at least nine carbons without loss of any analgesic potency; in fact, the compounds having straight chains and one of the branched chain compounds are more potent than meperidine itself.

EXPERIMENTAL

Ethyl 1-heptyl-4-phenylpiperidine-4-carboxylate hydrochloride. A mixture of ethyl 4-phenylpiperidine-4-carboxylate hydrochloride (13.5 g., 0.05 mole), *n*-heptyl bromide (8.95 g., 0.05 mole), sodium carbonate (20 g.), and *n*-butyl alcohol (100 ml.) was refluxed with stirring for 24 hr. The solids were removed by filtration and a small piece of Dry Ice added to the filtrate to precipitate any secondary amine still present. The filtrate was then concentrated *in vacuo* on a steam bath and the residual oil taken up in ether. A small amount of precipitate was removed by filtration and ethereal hydrogen chloride was added to the filtrate. The product was collected and crystallized from ethyl acetate (150 ml.), then recrystallized from a mixture of benzene (65 ml.) and cyclohexane (65 ml.). There was obtained 14.3 g. (78.0%) of product, m.p. 146.4–149°.

2-Hexyl-p-toluenesulfonate. 2-Hexanol (255 g., 2.5 moles) and pyridine (595 g., 7.5 moles) were stirred in an open beaker and cooled to 0°. *p*-Toluenesulfonyl chloride (858 g., 4.5 moles) was added portionwise over 3 hr. at such a rate as to keep the temperature at about 15°. When the addition was completed, the reaction mixture was allowed to reach room temperature. The unchanged *p*-toluenesulfonyl chloride was hydrolyzed by addition of 150 ml. of water and 200 ml. of pyridine. After hydrolysis was completed, concd. hydrochloric acid was added, the aqueous layer was separated, and the organic layer was washed with water, dilute sodium bicarbonate solution, and water again. Traces of water were removed from the organic layer by heating at 50–60° at reduced pressure, first with a water pump and then with a mechanical pump. There was obtained 533 g. (82%) of yellow oil which was used without further purification.

Ethyl 1-(2-hexyl)-4-phenylpiperidine-4-carboxylate. Methane sulfonate. Ethyl 4-phenylpiperidine-4-carboxylate hydrochloride (1700 g., 6.3 moles) was dissolved in 2.5 l. of water. The solution was made basic with 35% aqueous sodium hydroxide, extracted with ether, the extract dried over anhydrous sodium sulfate, and concentrated to an oil. 2-Hexyl-*p*-toluenesulfonate (768 g., 3.0 moles) was added all at once. The reaction mixture turned into a thick magma after stirring for 3 hr. at room temperature. Heating on the steam bath caused the mixture to liquify, then resolidify after 1 hr. Heating was continued for 1 hr. more and the mixture allowed to stand overnight. Three liters of water was added to the solid reaction mixture, which was heated on the steam bath until solution was complete. The cooled solution was extracted with ether several times. A 750-ml. portion of water was added to the ether extracts and 252 ml. of concd. hydrochloric acid added with cooling. In 15 min. the product precipitated. After drying there was obtained 848 g. (80%) of ethyl 1-(2-hexyl)-4-phenylpiperidine-4-carboxylate hydrochloride, m.p. 162–164. A 1098-g. sample (3.1 moles) of the above hydrochloride was dissolved in 3 l. of water, made basic with 35% sodium hydroxide, and extracted with benzene. The extract was concentrated *in vacuo* and the oily residue dissolved in 250 ml. of isopropyl alcohol and 4 l. of ether. Methanesulfonic acid (328 g., 3.41 moles) was added with cooling and stirring. The product

(1) Present address: Cutter Laboratories, Berkeley, Calif.

(2) R. H. Thorp and E. Walton, *J. Chem. Soc.*, 559 (1948).

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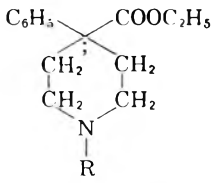
TABLE I

ETHYL 1-ALKYL-4-PHENYLPIPERIDINE-4-CARBOXYLATES



R—	Formula	Yield, %	M.P.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found	Activity[d]
$CH_3(CH_2)_5$—	$C_{20}H_{32}ClNO_2 \cdot HCl$	48.6	160.0–161.4	67.87	67.81	9.12	9.10	10.02	10.02	6.7
$CH_3(CH_2)_6$—	$C_{21}H_{34}ClNO_2 \cdot HCl$	78.0	146.4–149.0	68.54	68.40	9.31	9.26	9.64	9.49	3.3
$CH_3(CH_2)_7$—	$C_{22}H_{36}ClNO_2 \cdot HCl$	68.4	137.0–138.0	69.16	69.44	9.50	9.09	9.28	8.99	4.0
$CH_3(CH_2)_8$—	$C_{23}H_{38}ClNO_2 \cdot HCl$	43.0	132.4–134.2	69.76	69.58	9.67	9.47	8.95	8.77	2.5
$CH_3(CH_2)_9$—	$C_{24}H_{40}ClNO_2 \cdot HCl$	28.7	135.4–136.2	70.30	70.61	9.83	10.48	8.65	8.60	0
$CH_3(CH_2)_{11}$—	$C_{26}H_{44}ClNO_2 \cdot HCl$	16.4	131.6–132.6	71.27	71.35	10.13	10.01	8.09	8.16	0
CH_3 \ $CHCH_2CH_2$— / C_2H_5	$C_{20}H_{32}ClNO_2 \cdot HCl$	59.9	163.4–165.4	67.87	67.97	9.12	9.59	10.02	9.99	3.0
CH_3 \ CH— / C_4H_9	$C_{20}H_{31}NO_2$[c]	68.8	120–122	60.97	61.01	8.53	8.56	7.75[a]	7.78	5.8
C_2H_5 \ CH— / C_4H_9	$C_{21}H_{34}ClNO_2 \cdot HCl$	17.6	145.0–147.4	8.69[b]		8.70		9.63	9.54	1.7
C_2H_5 \ CH— / C_3H_7	$C_{20}H_{32}ClNO_2 \cdot HCl$	35.6	179.6–182.6	9.04[b]		8.95		10.02	9.99	0.23
Meperidine										1

[a] Analyzed for sulfur. [b] Analyzed for oxygen. [c] B. CH_3SO_3H salt. [d] Relative to meperidine.

precipitated after a few minutes of stirring The product was collected, washed with ether and dried; yield 1089 g. (86%), m.p. 120–122°.

Anal. Calcd. for $C_{20}H_{31}NO_2 \cdot CH_3SO_3H$: C, 60.97; H, 8.53; S, 7.75. Found: C, 61.01; H, 8.56; S, 7.78.

Acknowledgment. We are greatly indebted to Messrs. M. E. Auerbach, K. D. Fleischer, and staff for the chemical analysis and to Miss L. Oona, Mrs. H. Lawyer, and Mrs. A. Pierson for technical assistance in the pharmacological evaluations.

STERLING-WINTHROP RESEARCH INSTITUTE,
RENSSELAER, N. Y.

N-Substituted *N'*-Phenylureas

CHARLES G. SKINNER AND WILLIAM SHIVE

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A factor which stimulated growth in mature carrot phloem cells has been identified as 1,3-diphenylurea.[1] The possibility that other phenylurea derivatives might possess physiological activity is suggested by the fact that various structural modifications of another plant growth factor, Kinetin[2] [6-(2-furfurylamino)purine], have been found to be effective in stimulating biological responses in a number of assay systems. For example, the furfuryl group of Kinetin can be replaced, with retention of biological activity, by phenyl-,[3] ω-phenylalkyl-,[4] ω-cyclohexylalkyl-,[5] and heterocyclicaminopurines.[6] Accordingly, a number of substituted amines were condensed with phenylisocyanate to produce the corresponding *N*-substituted *N'*-phenylureas. These compounds were subsequently examined in several biological assay systems.

(1) E. M. Shantz and F. C. Steward, *J. Am. Chem. Soc.*, 77, 6351 (1955).

(2) C. O. Miller, F. Skoog, F. S. Okumura, M. H. Von Saltza, and F. M. Strong, *J. Am. Chem. Soc.*, 77, 2662 (1955).

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TABLE I

N-SUBSTITUTED *N'*-PHENYLUREAS[a]

$$C_6H_5—NH—\overset{\overset{O}{\|}}{C}—NH—R$$

R	M.P.[b]	Empirical Formula	Calcd. C,%	Calcd. H,%	Calcd. N,%	Found C,%	Found H,%	Found N,%
3-Phenylpropyl-	87– 90	$C_{16}H_{18}N_2O$	75.56	7.13		75.30	7.03	
4-Phenylbutyl-	107–110	$C_{17}H_{20}N_2O$			10.44			10.44
5-Phenylpentyl-	98–100	$C_{18}H_{22}N_2O$	76.56	7.85	9.92	76.11	7.87	10.00
7-Phenylheptyl-	95– 96	$C_{20}H_{26}N_2O$			9.02			8.89
(2-Methyl-2-phenyl)ethyl-	136–137	$C_{16}H_{18}N_2O$	75.56	7.13		75.19	6.75	
2-α-Naphthylethyl-	154–156	$C_{19}H_{18}N_2O$	78.62	6.25		78.20	6.35	
3-Cyclohexylpropyl-	112–113	$C_{16}H_{24}N_2O$	73.80	9.29		73.66	8.90	
6-Cyclohexylhexyl-	117–120	$C_{19}H_{30}N_2O$	75.45	10.00	9.26	74.35	9.83	9.34
2-Pyridylmethyl-	128–130	$C_{13}H_{13}N_3O$	68.70	5.77	18.55	68.55	5.55	18.46
3-Pyridylmethyl-	103–105	$C_{13}H_{13}N_3O$	68.70	5.77		68.55	5.80	
4-Pyridylmethyl-	134–136	$C_{13}H_{13}N_3O$			18.50			18.88
2-Thenyl-	165–168	$C_{12}H_{12}N_2OS$	62.04	5.21	12.06	62.01	5.24	12.11
2-Furfuryl-	118–120	$C_{12}N_{12}N_2O_2$	66.65	5.59	12.96	66.77	5.79	13.04
3-Methoxypropyl-	248–249	$C_{11}H_{16}N_2O_2$			13.45			13.23

[a] The authors are indebted to Mr. B. S. Gorton for technical assistance with some of these syntheses. [b] M.p. are uncorrected.

The various *N*-substituted *N'*-phenylureas were prepared through the usual procedure by condensing the appropriate amine with phenylisocyanate under anhydrous conditions as indicated in the accompanying equation, and were obtained in essentially quantitative yields. Some physical

$$RNH_2 + C_6H_5—N=C=O \longrightarrow C_6H_5NHCONHR$$

properties and analytical data for the previously unreported derivatives which were prepared are summarized in Table I.

Because of the limited solubility of many of these *N*-substituted *N'*-phenylureas in water, most of the biological assays were carried out using a saturated aqueous solution of the compound as the highest concentration tested. The biological systems studied included an attempt to (a) augment the rate of lettuce seed germination,[7] (b) inhibit hydra tentacle regeneration,[8] (c) inhibit the growth of *Escherichia coli*, and (d) augment the growth inhibition of 2,4-diamino-6,7-diphenylpteridine in *Lactobacillus arabinosus*.[9] Under the testing conditions cited in the references, representative members of each of the homologous series of 6-substituted purine derivatives possessed a significant biological response; however, none of the *N*-substituted *N'*-phenylurea analogs were found to be appreciably active in any of these assay systems. Recently, these compounds were also tested for their ability to stimulate growth in carrot tissue, and no significant growth-promoting effects were observed; in contrast, several of the corresponding 6-substituted aminopurines were active in this test system.[10]

CLAYTON FOUNDATION BIOCHEMICAL INSTITUTE
AND THE DEPARTMENT OF CHEMISTRY
THE UNIVERSITY OF TEXAS
AUSTIN 12, TEX.

(7) C. G. Skinner, J. R. Claybrook, F. D. Talbert, and W. Shive, *Plant Physiol.*, **32**, 117 (1957.)

(8) C. G. Skinner, W. Shive, R. G. Ham, D. C. Fitzgerald, Jr., and R. E. Eakin, *J. Am. Chem. Soc.*, **78**, 5097 (1956).

(9) E. M. Lansford, Jr., C. G. Skinner, and W. Shive, *Arch. Biochem. Biophys.*, **73**, 191 (1958).

(10) The authors are indebted to Dr. E. M. Shantz, Cornell University, for a preliminary report of these data.

The Mechanism of the *N,N*-Dichloro-*sec*-alkylamine Rearrangement

G. H. ALT AND W. S. KNOWLES

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In recent papers[1,2] on the rearrangement of *N,N*-dichloro-*sec*-alkylamines to α-amino ketones Baumgarten and coworkers visualize a mechanism similar to that proposed by Cram and Hatch[3,4] for the Neber rearrangement of oxime tosylates. A key intermediate in this reaction sequence is the dehydrohalogenation of the *N,N*-dichloroamine to

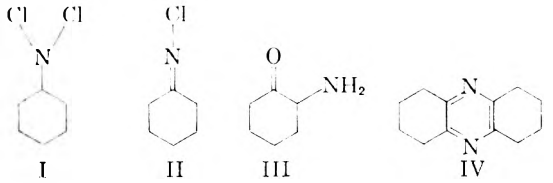
(1) H. E. Baumgarten and F. A. Bower, *J. Am. Chem. Soc.*, **76**, 4561 (1954).

(2) H. E. Baumgarten and J. H. Petersen, *J. Am. Chem. Soc.*, **82**, 459 (1960).

(3) D. J. Cram and M. S. Hatch, *J. Am. Chem. Soc.*, **75**, 33 (1953).

(4) M. S. Hatch and D. J. Cram, *J. Am. Chem. Soc.*, **75**, 38 (1953).

the *N*-chloroimine. The *N*-chloroimine being isoelectronic with the oxime tosylate can then undergo closure to an azirine intermediate, evidence for which has already been presented.[2] Positive evidence that the *N*-chloroimine is an intermediate is now submitted.



Treatment of *N,N*-dichlorocyclohexylamine, I, with potassium acetate in ethanol at the reflux temperature gave *N*-chlorocyclohexylimine, II,[5,6] as a colorless liquid. The compound was characterized by its infrared spectrum, elemental analysis and by its conversion to cyclohexanone on hydrolysis with aqueous acid. Treatment of II with one mole of sodium methoxide in absolute methanol gave an excellent yield of 2-aminocyclohexanone, III, isolated and characterized by its conversion to 1,2,3,4,6,7,8,9-octahydrophenazine, IV.[7]

The conversion of II to III with one mole of base proceeds at least as well as the conversion of I to III with two moles of base, so that the *N*-chloroimine II appears to be an intermediate in the *N,N*-dichloro-*sec*-alkylamine rearrangement.

EXPERIMENTAL

N-Chlorocyclohexylimine. To a solution of 25 g. (0.25 mole) of potassium acetate in 130 ml. of absolute ethanol at the reflux temperature was added dropwise over a period of 30 min. 16.8 g. (0.1 mole) of *N,N*-dichlorocyclohexylamine.[1] The reaction mixture was heated for a further 3 hr., cooled to room temperature and 200 ml. of ether and 100 ml. of benzene added. The ethereal solution was washed with 3 × 100 ml. of water, then with 3 × 50 ml. of 2*N* hydrochloric acid and again with water. The solvent layer was dried with calcium sulfate and the solvent removed at room temperature under vacuum. The residue consisted of 13 g. of an oil which was submitted to vacuum distillation through a column at 3 mm. of mercury. After a small forerun, the product distilled at 53–54°. The product was redistilled to give 7.5 g. (57%) of *N*-chlorocyclohexylimine, b.p. 36°/1.5 mm., n_D^{25} 1.5056. The infrared spectrum showed absorption due to C=N at 1612 cm.$^{-1}$, probably displaced from its normal position because of the chlorine.

Anal. Calcd. for $C_6H_{10}ClN$: C, 54.75; H, 7.66; Cl, 26.94; N, 10.65. Found: C, 54.92; H, 7.82; Cl, 26.68; N, 10.53.

Acid hydrolysis of N-chlorocyclohexylimine. A solution of 0.2 g. of *N*-chlorocyclohexylimine in aqueous ethanol was heated on the steam bath with 1 ml. of concd. hydrochloric acid for 30 min. The reaction mixture was treated with 2,4-dinitrophenylhydrazine reagent and on cooling cyclohexanone 2,4-dinitrophenylhydrazone, m.p. and mixture m.p. 160–162° crystallized.

Rearrangement of N-chlorocyclohexylimine. A solution of 1.0 g. (0.0075 mole) of *N*-chlorocyclohexylimine in 20 ml. of methanol was treated with 8 ml. of a 1.0*N* solution of sodium methoxide in methanol at the reflux for 1 hr. The solution was cooled and 30 ml. of dry ether added. The sodium chloride produced was filtered and amounted to 410 mg. (92%). The ethereal solution was extracted with 3 × 70 ml. of 10% hydrochloric acid and with water. The combined aqueous extracts were heated on the steam bath for 15 min., 30 ml. of 50% sodium hydroxide solution and 5 ml. of 30% hydrogen peroxide were then added, and the heating was continued for a further 15 min. The reaction mixture was cooled in ice and the precipitate filtered. The solid was recrystallized from acetone giving 530 mg. (74%) of 1,2,3,4,6,7,8,9-octahydrophenazine, m.p. 108–109°; mixture melting point with an authentic sample[7] was not depressed.

Acknowledgment. The authors are indebted to Dr. B. Katlafsky for the interpretation of the infrared spectra.

ORGANIC CHEMICALS DIVISION
ST. LOUIS RESEARCH DEPARTMENT
MONSANTO CHEMICAL CO.
ST. LOUIS, MO.

(5) S. Reid and D. Sharpe of Central Research Laboratories, Monsanto Chemical Company, Dayton, Ohio (private communication) have also prepared this compound by a different method.

(6) U. S. Patent 2,894,028 claims the preparation of this compound as a crystalline solid, m.p. 20°, by the action of chloramine on cyclohexanone; however, no analysis is given and in our hands the compound failed to crystallize.

(7) P. A. S. Smith, *J. Am. Chem. Soc.*, **70**, 323 (1948).

Three 2-Fluoroalkyl-5-nitrofurans

WILLIAM R. SHERMAN, MORRIS FREIFELDER, AND GEORGE R. STONE

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In an excellent series of papers[1] sulfur tetrafluoride has recently been introduced as a unique fluorinating agent. By means of this reagent aldehydes and ketones are readily converted to *gem*-difluoro compounds and carboxylic acids to trifluoromethyl derivatives. Using sulfur tetrafluoride we have been able to obtain three 2-fluoroalkyl-5-nitrofurans. This type of nitrofuran has not previously been reported. Thus sulfur tetrafluoride reacted with 5-nitro-2-furaldehyde to form 2-difluoromethyl-5-nitrofuran, with 2-acetyl-5-nitrofuran to give 2-(α,α-difluoroethyl)-5-nitrofuran, and with 5-nitro-2-furoic acid to produce 2-trifluoromethyl-5-nitrofuran.

All of the fluoroalkylnitrofurans had antibacterial activity. The most active member of the group was 2-difluoromethyl-5-nitrofuran. In a two-fold agar dilution test[2] this compound completely inhibited the growth of *Escherichia coli* and *Salmonella typhimurium* at a concentration of 6 mcg. per ml., *Staphylococcus aureus* at 12 mcg. per ml. and *Proteus vulgaris* at 25 mcg. per ml.

(1) W. C. Smith, *et. al.*, *J. Am. Chem. Soc.* **81**, 3165 (1959); C. W. Tullock, *et. al.*, *J. Am. Chem. Soc.*, **82**, 539 (1960); W. R. Hasek, *et. al.*, *J. Am. Chem. Soc.*, **82**, 543 (1960); W. C. Smith, *et. al.*, *J. Am. Chem. Soc.*, **82**, 551 (1960).

(2) Carried out by R. J. Otto and staff of Abbott Laboratories.

EXPERIMENTAL[3]

2-Trifluoromethyl-5-nitrofuran. 5-Nitro-2-furoic acid (15.7 g., 0.1 mole) was placed in a 183 ml. stainless steel bomb, which was sealed and cooled in an acetone–Dry Ice bath. After evacuation to about 0.3 mm. pressure, the vessel was charged with sulfur tetrafluoride[4] (43 g., 0.4 mole). After allowing the mixture to warm to room temperature, the reactor was heated to 120° for 7 hr. under autogenous pressure. Following the reaction the cooled bomb was vented and the oily residue taken up in chloroform. The chloroform extract was washed with sodium carbonate solution followed by water, then dried and the solvent removed. The residual oil was fractionally distilled to give 5.47 g. of a light yellow liquid with a camphor-like odor, b.p. 108° (102 mm), n_D^{25} 1.4368. When the sodium carbonate extract was neutralized with acetic acid and cooled, 3.5 g. of the sodium salt of 5-nitro-2-furoic acid (explodes at 247°) was obtained. Based on recovered starting material the yield of pure trifluoromethyl compound was 37%.

Anal. Calcd. for $C_5H_2F_3NO_3$: C, 33.16; H, 1.11; N, 7.74. Found: C, 33.39; H, 1.39; N, 7.60.

2-Difluoromethyl-5-nitrofuran. Sulfur tetrafluoride (42 g., 0.39 mole) was added to 5-nitro-2-furaldehyde (26.4 g., 0.187 mole) in the manner described above. After heating for 8 hr. at 65°, the bomb was cooled and vented. The residue was worked up as before and distilled to provide 6.7 g. of the difluoromethyl compound, b.p. 96–98° (13 mm), $n_D^{21.3}$ 1.4910–1.4922 and 6.2 g. of starting nitrofuraldehyde. Based on recovered starting material the yield was 28%.

Anal. Calcd. for $C_5H_3F_2NO_3$: C, 36.82; H, 1.85; N, 8.59. Found: C, 36.88; H, 1.99; N, 8.56.

2-(α,α-Difluoroethyl)-5-nitrofuran. A mixture of 2-acetyl-5-nitrofuran (31 g., 0.2 mole) and water (1 ml.) was charged with sulfur tetrafluoride (63.0 g., 0.575 mole) as described above. The addition of water was necessary in order to generate hydrofluoric acid to catalyze the reaction. After heating at 75° for 10 hr., the reaction was worked up in the usual way to give 8.9 g. (25%) of the difluoroethyl derivative b.p. 58–60° (0.5 mm.), n_D^{25} 1.4717. When the reaction was carried out at 55–60° for 10 hr., the yield was increased to 34%.

Anal. Calcd. for $C_6H_5F_2NO_3$: C, 40.68; H, 2.84; N, 7.91. Found: C, 40.81; H, 3.09; N, 7.98.

In an attempt to prepare the difluoroethyl compound by carrying out the reaction with catalyst at 40° for 10 hr. only starting ketone was recovered, in 70% yield. When the reaction was run at 75° for 10 hr. in the absence of catalyst, starting material was again recovered, this time in 50% yield. At 110° only tars were formed.

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RESEARCH DIVISION, ABBOTT LABORATORIES
NORTH CHICAGO, ILL.

(3) Boiling and melting points are uncorrected. Analyses were carried out by E. F. Shelberg and staff of Abbott Laboratories.

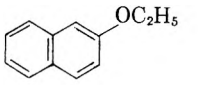
(4) Purchased from E. I. du Pont de Nemours and Company.

Novel Synthesis of Heterocyclic Ketones

WILLIAM C. ANTHONY

Received March 3, 1960

The introduction of an aldehyde function into aromatic (I)[1] and heterocyclic (II)[2] compounds

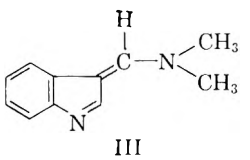


I

II

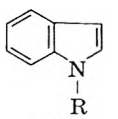
by use of phosphorus oxychloride and methyl formanilide or dimethylformamide has been described in the literature. In this paper we report the introduction of a ketone function into certain indoles and pyrroles by means of phosphorus oxychloride and the appropriate amide. The compounds which were prepared by this method are listed in Table I. All attempts to acylate β-ethoxynaphthalene, thiophene, dimethylaniline, and fluorene by this method failed.

It has been stated[1] that only *one* replaceable hydrogen on the aromatic system is necessary for the reaction with formamides to proceed. Smith[3] has applied this procedure to the preparation of indole-3-carboxaldehyde. He isolated and characterized the intermediate III and proposed a reaction mechanism which would require two replaceable hydrogens on the nucleophile.



III

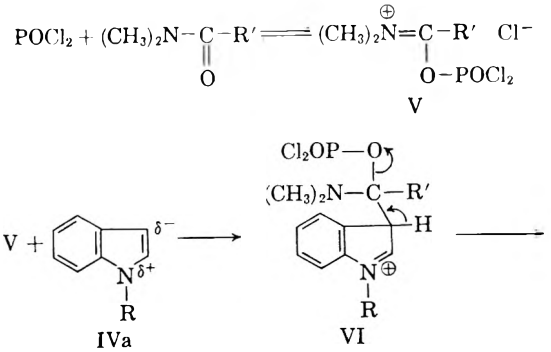
In the course of our investigation of indole and pyrrole ketone formations, we have found that an indole compound (IV) with only one replaceable hydrogen, is also convertible into a ketone. With such a starting material, an intermediate similar to III is not possible.



IV

R = ethyl

The following reaction scheme may apply to acylations of indoles and pyrroles which contain either one or two replaceable hydrogens:



V

IVa

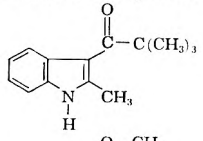
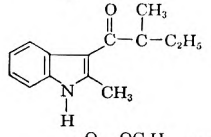
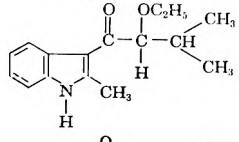
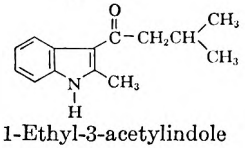
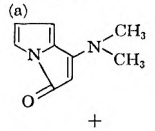
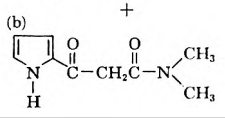
VI

(2) E. Campaigne and W. L. Archer, *J. Am. Chem. Soc.*, 75, 989 (1953).

(3) G. F. Smith, *J. Chem. Soc.*, 3842 (1954).

(1) *Org. Syntheses*, Coll. Vol. III, 98 (1955).

TABLE I

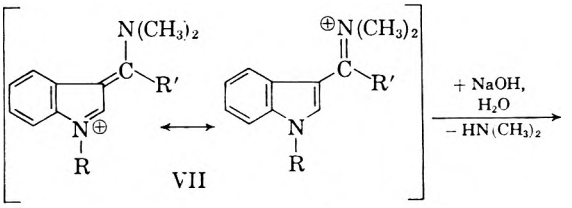
Nucleophile	Electrophile	Product	M.P.	Yield, %	C, % Calcd.	C, % Found	H, % Calcd.	H, % Found	Z, % Calcd.	Z, % Found	Recrystallization Solvent
1. 5-Benzyl oxyindole	*N,N*-Dimethylacetamide	5-Benzyloxy-3-acetylindole	189–190[a]	71							95% Ethanol
2. Indole	*N,N*-Dimethylpropionamide	3-Propionylindole	171–173[a]	85.5							Benzene-petroleum ether, b.p. 60–71°
3. Indole	*N,N*-Dimethylchloracetamide	3-Chloroacetylindole	233–234[b]	36.6							95% Ethanol
4. Indole	*N,N*-Dimethylbenzamide	3-Benzoylindole	241–243.5[c]	51	81.42	81.35	5.01	5.03	6.33	6.39	95% Ethanol
5. Indole	*N*-Methylacetamide	3-Acetylindole	191–193[d]	22.4							95% Ethanol
6. 2-Methylindole	*N,N*-Dimethylacetamide	2-Methyl-3-acetylindole	195–196[e]	98.0							95% Ethanol
7. 2-Methylindole	*N,N,α,α,α*-Pentamethylacetamide		134–135	49.0	78.11	78.20	7.94	8.53	6.50	6.32	Benzene petroleum ether, b.p. 60–71°
8. 2-Methylindole	*N,N,α*-Trimethylbutyramide		101–103	18.0	78.11	78.01	7.94	8.28	6.50	6.28	Petroleum ether, b.p. 60–71°, 95% ethanol
9. 2-Methylindole	*α*-Ethyl-*N,N,β*-trimethylbutyramide		106–109	24.0	78.92	78.97	8.65	9.11	5.75	5.74	95% Ethanol
10. 2-Methylindole	*N,N*-Dimethylisovaleramide		139–141	62	78.09	78.21	7.56	7.85	6.50	6.35	95% Ethanol
11. 1-Ethylindole	*N,N*-Dimethylacetamide	1-Ethyl-3-acetylindole	87–89[f]	76							95% Ethanol
12. Pyrrole	*N,N*-Dimethylacetamide	2-Acetylpyrrol	91–92[g]	49							Pet. ether, b.p. 60–71°
13. Pyrrole	*N,N,N',N'*-Tetramethylmalonamide	(a)  + (b) 	143–144 B.p. 154°/ 1 mm.	6 Undetermined	66.58 59.42	66.99 60.28	6.21 6.71	6.03 6.24	17.27 15.54	17.20 15.73	Benzene

[a] Identical with a sample prepared according to the method described by J. Szmuszkovicz in *J. Am. Chem. Soc.*, 82, 1180 (1960). [b] D. E. Ames, R. E. Bowman, D. D. Evans, and W. A. Jones, *J. Chem. Soc.* (1956) 1958. [c] Bernardo Oddo and Fuigi Sessa, *Gazz. Chim. Italia*, 41, I, 243 (1911). [d] Carlo Zatti, *Ber.*, 22, 662 (1889). [e] O. R. Jackson, *Ber*, 14, 880 (1881). [f] Yu A. Baskakov and N. N. Meljnikov Solbrnik, *Sbornik Statei Obshcheĭ Khim., Akad. Nauk, U.S.S.R.*, 1, 712–713 (1953). [g] Robert Schiff, *Ber.*, 10, 1501 (1877).

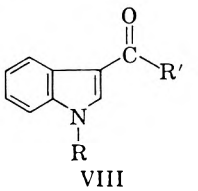
TABLE II

ABSORPTION SPECTRA OF NEW COMPOUNDS PREPARED

Compd. No.	Infrared, cm.$^{-1}$	Ultraviolet, mμ (^{d}) 95% ethanol
4	NH (3085); C=O (1595); amide vinylog (1565); C=C (1515, 1490); aromatic (747, 713, 697)	313 (12,000); 263 (10,550); 247 (15,075); 303 (14,325); 260 (10,975); 243 (15,400); 206 (47,935)
7	NH (3140); C=O (1592); C=C (1574, 1560, 1527, 1483); C—N (1270, 1205, 1128, 1058, 990); aromatic (795, 752, 740, 720)	302 (10,300); 270 (9,525); 244 (10,675); 216 (29,300)
8	NH (3150, 3080sh); C=O (1592); C=C (1573, 1523, 1485); C—N (1173, 1147, 973); aromatic (785, 751, 747, 735)	301 (10,725); 269 (9,900); 244 (11,675); 216 (29,600)
9	NH (3280); C=O [(plus C=C) 1613]; C=C (1585, 1573, 1485); vinylog (1520); C—N (1267, 1172, 1110); aromatic (757, 738, 728, 700)	303 (11,800); 269.5 (10,375); 245 (11,975); 216 (31,000)
10	NH (3230); C=O (1625, 1610); C=C (1580 sh., 1532, 1492); C—N (1260, 1178, 1052); aromatic (757, 743, 728)	301 (11,450); 268 (10,600); 243 (12,850); 215 (29,400)
13	(a) NH/OH (absent); C=O (1687); C=C (1615, 1357); aromatic (13070); (748, 740sh, 713, 677); other bonds (1430, 1408, 1310, 1250, 1240, 1160, 1073)	431 (2,113); 308 (12,650); (16,375); 274 (15,010); 212 (13,547)
	(b) NH/OH (3200); 6μ region (1680sh, 1655sh, 1625, 1610sh, 1545sh); other bonds (1131, 1107, 1050, 920, 750)	433 (357); 292 (16,269)



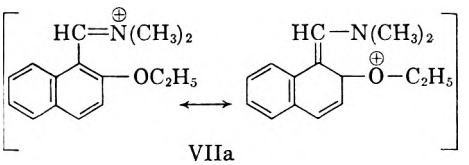
VII



VIII

R = H or alkyl
R' = alkyl or aryl

A comparison between the behavior of pyrrole and other systems such as β-ethoxynaphthalene in this type of acylation reaction is informative. Although the latter form only aldehydes, the former give both aldehydes and ketones. Furthermore, intermediates such as III have been isolated in the synthesis of compounds containing a pyrrole nucleus but not with other systems. Even in the acetylation of indoles and pyrroles with *N*,*N*-dimethylcarboxamides, a water soluble compound is formed when water is added to the reaction mixture. This fact lends support to the intervention of intermediates such as VII in the reaction sequence. The counterpart of this intermediate in reactions such as the formylation of β-ethoxynaphthalene would be VIIa. Unlike VII, which probably is sufficiently stabilized by resonance to permit its detection, VIIa may be expected to hydrolyze much more rapidly. The failure of β-ethoxynaphthalene to acetylate with *N*,*N*-dimethylacetamide is attributable to the relatively low nucleophilicity and higher steric requirements in the former compound.



VIIa

When this work was essentially complete the existence of German Patent 614,326 was brought to our attention. This patent claims the preparation of 1-methyl-3-*p*-chlorobenzoylindole using *p*-chlorobenzanilide and 1-methylindole. We applied the German procedure to the preparation of 3-acetylindole and found that the procedure reported in this paper is superior to the patented method as the yields were much better and the isolation and purification of the product was simpler. In addition, considerably less time is required to obtain the product.

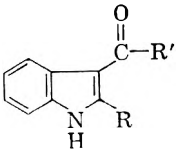
In the course of these experiments some interesting chemical and physical properties of the indolic ketones were observed. It was found that when a carbonyl group is attached to the indole nucleus in the 3-position, the 1-position can be readily alkylated with an alkyl halide and potassium carbonate.[4] When the side chain of the indole ketone was branched, *N*-alkylation could not be achieved under these mild conditions, but could be achieved using much stronger basic conditions.[5]

In the ultraviolet region an alcoholic solution of a 1-unsubstituted 3-acyl indole exhibits a new maximum at 332 mμ in the presence of alkali which is an indication of the degree of enolization. When the 2-position is substituted, branching in the side chain lowers the intensity at this wave length until

(4) W. B. Whalley, *J. Chem. Soc.*, 1651 (1954).
(5) Hans Plieninger, *Ber.*, **87**, 127 (1954).

TABLE III

ULTRAVIOLET ABSORPTIVITY OF[a]

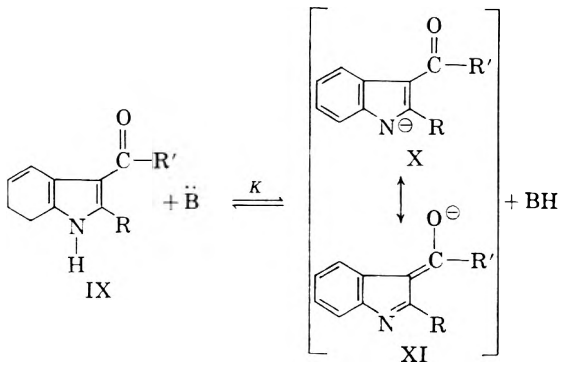


Compd. No.	R	R′	a_M Neutral	a_M KOH	a_M KOH/a_M neutral
5	H	$-CH_3$	483	4750	13.95
2	H	$-CH_2CH_3$	216	2435	11.25
6	$-CH_3$	$-CH_3$	515	1275	2.48
10	$-CH_3$	$-CH_2CH(CH_3)_2$	781	1334	1.71
7	$-CH_3$	$-C(CH_3)_3$	1225	1700	1.38
11[b]	H	$-CH_3$	1071	1047	0.98

[a] (Table I) at 332 mμ (ε) in 95% ethanol and in 0.01*N* 95% ethanolic potassium hydroxide. [b] The compound has a 1-ethyl substituent.

it approaches the value observed in neutral solution as shown in Table III.

The difference in ease of alkylation of the ketones in Table III can be explained on the basis of differences in the degree of steric inhibition of resonance for the various compounds and their respective anions.



The value of K depends on the size of R and R′. If R and R′ are large, then XI is destabilized relative to IX since all the groups cannot become coplanar. Thus the acyl indole becomes a weaker acid, and the value of K is diminished. As a result, a stronger base is needed to effect alkylation. The ultraviolet absorption data of Table III supports this contention.

EXPERIMENTAL[6,7]

The necessary amides which were utilized in this investigation were obtained commercially or were prepared according to literature procedures and used in their crude state. The ketones were prepared essentially as described in the following examples.

5-Benzyloxy-3-acetylindole (I). An 18-ml. sample of *N,N*-dimethylacetamide was cooled to 5° and 7.0 ml. (0.072 mole) of phosphorus oxychloride was slowly added keeping the temperature below 20°. After the addition was complete, a solution of 12.5 g. (0.056 mole) of 5-benzyloxyindole and 9 ml. of *N,N*-dimethylacetamide was slowly added keeping the temperature below 40°. The mixture was heated to 87° for 2 hr. and allowed to cool. The red mass was dissolved in water and extracted with ether. The water solution was made basic with sodium hydroxide and filtered. The solid was washed well with water, refluxed in alcohol containing Darco "60" and filtered. Upon cooling the solution deposited 10.5 g. (71%) of product, m.p. 189–190°. This solid caused no depression in melting point when mixed with an authentic sample (see Table I, footnote *a*).

3-Benzoylindole (4). A mixture of 14 ml. (0.15 mole) of phosphorus oxychloride, 36 g. (0.24 mole) of *N,N*-dimethylbenzamide and 13.0 g. (0.122 mole) of indole was heated to 84° for 2 hr., cooled, and dilute sodium hydroxide was added. The mixture was stirred until a fine suspension was obtained and then filtered. The solid was thoroughly extracted with alcohol to yield 13.5 g. (51%) of product, m.p. 241–243.5°.

Reaction of pyrrole and N,N,N′,N′-tetramethylmalonamide (13). A 93-g. (0.57 mole) sample of phosphorus oxychloride was slowly added to 47.4 g. (0.3 mole) of *N,N,N′,N′*-tetramethylmalonamide at 10–20°. The mixture was cooled to 10° and 20.1 g. (0.3 mole) of pyrrole was slowly added keeping the temperature below 45°. After the addition was complete the mixture was heated over 45 min. to 55–60°. The mixture was maintained at this temperature for 30 min., then cooled and poured into ice water. The solution was made basic with sodium hydroxide and filtered. The solid (7.9 g.) was washed well with water and dried. The solid was shaken twice with 300 ml. of ether and filtered. The ether solution was concentrated yielding 3.5 g. of residue. After three recrystallizations from benzene compound no. 13a was obtained, m.p. 143–144°.

The original basic solution was extracted with ether for 24 hr. and concentrated yielding 16.2 g. of an oil. The oil was dissolved in ether, with a trace of ethyl acetate, and treated with anhydrous hydrogen chloride. The precipitate was washed with ether until free of acid and then treated with potassium hydroxide solution. The mixture was extracted with ethyl acetate. Concentration of the organic layer

(6) All melting points were taken by capillary and are uncorrected.

(7) The author wishes to express his appreciation to Drs. Jacob Szmuszkovicz and R. V. Heinzelman of our Department of Chemistry for their helpful discussions and advice in this work and to Professor D. J. Cram of the University of California, Los Angeles, for his criticisms of and assistance in preparing this paper. The author is also indebted to Dr. J. L. Johnson and associates for spectral data and Mr. W. A. Struck and staff for analytical determinations.

yielded an orange colored oil. A sample of the oil was distilled at 154°/1 mm. to yield compound no. 13b.

Supporting evidence for structure 13a. A 0.003-mole sample of 13a was dissolved in one equivalent of 0.1 *N* hydrochloric acid. After 30 min. bubbles appeared and the solution began to decolorize. After 2 hr. the colorless solution deposited 2-acetylpyrrol, m.p. 91–92°, in quantitative yield.

RESEARCH DIVISION
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Halogenated Aminobenzaldehydes and Aminostyrylquinolines[1]

CARL TABB BAHNER, WILLIAM CHAPMAN, CLARENCE COOK, OAKLEY CRAWFORD, CHARLES HANNAN, NORVELL HUNT, LYDIA M. RIVES, WARREN YEE, AND WILLIAM EASLEY

Received April 11, 1960

4-(4′-Dimethylaminostyryl)quinolines bearing a halogen atom on the benzene ring of the quinoline portion of the molecule have been prepared from halogen substituted anilines.[2] Additional halogenated styrylquinolines listed in Table I have been prepared, for testing against animal tumors at the Chester Beatty Research Institute. The presence of a bromine atom usually seems to make the compounds less toxic and less active against tumors. Chloride atoms have similar but smaller effect and fluorine atoms have even less effect, but even a fluorine atom in the 2′ position reduces biological activity sharply. The ratio of maximum tolerated dose to minimum effective dose is not necessarily greatest in the most potent compounds and the position of the halogen atom makes a great deal of difference.

EXPERIMENTAL

The 2-chloro-, 2-fluoro-, 3-fluoro-, and 2,5-difluorobenzaldehydes were prepared from the corresponding halodimethylanilines by the method of Campaigne and Archer.[3] 3-Bromo- and 3-chloro-4-dimethylaminobenzaldehyde were prepared by halogenation of 4-dimethylaminobenzaldehyde.[4] Attempts to prepare 3,5-dibromo- and 3-chloro-5-bromodimethylaminobenzaldehyde by treatment of the monohalo compounds with bromine in glacial acetic acid produced crystalline products which seemed to be perbromide hydrobromides of the monohalo compounds. Heating these crystals 3 hr. at 110–130° formed crystalline substances whose composition corresponded to 3,5-dibromo-4-aminobenzaldehyde and 3-chloro-5-bromo-4-aminobenzaldehyde. The loss of the alkyl groups from the dialkylamino group was less surprising in view of Fries[5] report that 2,4,6-tribromo-*N*,*N*-dimethylaniline perbromide hydrobromide on treatment with water in glacial acetic acid formed 2,4,6-tribromo-*N*-monomethylaniline. Molecular models indicate that the crowding of large groups at the amino end of the molecule would produce severe strain, and that even a single bromine or chlorine atom adjacent to the dimethylamino group would cause some strain. It is interesting to note that, although a halogen atom on the benzene ring in the quinoline portion of the styrylquinolines tends to raise the melting point, 4-(4-dimethylamino-3-bromostyryl)quinoline, 4-(4-dimethylamino-3-chlorostyryl)quinoline, and 4-(4-dimethylamino-3-fluorostyryl)quinoline melt approximately 25°, 40°, and 50° lower, respectively, then the unhalogenated parent compound.

3-Bromo- and 3-chlorolepidine, obtained in poor yield by the method of Ellinger,[6] formed styryl derivatives without undue difficulty. In a modification of the Leese method, the picrate was used instead of the hydrochloride, keeping in mind the possible explosive character of the picrate. Numerous efforts to condense 2-chlorolepidine with 4-dimethylaminobenzaldehyde failed, but this base did condense with 4-nitrobenzaldehyde and the resulting nitrocompound was reduced by stannous chloride to 4-(4-aminostyryl)-2-chloroquinoline. 6-Fluorolepidine, b.p. 135° (23 mm.), was prepared from 4-fluoroaniline by William K. Easley, L. Free, and Frank Howell at East Tennessee State College using the method of Campbell and Schaffner.[7] 6-Fluoroquinaldine, m.p. 49.5–51°[8] was provided by Dr. W. F. Little and Mr. Clarence Cook, of the University of North Carolina.

3-Bromo-4-dimethylaminobenzaldehyde perbromide hydrobromide was prepared by adding 171 g. (1.07 moles) of bromine in 100 ml. of glacial acetic acid dropwise, with stirring, during 15 min., to 75 g. of 4-dimethylaminobenzaldehyde in 240 ml. of glacial acetic acid, then continuing to stir 45 min. while cooling with an ice bath. The orange crystals were washed well with benzene and dried overnight over sodium hydroxide; yield 216 g., m.p. 128.5–129.3°.

Anal. Calcd. for $C_9H_{10}NOBr.HBr.Br_2$: Oxidizing bromine 34.1%; total bromine 68.18%. Found: Oxidizing bromine 34.19, 34.01; total bromine 68.1, 68.3.[8]

3,5-Dibromo-4-aminobenzaldehyde was prepared by heating 67 g. of the above perbromide 3 hr. at 110–130°. The remaining porous mass was recrystallized from ethanol, from isohexane, and again from ethanol; yield 9.0 g., m.p. 149.5–150.8°; after sublimation m.p. 151.7–152.7°.[10]

Anal. Calcd. for $C_7H_5Br_2NO$: C, 30.14; H, 1.81. Found: C, 30.83; H, 2.10, 1.81.[8]

3-Chloro-4-dimethylaminobenzaldehyde perbromide hydrobromide was prepared similarly from 50 g. of 3-chloro-4-dimethylaminobenzaldehyde; yield 66.4 g., m.p. 125.4–127.1°.

Anal. Calcd. for $C_9H_{10}NOCl.HBr.Br_2$: Oxidizing bromine, 37.61; total halogen 64.84. Found: Oxidizing bromine, 36.68, 36.55; total halogen, 63.7, 63.8.[8]

3-Chloro-5-bromo-4-dimethylaminobenzaldehyde was prepared by heating 51.8 g. of the perbromide 8 hr. at 115°,

(1) The research was supported in part by grants from the American Cancer Society and the National Cancer Institute. Some of the compounds described were prepared in the laboratories of the Chester Beatty Research Institute. A portion of this paper was presented at the Southeastern Regional Meeting, ACS, at Raleigh, N. C., in November 1957.

(2) C. T. Bahner, C. Cook, J. Dale, J. Fain, E. Franklin, J. C. Goan, W. Stump, and J. Wilson, *J. Org. Chem.*, **22**, 682 (1956).

(3) E. Campaigne and W. L. Archer, *Organic Syntheses*, **33**, 27 (1953).

(4) D. L. Brady and R. Truskowski, *J. Chem. Soc.*, 2434 (1923).

(5) K. Fries, *Ann.*, **346**, 193 (1906).

(6) A. Ellinger, *Ber.*, **39**, 2515–2522 (1906).

(7) K. N. Campbell and J. Schaffner, *J. Am. Chem. Soc.*, **67**, 86 (1945).

(8) Analyses by Weiler and Strauss.

(9) C. T. Bahner, C. Cook, J. Dale, J. Fain, F. Hannan, P. Smith, and J. Wilson, *J. Org. Chem.*, **23**, 1060 (1958).

(10) J. J. Blanksma, *Centr.*, 1910, I, 260 (1910).

TABLE I

HALOGEN SUBSTITUTED STYRYLQUINOLINES

Compound	M.P.	Reaction Method	Reaction Temp.	Reaction Time	Yield, %	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
4-(4-Dimethylaminostyryl)quinolines												
2′-Chloro[f]	159.4–160.6	Leese[g]	150–170	10 min.		$C_{19}H_{17}N_2Cl$	73.90	5.55		73.55	5.50	9.4[b]
										73.62	5.47	9.5
2′-Fluoro	126.3–127.5	Leese	150 160	1 hr.	22.8	$C_{19}H_{17}N_2F$	78.04	5.86		73.29	5.71[a]	
										78.29	5.81	
3′-Bromo	117.4–119.1	Fain[2]	119–120	20 hr.	34	$C_{19}H_{17}N_2Br$	64.56	4.83		64.72	4.83[a]	
										64.80	4.79	
3′-Chloro	103.5–104.6	Fain	115–120	23 hr.	13	$C_{19}H_{17}N_2Cl$	73.90	5.55		73.94	5.61[a]	
										73.73	5.65	
3′-Fluoro	92.1–93.1	Leese	150–160	1 hr.	14	$C_{19}H_{17}N_2F$	78.04	5.86		77.78	6.02[a]	
										78.06	5.82	
2′,5′-Difluoro	107.8–108.5	Leese	150–160	1 hr.	23.5	$C_{19}H_{16}N_2F_2$	73.53	5.20		73.50	5.09[a]	
										73.65	5.12	
3-Bromo	193–194.5	Picrate	95–100	2 hr.		$C_{19}H_{17}BrN_2$	64.56	4.83	7.91	64.59	4.85	7.93[c]
3-Chloro	165.9–167.2	Leese	150	25 min.	23	$C_{19}H_{17}ClN_2$	73.90	5.55	9.07	73.95	5.52	9.10[c]
6-Fluoro	159–160.5	Leese	150–154	1 hr.	9.45	$C_{19}H_{17}N_2F$	78.03	5.86		77.81	5.76[a]	
										77.73	5.77	
2-(4-Dimethylaminostyryl)quinolines												
6-Fluoro	195–196	Leese	155–160	1 hr.	25.2	$C_{19}H_{17}N_2F$	78.04	5.86		77.73	5.68[a]	
										77.85	5.90	
4-(4-Nitrostyryl)quinoline												
2-Chloro	240–241	Leese	130	3 hr.	38.3	$C_{17}H_{11}N_2ClO_2$	65.70	3.57		65.53	3.61[a]	
										65.80	3.77	
4-(4-Aminostyryl)quinoline												
3′,5′-Dibromo	222.5–224.0	Leese	145–150	2 hr.		$C_{17}H_{12}N_2Br_2$	50.52	2.99		50.50	2.98[d]	
										50.39	2.84	
2-Chloro	203–204	$SnCl_2$[e]			9.4	$C_{17}H_{13}N_2Cl$	72.71	4.67		72.43	4.60[a]	
										72.47	4.75	

[a] Analysis by Galbraith. [b] Analysis by Weiler and Strauss. [c] Analysis by Burroughs Wellcome. [d] Calcd. Br 39.6. Found: Br 39.6, 39.2 (analysis by Weiler & Strauss). [e] Reacted in concd. hydrochloric acid at room temperature, then heated at 80–90°, 1 hr. [f] Numbers having a prime refer to positions on the styryl portion of the molecule.

TABLE II

FLUOROALDEHYDES

Name	M.P.	Yield, %	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
4-Dimethylamino-2-fluorobenzaldehyde	62.9–64.5°	74.3	$C_9H_{10}FNO$	64.66	6.03	64.31	5.83[a]
						64.46	5.83
4-Dimethylamino-2,5-difluorobenzaldehyde	60.8–62.0°	17.3	$C_9H_9F_2NO$	58.37	4.90	58.43	5.00[a]
						58.45	5.20

[a] Analysis by Weiler and Strauss.

recrystallizing the residue repeatedly from ethanol, and subliming in vacuum, m.p. 145.7–147.0°.

Anal. Calcd. for $C_7H_5BrClNO$: C, 35.85; H, 2.15. Found: C, 35.63, 35.48; H, 2.23, 2.33.[8]

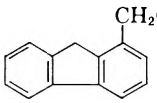
CARSON-NEWMAN COLLEGE
JEFFERSON CITY, TENN.

Synthesis of *dl*-β-(1-Fluorenyl)alanine

D. C. MORRISON

Received January 26, 1960

In continuation of work begun with the synthesis of *dl*-β-(2-fluorenyl)alanine[1] the corresponding 1-fluorenyl isomer has been prepared. The substance I may be of interest in cancer chemotherapy and as an aromatic amino acid.



I

It was obtained from fluorene-1-carboxylic acid[2] II as starting material by a route similar to that used for the 2-isomer. Reduction of the 1-methyl ester by lithium aluminum hydride gave the 1-carbinol[3] III, which was converted to the corresponding bromide[3] with phosphorus tribromide. The bromide was employed to alkylate the sodium derivative of diethyl acetamidomalonate, and the intermediate ester was hydrolyzed by hydrochloric acid to the amino acid hydrochloride. This salt, when dissolved in dilute alkali and acidified with acetic acid gave the free amino acid. The hydrochloride serves to characterize the compound.

The amino acid was a very sparingly soluble crystalline powder, similar in most physical properties to the 2-isomer. The melting point and that of the hydrochloride were not very sharp as is usually observed with this type of compound.

The infrared spectrum of the free amino acid in a potassium bromide disk showed a wide multicomponent band between 3100–2900 cm.$^{-1}$, probably due to C—H stretching and NH_3^+ stretching. A series of peaks at 1640 (sh), 1613, 1584, 1486, and 1410 cm.$^{-1}$ may be ascribed to C=C stretching, NH_3^+ deformation, and carboxylate ion vibrations but single assignments would be difficult. A very strong band at 759 cm.$^{-1}$ is attributable to C—H out of plane bending.

(1) D. C. Morrison, *J. Org. Chem.*, **24**, 463 (1959).

(2) D. C. Morrison, *J. Org. Chem.*, **23**, 1772 (1958).

(3) L. A. Pinck and G. E. Hilbert, *J. Am. Chem. Soc.*, **68**, 752 (1946).

EXPERIMENTAL

Melting points are uncorrected and were taken on a Fisher-Johns block.

1-Hydroxymethylfluorene. Methyl fluorene-1-carboxylate was prepared by conventional esterification with methanol and sulfuric acid. It was distilled from a small still at 1 mm. pressure and recrystallized from acetone-water. The greater solubility of the ester in organic solvents was an advantage over use of the free acid in reductions. The methyl ester (8.4 g. or 0.038 mole) was treated with lithium aluminum hydride as described for the 2-isomer[1] and gave a nearly theoretical yield (7.4 g.) of crude fluorenyl-carbinol. This melted at 137–146°, and after several recrystallizations from ether–petroleum ether (b.p. 30–60°) had a melting point of 146.5–147.5°. Pinck and Hilbert[3] give 148° corr. The carbinol could also be distilled at 1 mm. to aid in its purification.

1-Bromomethylfluorene. This was prepared by a process similar to that used for the 2-isomer[1] and was obtained in nearly theoretical yield. If insufficient phosphorus tribromide is used, some starting material may be recovered unchanged. The crude product melted at 97–102° and when recrystallized from ether and petroleum ether, this was raised to 100–101.5° with previous sintering; lit.[3] m.p. 104° corr.

Diethyl (1-fluorenylmethyl)acetamidomalonate. A solution of 0.92 g. (0.04 mole) of sodium in absolute ethyl alcohol was treated with 8.7 g. (0.04 mole) of diethyl acetamidomalonate and warmed for solution. Now 10.4 g. (0.04 mole) of the bromide (m.p. 97–102°) was added and the mixture refluxed 16 hr. If variations from the theoretical amounts are used, the product cannot be purified easily. Most of the ethanol was distilled and 3 ml. of acetic acid and an excess of water were added. After leaving overnight on ice, the solid product was filtered, washed with water, and dried. It weighed 15 g. or 94.9%. The ester could be recrystallized from aqueous acetone with difficulty. Slow crystallizations from clear solutions, taking center fractions, were carried out twelve times to obtain a pure product. This was a cream-white powder, m.p. 120–121°.

Anal. Calcd. for $C_{23}H_{25}NO_5$: C, 69.87; H, 6.33. Found: C, 69.91; H, 6.19.

DL-β-(1-Fluorenyl)alanine hydrochloride. A solution of 14.8 g. (0.0375 mole) of the crude ester in 150 ml. of glacial acetic acid was heated to boiling under reflux. While boiling, a mixture of 60 ml. of coned. hydrochloric acid and 10 ml. of water was added and reflux continued for 48 hr. Most of the solvent was now distilled and the residue extracted repeatedly with boiling 2*N* hydrochloric acid until nothing further was removed. The extracts were filtered at 90° or higher and the filtrates cooled to obtain the product. This was filtered and the filtrates concentrated to a small volume for a second crop. The combined weight of hydrochloride was 9.3 g. or 85.8%. The hydrochloride could be

recrystallized from hot dilute hydrochloric acid but it was best to cause slow deposition of the salt from the dilute acid at room temperature on standing. After several recrystallizations in this way, it was further recrystallized from ethanol-toluene and then formed a nearly white crystalline powder. The best material, on heating, began to turn orange at 210–215° with melting at 228–234° to an orange-brown melt.

Anal. Calcd. for $C_{16}H_{16}NO_2Cl$: C, 66.32; H, 5.53. Found: C, 66.69; H, 5.80.

DL-β-(*1-Fluorenyl*)*alanine.* The hydrochloride could be converted to the free amino acid by extraction with ammonium hydroxide and acidification with acetic acid. This tended to form a pink product, especially if heated. It was found preferable to acidify a very dilute solution of the hydrochloride in dilute potassium hydroxide with acetic acid so that the amino acid slowly deposited at room temperature. In this way, a nearly white crystalline product was formed. On heating, the best sample began to turn orange at 210–212° and melted 221–230° to an orange-brown melt.

Anal. Calcd. for $C_{16}H_{15}NO_2$: C, 75.89; H, 5.93. Found: C, 76.04; H, 5.96.

Reaction with ninhydrin. The amino acid was suspended in dilute acetic acid and treated with an excess of ninhydrin and heated. A greenish-gray solution was formed at first which became dark blue-gray on further heating. On boiling a few minutes, a purple solution was produced with dark blue-gray particles (from undissolved amino acid) in suspension.

DEPT. OF PHYSIOLOGICAL CHEMISTY
UNIVERSITY OF CALIFORNIA SCHOOL OF MEDICINE
BERKELEY, CALIF.

Preparation of *N*-Substituted Glycines. II. *N*-(3,5-Dinitro-2-thienyl)glycine[1,2a]

JACK M. TIEN AND I. MOYER HUNSBERGER[2b]

Received March 18, 1960

Our interest in *N*-heteroaryl derivatives of the sydnone ring system[3] led us to attempt the preparation of an *N*-thienylsydnone. As no *N*-thienylglycines have been reported in the literature, we first attempted to prepare *N*-2-thienylglycine by condensation of 2-chlorothiophene with glycine ethyl ester hydrochloride (I); however, only unchanged chlorothiophene was isolated. The more reactive 2-bromo-5-nitrothiophene (II) also failed to condense with I. Finally, the hitherto unreported 2-bromo-3,5-dinitrothiophene (III) was prepared in high yield by nitration of 2-bromo-5-nitrothiophene with mixed acid at low temperature. After considerable difficulty the condensation of III with I was effected by heating in absolute ethanol containing a rather carefully regulated amount of zinc oxide. In this way the ethyl ester (IV) of *N*-(3,5-dinitro-2-thienyl)glycine, m.p. 125–126°, was obtained in good yield. Acid hydrolysis of IV then afforded the desired *N*-(3,5-dinitro-2-thienyl)glycine (V). Esterification of V regenerated IV.

All attempts to nitrosate both the glycine (V) and its ethyl ester (IV) were unsuccessful; methods specifically designed for nitrosating weakly basic amines gave only unchanged starting material. As 3,5-dinitro-2-thienol[4] is a much stronger acid than 2,4-dinitrophenol, it seems likely that IV and V also are weaker bases than the corresponding benzene derivatives. Apparently, two nitro groups on the thiophene ring exert effects comparable to three nitro groups on the benzene ring. In this connection it is noteworthy that V separated as the free base from aqueous hydrochloric acid and that IV did not form a hydrochloride salt in absolute ethanol saturated with dry hydrogen chloride.

Further work in this series was abandoned because of the extremely potent vesicant action of both II and III (see Experimental).

EXPERIMENTAL[5]

2-Bromo-3,5-dinitrothiophene (III).[6] Concentrated sulfuric acid (45 ml.) and 60 ml. of yellow fuming nitric acid (sp. gr. 1.49–1.50)[7] were mixed at −5°. The mixed acid was kept at −5° (ice-salt bath) while 14.6 g. (0.070 mole) of II[8] was added portionwise (stirring) during 25 min. After about 10 min. a pasty mass had formed. The ice-salt bath was replaced by a water bath, and stirring was continued for another 25 min. The yellow slurry was poured onto chipped ice to yield 17 g. (96%) of III as a pale yellow crystalline powder, m.p. 135–136°. Recrystallization from hot ethanol afforded colorless plates of unchanged m.p.

Anal. Calcd. for $C_4HN_3O_4BrS$: Br, 31.59; S, 12.67. Found: Br, 31.51; S, 12.53.

This compound was very soluble in acetone, chloroform, dioxane, and petroleum ether; it was soluble in ether but insoluble in benzene, water, and concentrated or dilute hydrochloric acid.

Ethyl ester (IV) *of N-(3,5-dinitro-2-thienyl)glycine.* A hot solution of 6.3 g. (0.045 mole) of I in 450 ml. of absolute ethanol was treated with 11.0 g. (0.0435 mole) of III and 1.40 g. (0.0172 mole) of zinc oxide. The reagents were added alternately and in about six equal portions, a given portion not being added until the preceding one had dissolved. The yellow solution was refluxed in a hot water bath for 2 hr. On cooling, the solution deposited 9.80 g. (82%) of crude IV as yellow to brown needles. Recrystallization from hot

(1) Paper I: J. M. Tien and I. M. Hunsberger, *J. Am. Chem. Soc.* **77**, 6696 (1955).

(2) (a) Supported, in part, by a research grant (CY-2962) from the National Cancer Institute of the Public Health Service and by the U. S. Air Force under Contract No. AF 18(603)-127, monitored by the Air Force Office of Scientific Research of the Air Research and Development Command. Reproduction in whole or in part is permitted for any purpose of the United States government. (b) To whom all inquiries should be sent: Department of Chemistry, University of Massachusetts, Amherst, Mass.

(3) J. M. Tien and I. M. Hunsberger, *J. Am. Chem. Soc.*, **77**, 6604 (1955).

(4) C. D. Hurd and K. L. Kreuz, *J. Am. Chem. Soc.*, **74**, 2965 (1952).

(5) All combustion analyses were performed by Schwarzkopf Microanalytical Laboratories, Woodside, N. Y.

(6) This procedure is similar to that used[4] for nitrating 2-chloro-5-nitrothiophene.

(7) Red fuming nitric acid produced virtually identical results.

(8) V. S. Babasinian, *J. Am. Chem. Soc.* **57**, 1764 (1935).

ethanol saturated with hydrogen chloride[9] afforded the analytical sample as thin lemon-yellow needles, m.p. 125–126°, which contained no halogen.

Anal. Calcd. for $C_8H_9N_3O_6S$: C, 34.91; H, 3.27; N, 15.27; S, 11.64. Found: C, 35.18; H, 3.27; N, 15.00; S, 11.57.

Both the nature of the solvent and the proportion of zinc oxide used in this preparation are critical. Thus, the above-stated proportion of zinc oxide in 95% ethanol produced only a red gum. Larger proportions of zinc oxide in absolute ethanol gave about 70% yields of IV, but the product had a dark purplish-brown color. Use of absolute ethanol containing no zinc oxide produced a small amount of unidentified white flakes, m.p. 120–121°. With pyridine as solvent, an intractable black product formed immediately. The effect of the varying reflux periods used in these experiments is believed to be slight.

Using pyridine as a solvent, we were unable to effect condensation of I with either 2-chlorothiophene or II. II and I also did not react in absolute ethanol containing zinc oxide.

N-(3,5-Dinitro-2-thienyl)glycine (V). A solution of 0.275 g. (1.00 mmole) of the ethyl ester IV in 12 ml. of concd. hydrochloric acid and 12 ml. of water was boiled, diluted with 20 ml. of water, and then refrigerated to yield 0.235 g. (95%) of V as tiny yellow needles, m.p. 215–217°, with some prior decomposition and sublimation.

Anal. Calcd. for $C_6H_5N_3O_6S$: C, 29.15; H, 2.02. Found: C, 29.64; H, 2.53.

The glycine V was reconverted to IV by saturating its solution in absolute ethanol with dry hydrogen chloride. Concentration and cooling afforded IV as lemon-yellow needles, m.p. 125–126°; no depression when mixed with a sample prepared as described above.

Vesicant properties. Both II and III produced a very persistent skin rash and painful blisters. More than 6 months was required for the irritation to disappear completely, even after treatment with certain cortisone ointments. The person most seriously affected had worked with a large variety of thiophene compounds of other types for several years without any ill effects. In addition to its vesicant properties, III exhibited a potent corrosive action similar to that of the phenols. An acetone solution of III removed the skin in a short time.

Acknowledgment. The authors are indebted to Mr. Jean-Pierre Anselme for repeating and checking the preparations described in this paper.

DEPARTMENT OF CHEMISTRY
FORDHAM UNIVERSITY
NEW YORK 58, N. Y.

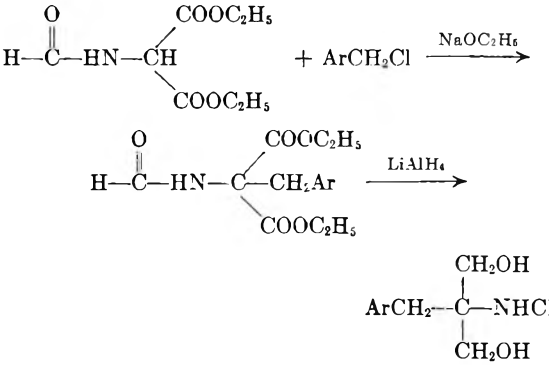
(9) The hydrogen chloride is necessary to remove the color from crude IV.

Syntheses of Some 1-Alkylamino-1,1-di(hydroxymethyl)-2-phenylethanes

B. VITHAL SHETTY AND ALLAN R. DAY[1]

Received March 23, 1960

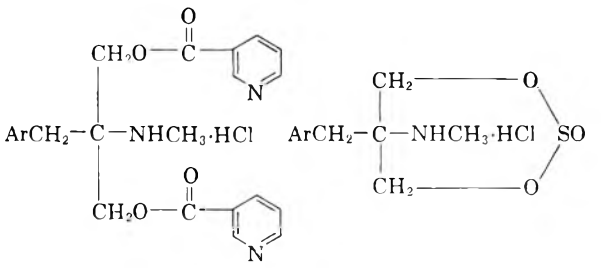
Many derivatives of β-phenylethylamine have been synthesized by earlier investigators with the hope of obtaining physiologically active compounds. In the present study a number of derivatives of β-phenylethylamine, having a trisubstituted carbon atom attached to the amino group, have been synthesized. In all cases the trisubstituted carbon is attached to two hydroxymethyl groups, to a benzyl or a substituted benzyl group and to an alkylamino group. The synthetic steps may be illustrated by the following example:



Ar = C_6H_5, 2-$CH_3C_6H_4$, 3-$CH_3C_6H_4$, 4-$CH_3C_6H_4$, 4-$CH_3OC_6H_4$, 4-HOC_6H_4.

In one case the ethylamino group was introduced in place of the methylamino group. Diethyl acetamidomalonate was the starting material for the preparation of the ethylamino compound.

The dinicotinates and the sulfites of most of these compounds were also prepared.



EXPERIMENTAL

Ethyl isonitrosomalonate, I. This compound was prepared by the procedure of Cerchez.[2] The yield was 81%.

Ethyl formamidomalonate, II. Compound I was reduced with zinc dust and formic acid by the method of Conrad and Schulze.[3] The crude yield was 71%. The product was sufficiently pure for the subsequent steps.

Ethyl α-formamido-α-carbethoxy-β-phenylpropionate, III. Compound III was prepared from II by treatment with sodium ethoxide and benzyl chloride.[4] The yield was 96%, m.p. 105–107°.

N-Methyl-1,1-di(hydroxymethyl)-2-phenylethylamine hydrochloride, IV. Lithium aluminum hydride (19.9 g., 0.52 mole) was added to 470 ml. of dry ether and the mixture stirred for 20 min. at room temperature and then for 20 min. while cooling in an ice bath under an atmosphere of dry nitrogen. Then 50 g. (0.17 mole) of compound III, suspended in 250 ml. of dry ether, was added in small amounts during a period of 45 min. while maintaining the temperature below 30°. After the addition was complete, the stirring was continued for 6 hr. The cooled reaction mixture was carefully

(1) The authors are indebted to the Wyeth Institute for Medical Research for their assistance during this investigation.

(2) V. Cerchez, *Bull. soc. chim. France*, **47**, 1279 (1930).

(3) M. Conrad and A. Schulze, *Ber.*, **42**, 733 (1909).

(4) A. Cohen, E. G. Hughes, and J. A. Silk, British Patent **621,706** (1949).

TABLE I

$$ArCH_2-\overset{CH_2OH}{\underset{CH_2OH}{C}}-NHR\cdot HCl$$

	Formula	Ar	R	Yield, %	M.P.	C, %		H, %		N, %		Cl, %	
						Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
IV	$C_{11}H_{18}ClNO_2$	C_6H_5	CH_3	41	153–155	57.02	56.95	7.77	7.54	6.04	6.22	15.31	15.51
V	$C_{18}H_{24}ClNO$	C_6H_5		13	218–220	67.60	67.70	6.88	6.99	4.38	4.28	11.11	11.14
VI	$C_{12}H_{20}ClNO_2$	o-$CH_3C_6H_4$	CH_3	35	163–165	58.67	58.75	8.14	8.24	5.70	5.87	14.42	14.40
VII	$C_{12}H_{20}ClNO_2$	m-$CH_3C_6H_4$	CH_3	30	117–110	58.67	58.40	8.14	8.40	5.70	5.90	14.42	14.21
VIII	$C_{12}H_{20}ClNO_2$	p-$CH_3C_6H_4$	CH_3	56	157–158	58.67	58.87	8.14	8.22	5.70	5.70	14.42	14.20
IX	$C_{12}H_{20}ClNO_2$	C_6H_5	C_2H_5	15	141–143	58.67	58.52	8.14	8.27	5.70	5.91	14.42	14.27
X	$C_{12}H_{20}ClNO_3$	p-$CH_3OC_6H_4$	CH_3	40	168–170	55.08	55.00	7.65	7.80	5.35	5.65	13.54	13.49
XI	$C_{11}H_{18}ClNO_3$	p-HOC_6H_4	CH_3	33	174–176	53.33	53.19	7.27	7.54	5.65	5.87	14.34	14.53

treated with water to decompose the lithium aluminum compounds and the ether layer then separated. The aqueous layer was extracted with ether and the combined ether extracts were then dried over anhydrous sodium sulfate. The ether was removed under reduced pressure and the residue was dissolved in 300 ml. of dry ether. The ether solution was treated with dry hydrogen chloride and the gummy precipitate so obtained was extracted with dry ether until it solidified. The solid was dissolved in 75 ml. of dry methanol and the solution decolorized with charcoal. Fifty milliliters of dry acetone was then added followed by 300 ml. of dry ether. After standing overnight at −10°, 18 g. of the hydrochloride was obtained.

The dinicotinate of compound IV was prepared by refluxing a solution of 2 g. of nicotinic anhydride[5] and 1 g. of IV in 200 ml. of dry benzene for 28 hr. The mixture was filtered while hot and the residue washed with hot benzene. The benzene filtrate and washings were combined and the benzene removed *in vacuo*. The residue was dissolved in 50 ml. of dry ethanol, decolorized with charcoal, 300 ml. of dry ether added, and the solution then allowed to stand overnight at −10°. The colorless crystals so obtained were dried *in vacuo*, yield 51%, m.p. 189–190°.

Anal. Calcd. for $C_{23}H_{24}ClN_3O_4$: C, 62.51; H, 5.43; Cl, 8.04; N, 9.41. Found: C, 62.29; H, 5.33; Cl, 8.0; N, 9.44.

The hydrochloride of the sulfite of compound IV was also prepared. Eight grams of *N*-methyl-1,1-di(hydroxymethyl)-2-phenylethylamine hydrochloride was thoroughly mixed with 83 ml. of freshly distilled thionyl chloride. The mixture was allowed to stand for the 30 min. The solid was then removed by filtration and washed with petroleum ether (b.p. 30–60°). It was recrystallized from 60 ml. of methanol with the aid of decolorizing carbon. The yield was 62%, m.p. 157–158°.

Anal. Calcd. for $C_{11}H_{16}ClNO_3S$: C, 47.56; H, 5.76; Cl, 12.79; N, 5.04; S, 11.52. Found: C, 47.53; H, 5.80; Cl, 12.60; N, 5.02; S, 11.30.

N-[1,1-Di(hydroxymethyl)-2-phenylethyl]-1,3-dihydroisoindole, V. Ethyl phthalimidomalonate was prepared by the method of Sheehan and Bolhofer.[6] This compound was converted to sodium ethyl phthalimidomalonate by the procedure of Barger and Weichselbaum.[7]

Ethyl benzyl phthalimidomalonate was made by the method reported by Sorensen.[8] The yield was 90%, m.p. 105–106°.

Lithium aluminum hydride (3.5 g., 0.092 mole) was stirred with 200 ml. of dry ether at room temperature for 20 min. and then for 20 min. at 0°, in an atmosphere of nitrogen. Then 10 g. (0.025 mole) of ethyl benzyl phthalimidomalonate dissolved in 150 ml. of dry ether, was added over a period of 30 min. The mixture was stirred and refluxed for 3 hr. It was then cooled and treated carefully with water. The ether layer was separated and the aqueous layer extracted with ether. The combined ether extracts were dried over anhydrous sodium sulfate and the ether removed by distillation. The residue was warmed with 50 ml. of 20% hydrochloric acid and the solution filtered. On cooling, the product (V) separated.

N-Methyl-1,1-di(hydroxymethyl)-2-(2-methylphenyl)ethylamine hydrochloride, VI. Sodium (2.07 g., 0.09 g.-atom) was dissolved in 175 ml. of dry ethanol. To this solution was added 15.0 g. (0.09 mole) of ethyl formamidomalonate with stirring. Then 19.5 g. (0.13 mole) of *o*-methylbenzyl chloride[9] was added over a period of 10 min. with stirring. Stirring

(5) W. A. Schrecker and B. P. Maury, *J. Am. Chem. Soc.*, **76**, 5803 (1954).

(6) J. C. Sheehan and W. A. Bolhofer, *J. Am. Chem. Soc.*, **72**, 2786 (1950).

(7) G. Barger and T. E. Weichselbaum, *Org. Syntheses*, **Coll. Vol. II**, 384 (1943).

(8) S. P. L. Sorensen, *Centrl.*, **II**, 33 (1943).

(9) K. Kindler and E. Yehlhaar, *Archiv. Pharm.*, **274**, 385 (1936).

and refluxing were continued for 1 hr. The mixture was filtered while hot and the residue was washed with hot alcohol. The alcohol was removed under reduced pressure and the product, ethyl α-formamido-α-carbethoxy-β-2-methylphenylpropionate, was recrystallized from acetone-water, yield 68%, m.p. 92–94°.

Anal. Calcd. for $C_{16}H_{21}NO_5$: C, 62.54; H, 6.84; N, 4.56. Found: C, 62.60; H, 7.03; N, 4.67.

This product was reduced to compound VI with lithium aluminum hydride by the procedure used for making compound IV.

The corresponding sulfite was prepared as described for compound IV. The yield was 65%, m.p. 164–165°.

Anal. Calcd. for $C_{12}H_{18}ClNO_3S$: C, 49.39; H, 6.17; Cl, 12.17; N, 4.80; S, 10.97. Found: C, 49.30; H, 6.15; Cl, 12.40; N, 4.79; S, 10.89.

The corresponding dinicotinate, prepared by the method described for compound IV, melted at 193–194°, yield 38%.

Anal. Calcd. for $C_{24}H_{26}ClN_3O_4$: C, 63.22; H, 5.71; Cl, 7.79; N, 9.22. Found: C, 63.01; H, 6.05; Cl, 7.6; N, 8.92.

N-Methyl-1,1-di(hydroxymethyl)-2-(3-methylphenyl)ethylamine hydrochloride, VII. Ethyl α-formamido-α-carbethoxy-β-3-methylphenylpropionate was prepared by the procedure used for making α-formamido-α-carbethoxy-β-phenylpropionate except that *m*-methylbenzyl chloride was used in place of benzyl chloride. The yield was 84%, m.p. 94–96°.

Anal. Calcd. for $C_{16}H_{21}NO_5$: C, 62.54; H, 6.84; N, 4.56. Found: C, 62.50; H, 6.81; N, 4.76.

Ethyl α-formamido-α-carbethoxy-β-3-methylphenylpropionate was reduced with lithium aluminum hydride to compound VII.

The dinicotinate of VII was prepared in 38% yield, m.p. 185–186°.

Anal. Calcd. for $C_{24}H_{26}ClN_3O_4$: C, 63.22; H, 5.71; Cl, 7.79; N, 9.22. Found: C, 63.20; H, 5.88; Cl, 7.72; N, 9.37.

The sulfite of VII was prepared in 65% yield, m.p. 148–149°.

Anal. Calcd. for $C_{12}H_{18}ClNO_3S$: C, 49.39; H, 6.17; Cl, 12.17; N, 4.80; S, 10.97. Found: C, 49.26; H, 6.42; Cl, 12.20; N, 5.13; S, 10.75.

N-Methyl-1,1-di(hydroxymethyl)-2-(4-methylphenyl)ethylamine hydrochloride, VIII. Ethyl α-formamido-α-carbethoxy-β-4-methylphenylpropionate was prepared by the method used for making ethyl α-formamido-α-carbethoxy-β-phenylpropionate except that *p*-methylbenzyl chloride was used in place of benzyl chloride. The yield was 93%, m.p. 135–136°.

Anal. Calcd. for $C_{16}H_{21}NO_5$: C, 62.54; H, 6.84; N, 4.56. Found: C, 62.63; H, 7.26; N, 4.79.

Ethyl α-formamido-α-carbethoxy-β-4-methylphenylpropionate was reduced with lithium aluminum hydride to compound VIII.

The sulfite of VIII was prepared in 65% yield, m.p. 156–157°.

Anal. Calcd. for $C_{12}H_{18}ClNO_3S$: C, 49.39; H, 6.17; Cl, 12.17; N, 4.80; S, 10.97. Found: C, 49.68; H, 6.45; Cl, 12.15; N, 4.96; S, 10.81.

N-Ethyl-1,1-di(hydroxymethyl)-2-phenylethylamine hydrochloride, IX. Ethyl acetamidomalonate was the starting material for this preparation. Otherwise the procedure was similar to that used for making compound IV.

N-Methyl-1,1-di(hydroxymethyl)-2-(4-methoxyphenyl)ethylamine hydrochloride, X. Ethyl α-formamido-α-carbethoxy-β-4-methoxyphenylpropionate[4] was reduced with lithium aluminum hydride to compound X.

The dinicotinate of X melted at 172–173°, yield 33%.

Anal. Calcd. for $C_{24}H_{26}ClN_3O_5$: C, 61.08; H, 5.51; Cl, 7.52; N, 8.90. Found: C, 61.13; H, 5.56; Cl, 7.6; N, 8.95.

The corresponding sulfite melted at 167–168°, yield 73%.

Anal. Calcd. for $C_{12}H_{18}ClNO_4S$: C, 46.82; H, 5.85; Cl, 11.54; N, 4.55; S, 10.40. Found: C, 46.93; H, 5.82; Cl, 11.45; N, 4.68; S, 10.55.

N-Methyl-1,1-di(hydroxymethyl)-2-(4-hydroxyphenyl)ethylamine hydrochloride, XI. One gram of compound X was refluxed in 2 ml. of 48% hydrobromic acid and 5 ml. of acetic acid for 20 min. On diluting with 20 ml. of water a dark gummy material separated. The gum was washed with dilute sodium hydroxide solution and then with water. The residue was dissolved in ether, the solution dried and treated with dry hydrogen chloride. The hydrochloride, which was quite hygroscopic, was recrystallized from propanol and dry ether.

Department of Chemistry
University of Pennsylvania
Philadelphia 4, Pa.

Synthesis of *N*-(2-Hydroxyethyl)-*N'*-(4-pentenyl)ethylenediamine

E. F. Cluff and H. F. McShane, Jr.

Received March 24, 1960

As an intermediate for the preparation of a certain polyurethane elastomer[1] the substituted ethylenediamine (I) was required in a state of high purity. Diamine syntheses involving alkylation reactions usually give mixtures which contain difficultly separable tertiary amine isomers. The latter materials act as chain terminating agents in polycondensation reactions and prevent the attainment of high molecular weight. Consequently the synthetic route shown in the flowsheet was chosen to provide a diamine of unequivocal structure.

Aminolysis of dimethyl oxalate (II) with *N*-(2-hydroxyethyl)ethylenediamine (III) provided crystalline *N*-(2-hydroxyethyl)piperazine-2,3-dione (IV) in 20–35% yield. This reaction has been shown to be general for many *N*-substituted ethylenediamines.[2] The present reaction most likely proceeds through the formation and subsequent breakdown of a linear polyamide. As the temperature was slowly raised to about 180°, an essentially quantitative yield of alcohol was obtained, and the reaction mass became increasingly more viscous. At this point, the product was insoluble in alcohol and no piperazinedione (IV) could be isolated. Increasing the temperature above 180° to about 220° produced a marked viscosity reduction in the reaction mass which was then alcohol soluble and deposited crystals of IV.

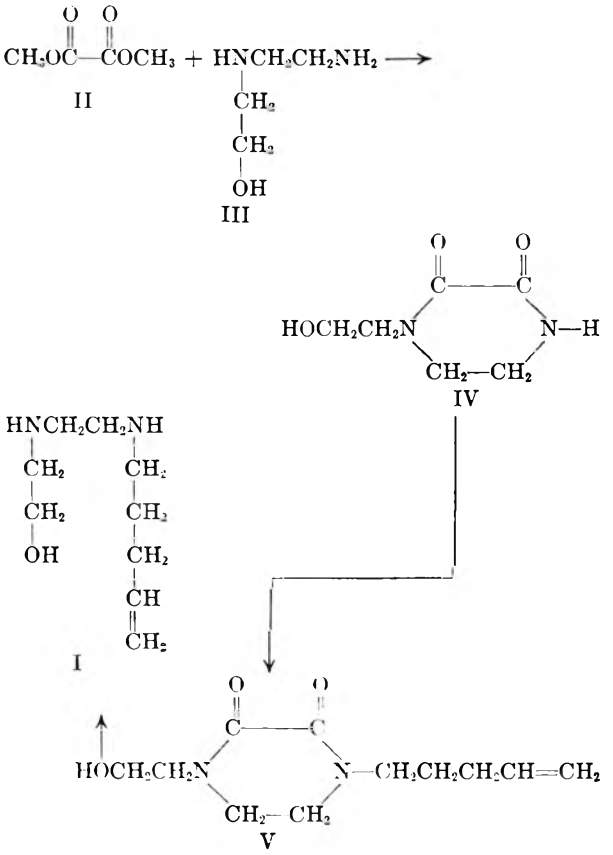
Conversion of IV to the monopotassium salt proceeded smoothly in refluxing *t*-butyl alcohol. The salt was not isolated but was alkylated directly with 1-bromo-4-pentene to provide the crystalline disubstituted piperazinedione (V) in 70% yield. Hydrolysis of V with aqueous-alcoholic potassium hydroxide provided an excellent yield of *N*-(2-hydroxyethyl) - *N'* - (4 - pentenyl)ethylenediamine (I). That alkylation of the piperazinedione (IV) had occurred on nitrogen and not on hydroxyl

(1) E. F. Cluff and E. K. Gladding, Proceedings International Rubber Conf., Washington, D. C., 1959, p. 543.

(2) J. L. Riebsomer, *J. Org. Chem.*, 15, 68 (1950).

was established by analysis of the diamine (I) for primary amino nitrogen which was absent. The purity of the diamine (I) was ultimately established by its polymerization with polytetramethylene-ether glycol bischloroformate to form a high molecular weight polyurethane.[1]

This sequence of reactions should provide a general route for the preparation of unsymmetrically *N,N'*-disubstituted ethylenediamines of high purity.



EXPERIMENTAL

N-(2-Hydroxyethyl)piperazine-2,3-dione (IV). A mixture of 343 g. (3.30 moles) of aminoethylethanolamine (III) and 5 ml. of concd. hydrochloric acid was added to 389 g. (3.30 moles) of dimethyl oxalate (II) over a period of 15 min. with good agitation. The temperature was raised gradually to 218° in about 1 hr., during which time 206 g. (6.44 moles, 97.6%) of methanol distilled from the reaction mixture. The reactants gradually formed a viscous polymer which broke down above 180° to form the piperazinedione (IV) and a red noncrystalline material which was not further investigated. The mixture was cooled to room temperature, taken up in 400 ml. of ethanol, cooled, and filtered. The crude product (199 g., 38%) was recrystallized from alcohol until pure, m.p. 163–164°.

Anal. Calcd. for $C_6H_{10}N_2O_3$: C, 45.56; H, 6.37; N, 17.72. Found: C, 45.2, 45.5; H, 5.9, 6.1; N, 17.4, 17.6.

N-(2-Hydroxyethyl)-N'-(4-pentenyl)piperazine-2,3-dione (V). A 3-l., four-necked flask equipped with a stirrer, thermometer, and reflux condenser fitted with a calcium sulfate drying tube was flamed out and cooled while being flushed with dry nitrogen. Distilled *t*-butyl alcohol (1600 ml.) was added followed by 61.4 g. (1.57 moles) of potassium. The mixture was refluxed and agitated until the metal had completely reacted. *N*-(2-Hydroxyethyl)piperazine-2,3-dione (248 g., 1.57 moles) was added, and the agitated suspension was refluxed overnight. The temperature was lowered to 70°, 234 g. (1.57 moles) of 1-bromo-4-pentene[3] was added, and the mixture was again refluxed overnight. After cooling, the solid potassium bromide was filtered (160 g., 86%), and the *t*-butyl alcohol was distilled. The last traces of solvent were removed under reduced pressure. The viscous residue was extracted with benzene (one 500-ml. and three 250-ml. portions) and then with tetrahydrofuran (three 500-ml., eight 250-ml., and six 100-ml. portions). The tetrahydrofuran was distilled, and the residue placed in a 0° coldbox overnight to crystallize. The solid was recrystallized from tetrahydrofuran (wt. 127 g.). The filtrate was diluted with 2 l. of tetrahydrofuran and the supernatant liquid was decanted from the precipitated oil. The tetrahydrofuran solution was again concentrated, seeded, and cooled to yield another 56 g. of solid. Further concentration of the filtrate yielded an additional 8.5 g. of product, bringing the total yield to 191.5 g. (54%). The residue from the benzene extract, combined with the end tetrahydrofuran filtrate from the recrystallizations, was chromatographed on 200-mesh activated alumina with tetrahydrofuran and ethanol. This resulted in the recovery of an additional 56.5 g. (16%) of material. Recrystallization of the combined solids from tetrahydrofuran afforded pure *N*-(2-hydroxyethyl)-*N'*-(4-pentenyl)piperazine-2,3-dione, m.p. 75–76.5°.

Anal. Calcd. for $C_{12}H_{18}N_2O_3$: C, 58.39; H, 8.02; N, 12.38. Found: C, 58.5, 58.5; H, 7.8, 7.9; N, 12.5, 12.7.

N-(2-Hydroxyethyl)-N'-(4-pentenyl)ethylenediamine (I). To a solution of 50 g. (0.770 mole) of 85% potassium hydroxide in 500 ml. of ethanol was added 0.1 g. of 2,6-di-*t*-butyl-*p*-cresol, a solution of 0.1 g. of sodium sulfite in 25 ml. of distilled water, and 83 g (0.376 mole) of *N*-(2-hydroxyethyl)-*N'*-(4-pentenyl)piperazine-2,3-dione (V). The clear solution was refluxed overnight under an atmosphere of nitrogen. A precipitate began forming after about 15 min. The mixture was cooled, the solid potassium oxalate monohydrate was filtered (65.5 g., 96.8%), and the solvent was distilled from the filtrate. Vacuum distillation of the residue yielded hydroxyethylpentenylethylenediamine (57.6 g., 91.5% yield, b.p. 97.5° (0.15 mm.), n_D^{25} 1.4772).

Anal. Calcd. for $C_9H_{20}N_2O$: C, 62.75; H, 11.70; N, 16.27; primary amino N, absent. Found: C, 62.5, 62.8; H, 11.4, 11.5; N, 16.1, 16.1; primary amino N, absent.

A drop of amine added to aqueous oxalic acid yielded the bisoxalate, m.p. 236–237°.

Anal. Calcd. for $C_{13}H_{24}N_2O_9$: C, 44.31; H, 6.87; N, 7.95. Found: C, 44.0, 44.2; H, 6.8, 6.9; N, 7.8, 7.8.

The amine forms a solid hemihydrate, m.p. 41.5–42°, on admixture with 0.5 mole equivalent of water.

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WILMINGTON, DEL.

(3) Prepared according to the method of P. Gaubert, R. P. Linstead, and H. N. Rydon, *J. Chem. Soc.*, 1971 (1937) and E. M. Van Heyningen, *J. Chem. Soc.*, 76, 2241 (1954), b.p. 124° (760 mm.), n_D^{25} 1.4615 (reported b.p. 124.5–128°, n_D^{25} 1.4642).

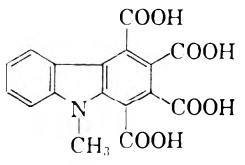
Decarboxylation of *N*-Methylaminoaromatic *ortho*-Carboxylic Acids

WAYLAND E. NOLAND AND GEORGE J. MEISTERS[1]

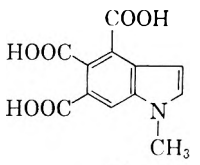
Received April 7, 1960

Dry distillation with soda-lime has been shown previously to produce *N*-demethylation (and con-

comitant decarboxylation to carbazole) of the salt of 9-methylcarbazole-1,2,3,4-tetracarboxylic acid (I).[2] No *N*-demethylation occurred under similar conditions, however, with 9-methylcarbazole[2] or with the salt of a triacid believed to be 1-methylindole-4,5,6-tricarboxylic acid (II).[3] The possibility that



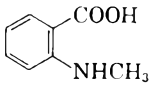
I



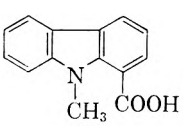
II

N-demethylation of I is occurring by neighboring group participation of the *ortho* carboxylate anion led us to test the generality of *N*-demethylation accompanying decarboxylation by use of selected *N*-methylaminoaromatic *ortho* carboxylic acids.

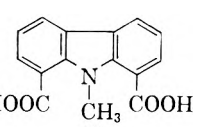
N-Methylanthranilic acid (III),[4] upon decarboxylation with soda-lime,[2] gave a liquid amine, which was isolated in 34% yield as the acetyl derivative, shown to be identical by mixed melting point and infrared comparison in Nujol with an authentic sample of *N*-methylacetanilide. 9-Methylcarbazole-1-carboxylic acid (IV)[5] and 9-methylcarbazole-1,8-dicarboxylic acid (V)[5] were similarly decarboxylated to 9-methylcarbazole in yields of 58% and 50%, respectively.



III

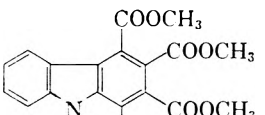


IV



V

These results show that *N*-demethylation accompanying decarboxylation of *N*-methylaminoaromatic *ortho* carboxylic acid salts is not a general phenomenon; that the presence of one or two *ortho* carboxylate groups is, in itself, insufficient cause for *N*-demethylation. It is concluded that, in the case in which it occurs (I), *N*-demethylation is favored by unusual stabilization of the resulting anion, attributable to the combined resonance and inductive effects of the four carboxylate substituent groups. In this connection, it is perhaps of interest to note that our efforts to *N*-methylate the sodium salt of the ester (VI)[2] of the corresponding unsubstituted



VI

compound have been unsuccessful. The results cited in this paper provide no evidence either for or against neighboring group participation by the *ortho* carboxylate group in *N*-demethylation in the case in which it occurs.[2]

Because of its importance to the conclusions drawn in this work, it appeared desirable to establish rigorously the position of the carboxyl group in 9-methylcarbazole-1-carboxylic acid (IV), prepared by action of *n*-butyllithium on 9-methylcarbazole, followed by reaction with carbon dioxide.[5] The structure had been logically assigned previously by analogy with numerous examples of *ortho* lithiation of aromatic amines[5] and with the fact that 9-ethylcarbazole-1-carboxylic acid, prepared similarly, had been shown to be identical with a sample prepared by ethylation of carbazole-1-carboxylic acid.[6]

Carbazole-1-carboxylic acid, most readily prepared from carbazole by reaction of its potassium salt[7] with carbon dioxide at 270°,[8] has been prepared unambiguously by two different methods,[9,10] and the product in the first case has been shown to be identical with a sample prepared from carbazole. After unsuccessful methylation attempts with dimethyl sulfate or methyl iodide in the presence of alkali,[11] we obtained 9-methylcarbazole-1-carboxylic acid (IV) in 11% yield from carbazole-1-carboxylic acid[8] by the action of sodamide and methyl iodide in liquid ammonia.[12] The sample was shown to be identical by mixed melting point (188.5–190°) and infrared comparison in Nujol with a sample[5] prepared from 9-methylcarbazole, thus constituting a proof of structure for 9-methylcarbazole-1-carboxylic acid (IV).

EXPERIMENTAL

Melting points were determined on a calibrated Kofler micro hot stage.

Decarboxylation of N-methylanthranilic acid (III). *N*-Methylanthranilic acid[4] (3.00 g., 0.0198 mole) was mixed thoroughly with powdered soda-lime (9 g.) and the mixture pyrolyzed under a stream of nitrogen with the aid of a Meker burner, in the manner previously described.[2] The liquid distillate was refluxed with acetic anhydride[13] for 30

(1) Graduate School research assistant, summer 1959. It is a pleasure to acknowledge the support of this work through a grant from the General Research Fund of the Graduate School of the University of Minnesota.

(2) W. E. Noland, W. C. Kuryla, and R. F. Lange, *J. Am. Chem. Soc.*, **81**, 6010 (1959).

(3) O. Diels, K. Alder, and H. Winckler, *Ann.*, **490**, 267 (1931).

(4) J. Houben and W. Brassert, *Ber.*, **39**, 3233 (1906). We are indebted to James A. Elberling[1] for this preparation.

(5) H. Gilman and S. M. Spatz, *J. Org. Chem.*, **17**, 860 (1952).

(6) H. Gilman and R. H. Kirby, *J. Org. Chem.*, **1**, 146 (1936).

(7) C. Graebe, *Ann.*, **202**, 19 (1880).

(8) G. L. Ciamician and P. Silber, *Gazz. chim. ital.*, **12**, 272 (1882); *J. Chem. Soc. Abstracts*, **42**, 1103 (1882).

(9) E. F. Briscoe and S. G. P. Plant, *J. Chem. Soc.*, 1990 (1928); W. M. Collar and S. G. P. Plant, *J. Chem. Soc.*, 808 (1926).

(10) P. Baumgarten and M. Riedel, *Ber.*, **75**, 984 (1942).

(11) T. S. Stevens and S. H. Tucker, *J. Chem. Soc.*, **123**, 2140 (1923).

(12) K. T. Potts and J. E. Saxton, *J. Chem. Soc.*, 2641 (1954).

(13) S. M. McElvain, *The Characterization of Organic Compounds*, rev. ed., The Macmillan Co., New York, N. Y., 1953, p. 210.

min., yielding a colorless precipitate (1.01 g., 0.0068 mole, 34%), m.p. 97–98.5°. After recrystallization from ether the sample melted at 99.5–100.5°, mixed m.p. 100.5–101.5° with a sample of *N*-methylacetanilide prepared[13] from Eastman Kodak Co. White Label *N*-methylaniline. The infrared spectra of the two samples in Nujol were identical. ν_{NH} none; $\nu_{C=O}$ 1672 cm.$^{-1}$ in Nujol.

Decarboxylation of 9-methylcarbazole-1-carboxylic acid (IV), 9-Methylcarbazole-1-carboxylic acid[5] (0.50 g., 0.00221 mole) was mixed thoroughly with powdered soda-lime (2.5 g.) and the mixture decarboxylated as described previously. The white sublimate (0.23 g., 0.00127 mole, 58%), m.p. 87.5–89.0°, did not depress the melting point of authentic 9-methylcarbazole,[5] and the infrared spectra in Nujol were identical. ν_{NH} none.

Decarboxylation of 9-methylcarbazole-1,3-dicarboxylic acid (V). 9-Methylcarbazole-1,8-dicarboxylic acid[5] (0.50 g., 0.00186 mole) was decarboxylated as described previously. The white sublimate (0.17 g., 0.00094 mole, 50%), m.p. 84–86°, did not depress the melting point of authentic 9-methylcarbazole[5] (it is interesting to note, however, that the mixed melting point of equal quantities of carbazole and 9-methylcarbazole is 83–87°) and the infrared spectra in Nujol were essentially identical, except for the presence of a medium weak NH or OH band at 3500 cm.$^{-1}$, suggesting contamination by a small amount of carbazole, the *N*-demethylation product.

SCHOOL OF CHEMISTRY
UNIVERSITY OF MINNESOTA
MINNEAPOLIS 14, MINN.

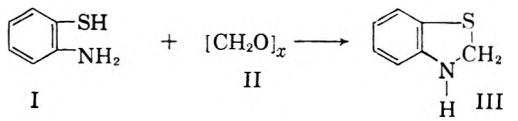
A New Synthesis of Benzothiazoline

GLENN L. JENKINS, ADELBERT M. KNEVEL, AND CHARLES S. DAVIS

Received April 25, 1960

Although a number of syntheses for benzothiazoline have been reported in the literature,[1–4] none offers the convenience of the method which we report here.

We found that benzothiazoline (III) was formed in good yields by refluxing 2-aminobenzenethiol (I) with paraformaldehyde (II) followed by distillation under reduced pressure.



I II III

EXPERIMENTAL

To 12.5 g. (0.1 mole) of 2-aminobenzenethiol (American Cyanamid, tech. grade) dissolved in 20 ml. of anhydrous methyl alcohol was added a mixture of 4 g. of paraformaldehyde (Eastman Kodak, pract. grade) suspended in 10 ml. of anhydrous methyl alcohol. The mixture was refluxed until the original yellow color disappeared (about 12 hr.).

Upon cooling to room temperature, two distinct layers formed. The bottom layer was withdrawn and distilled. The fraction collected at 146–149°/18 mm. was identified as benzothiazoline. The yield was 75–80% based on 2-aminobenzenethiol.

Identification of the product was accomplished as follows: (a) The infrared spectrum showed an intense nitrogen-hydrogen stretching band at 3.0 μ. (b) The boiling point was identical with that reported,[1,5] in the literature (b.p. 270°). (c) The phenylisocyanate derivative melted at 161–162°. The literature[5] value was 162°.

Acknowledgment. The authors are grateful to the American Cyanamid Co. for graciously supplying 2-aminobenzenethiol.

RESEARCH LABORATORIES
SCHOOL OF PHARMACY
PURDUE UNIVERSITY
LAFAYETTE, IND.

(1) M. Claaz, *Ber.*, **45**, 1031 (1912); **49**, 1141 (1916).

(2) M. T. Bogert and A. Stull, *J. Am. Chem. Soc.*, **47**, 3078 (1925).

(3) H. P. Lankelma and P. X. Sharnoff, *J. Am. Chem. Soc.*, **53**, 2654 (1931).

(4) K. Baker, *Helv. Chim. Acta*, **33**, 2011 (1950).

(5) R. A. Henry and W. M. Dehn, *J. Am. Chem. Soc.*, **71**, 2297 (1949).

Schiff Bases from 4-(4-Aminostyryl)quinoline and Aldose Sugars[1]

CARL TABB BAHNER, NORVELL HUNT, AND LYDIA M. RIVES

Received May 2, 1960

4-(4-Aminostyryl)quinoline (I) reacted readily with 4-dimethylaminobenzaldehyde to form a Schiff base that was less toxic than I.[2] It seemed that aldose sugars might produce similar products and that the sugar moiety might cause the compounds to be water soluble. The use of a small amount of dimethylformamide made it possible to bring the reactants into a homogeneous liquid reaction mixture at the desired temperature, 120–130°. Glyceraldehyde, ribose, galactose(II), glucose(III), lactose, and maltose all seemed to react smoothly under these conditions, but only II formed crystals that were purified readily by recrystallization. The other products tended to precipitate as gels or amorphous solids.

EXPERIMENTAL

Galactose Schiff base of 4-(4-aminostyryl)quinoline. A mixture of 30.0 g. of I and 15.0 ml. of dimethylformamide was heated to 130° to produce a clear solution. This solution was cooled to 110°, 21.6 g. of II was added slowly with stirring, and the mixture was heated 10 min. at 120–130°. The resulting solid mass was washed with benzene and with water to remove excess starting materials. One gram of solid was dissolved in 30 ml. of dimethylformamide, 20 ml. of the solvent was removed by distillation at 60° at 2.5 mm. The bright yellow crystals which formed were recrystallized

(1) This research was supported by a grant from the National Cancer Institute.

(2) Carl T. Bahner, Clarence Cook, John Dale, John Fain, Fred Hannan, Patricia Smith, and Joan Wilson, *J. Org. Chem.*, **23**, 1060 (1958).

four times in this way, darkening at 209°, melting with decomposition at 216–217°; yield 60%.

Anal. Calcd. for $C_{23}H_{22}N_2O_5$: C, 67.71; H 5.92. Found: C, 67.48–67.75; H, 5.85, 6.06.[3]

Dextrose Schiff base of 4-(4-aminostyryl)quinoline. To a solution formed by heating 9.8 g. of I and 5 ml. of dimethylformamide to 130°, 13.8 g. of III was added slowly, with stirring, at 110°. The mixture was then heated to 120–130° for 30 min., until it solidified. The product was washed with benzene and with water and recrystallized four times from isopropyl alcohol, using a Soxhlet extractor, and three times from methanol; m.p. 189.7–191.7° (dec.).

Anal. Calcd. for $C_{23}H_{23}N_2O_6$: C 67.71; H, 5.92. Found: C, 67.48, 67.75; H, 5.85, 6.06.[3]

These compounds were not readily soluble in water but dissolved readily in hot propyleneglycol and in dimethylformamide.

CHEMISTRY DEPARTMENT
CARSON-NEWMAN COLLEGE
JEFFERSON CITY, TENN.

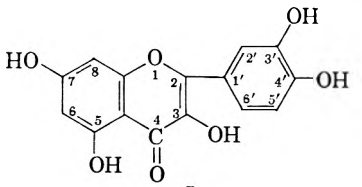
(3) Analyses by Galbraith Microanalytical Laboratories.

Methyl Ethers of Quercetin in Tobacco Flowers[1]

C. H. YANG, H. D. BRAYMER, E. L. MURPHY, W. CHORNEY, N. SCULLY, AND S. H. WENDER

Received February 26, 1960

Monomethyl and dimethyl ethers of quercetin (3,3′,4′,5,7-pentahydroxyflavone, I) having no methoxyl group at the 3-position, such as rhamnetin (quercetin-7-methyl ether), isorhamnetin (quercetin-3′-methyl ether), quercetin-4′-methyl ether, and rhamnazin (quercetin-3′,7-dimethyl ether) have been found previously in natural products, usually as glycosides. A 3,7,4′-trimethyl ether of quercetin, ayanin, has been isolated from the heartwood of the tree *Distemonanthus Benthamianus* by King, *et al.*[2] However, monomethyl and dimethyl ethers of quercetin that contain a methoxyl group at the 3-position have been obtained only by laboratory synthesis.[3–5] This note describes the isolation and identification of quercetin-3,3′-dimethyl ether from tobacco flowers. We have also found other related flavonol ethers in these flowers. One of these other compounds has been tentatively identified as quercetin-3-methyl ether.



I

EXPERIMENTAL

Separation of quercetin ethers. Samples each containing 100 g. of powdered, oven-dried flowers from tobacco plants, *Nicotiana tabacum*, one-sucker variety, grown in the greenhouse at Argonne National Laboratory during 1958, were extracted with 500 ml. of the following solvents in the order named: *n*-pentane, benzene, chloroform, ethyl acetate (anhydrous), and acetone. Each 500-ml. extract was concentrated *in vacuo* to 5 ml. and studied by paper chromatography. The flavonol ethers were mostly in the chloroform fraction, although at least two such compounds were present in small amounts in the ethyl acetate extract.

Each 5-ml. chloroform concentrate was streaked onto eight sheets of Whatman No. 3 MM chromatography paper (approx. 7″ × 22½″), and the chromatograms were developed by descending chromatography in 15% acetic acid–water for about 24 hr. The upper part of each chromatogram, containing the methylated flavonol compounds which moved only a relatively short distance in this solvent, was cut out and sewn onto a new sheet of S & S chromatography paper, No. 589, Red Ribbon. Each sheet was next developed in *n*-butyl alcohol–acetic acid–water (6:1:2 v./v.). After drying, the papers were viewed under long wave-length ultraviolet light (3660 Å). A dark brown zone was seen near the solvent front; it was poorly separated from some blue-fluorescing material. The broad, dark brown zone containing the mixture of methylated flavonols was cut from each chromatogram, eluted with methanol, and then subjected to further extended chromatography, first in 15% acetic acid for 36–48 hours, then on fresh sheets in 60% acetic acid–water. The latter effected separation of the quercetin dimethyl ether from a trace amount of another brown fluorescing substance which had the same mobility as authentic quercetin-3-methyl ether on chromatograms. The yield of this latter compound from the 1958 tobacco flowers was insufficient to confirm its identity. After elution of the brown fluorescing zone containing the quercetin dimethyl ether, the methanol eluates were subjected to further chromatography on S & S No. 589 paper, using four different solvent systems in the order: 15% acetic acid–water: ethyl acetate–formic acid–water (10:2:3 v./v., upper layer); *n*-butyl alcohol–acetic acid–water (6:1:2 v./v.); and finally 60% acetic acid–water. The quercetin dimethyl ether zone of each final chromatogram was then pure enough for identification studies.

Identification of quercetin-3,3′-dimethyl ether. On paper chromatograms, the quercetin dimethyl ether exhibited a dark brown fluorescence under ultraviolet light, but after the compound had been sprayed with a 1% solution of aluminum chloride in ethanol, it gave a yellow fluorescence. Flavone aglycones such as apigenin (4′,5,7-trihydroxyflavone); flavonol glycosides such as isoquercitrin (quercetin-3-glucoside); and certain 3-methyl ethers of flavonols, such as quercetin-3-methyl ether and quercetin-3,7-dimethyl ether exhibit this fluorescent behavior.

After the isolated tobacco quercetin dimethyl ether was refluxed with hydriodic acid, sp. gr. 1.7, for 4 hr., a product was obtained which proved to be quercetin. Identity was established by comparison of color tests, fluorescence, ultraviolet absorption spectra, and co-chromatography with authentic quercetin.

After the tobacco quercetin dimethyl ether was refluxed with dimethyl sulfate and sodium carbonate in acetone for 6 hr., the product showed a blue fluorescence under ultraviolet light and was identified as quercetin-3,3′,4′,5,7-pentamethyl ether by paper chromatographic comparison with an authentic sample. Thus, the unknown was definitely a methyl ether

(1) This work was performed in part under the auspices of the U. S. Atomic Energy Commission.

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of quercetin with at least one methoxy group at the 3-position.

An attempt was made to hydrolyze the quercetin dimethyl ether isolated from tobacco flowers by heating it in 7% sulfuric acid solution for 12 hr. on a steam bath. No sugar was found on paper chromatograms of the reaction mixture, nor was there any significant change observed in the unknown compound, although a trace of some nonflavonol material could be located on the chromatogram by observing the chromatogram under ultraviolet light. These tests indicated that the unknown compound was not a flavone nor a glycoside of quercetin.

When an ethanol solution of the tobacco quercetin dimethyl ether was shaken with sodium amalgam, and then acidified with hydrochloric acid, a salmon pink color was obtained. Thus, substitution of the 3-position of the quercetin was again indicated.[6]

Mixtures of quercetin-3-methyl ether and quercetin-3,7-dimethyl ether, which were synthesized and purified in our laboratory as described in later paragraphs, could be readily separated by paper chromatography, using the solvent system nitromethane-benzene-water (2:3:5 v./v., upper layer), with R_f values of 0.13 and 0.85, respectively. The naturally occurring compound had a R_f value of 0.83 in this solvent system, thus indicating the likelihood of its being a dimethyl, and not a monomethyl quercetin 3-methyl ether.

The fluorescence was quenched by the addition of acetic anhydride to the solid compound,[3] indicating a free 5-hydroxy group on the quercetin. The reaction of the isolated compound with alcoholic ferric chloride solution, and its behavior during methylation, likewise indicated a free phenolic group at the 5-position.

Addition of anhydrous sodium acetate to the solution of the tobacco quercetin dimethyl ether, by the method of Jurd and Horowitz,[7] caused a shift in the short wave-length band of its ultraviolet absorption spectrum from 254 to 275 mμ. This indicates that the 7-hydroxy position of the tobacco quercetin dimethyl ether is open.

The long wave-length band of the ultraviolet absorption spectrum of the tobacco unknown did not shift in absolute ethanol saturated with boric acid and anhydrous sodium acetate, by the spectral method of Jurd.[8] Thus, at least one hydroxyl of the *o*-dihydroxy group (3′,4′) of quercetin was blocked in the tobacco unknown in question.

Degradation of the isolated tobacco quercetin dimethyl ether was carried out by dissolving 1 mg. of the unknown in 30 ml. of a 2*N* solution of sodium hydroxide in a mixture of 50% ethanol and 50% water, and evaporating the solution to dryness in an oven at 120°. The residue was dissolved in water, acidified with hydrochloric acid to a *p*H of 2, and extracted four times with 20-ml. portions of ether. The ether solution was concentrated to 1 ml. and studied by paper chromatography. The acid obtained after degradation proved to be vanillic acid (4-hydroxy-3-methoxybenzoic acid) by the identification procedure of Hergert and Goldschmid.[9] Thus, the 4′-position of the tobacco quercetin dimethyl ether has a free phenolic group, whereas the 3′-position has a methoxy group on it. The structure of the isolated tobacco compound is, therefore, quercetin-3,3′-dimethyl ether.

Studies on both tobacco leaves and flowers obtained from a 1955 field-grown crop at Argonne indicated the presence in each of a quercetin dimethyl ether (which may have been quercetin-3,3′-dimethyl ether instead of the reported quercetin-3,7-dimethyl ether), plus a compound giving color tests similar to and co-chromatographing with authentic quercetin-3-methyl ether.[10] A third compound appeared to be kaempferol-3-methyl ether by preliminary tests. Kaempferol is 3,4′,5,7-tetrahydroxyflavone. The spectral tests of Jurd and Horowitz[7] and of Jurd[8] were not run on these 1955 samples, and their identifications were only tentative. On the 1958 greenhouse-grown tobacco flowers, the quercetin-3,3′-dimethyl ether was present in relatively larger amount, but the compounds which might have been flavonol monomethyl ethers were not present in sufficient amount to undertake the studies needed for unequivocal confirmation of their structures.

Preparation of pure quercetin-3-methyl ether and quercetin-3,7-dimethyl ether. Both of these compounds were synthesized by the method reported by Jain and co-workers[4] for quercetin-3,7-dimethyl ether. On paper chromatographic examination, the resulting methylated quercetin precipitate appeared to be a complicated mixture containing five or more different derivatives of quercetin. Using methanol as the suspending medium, the precipitate was adsorbed onto Magnesol (Food Machinery and Chemical Corp., New York). The column was developed with a solvent system containing two parts of water-saturated ethyl acetate and one part nitromethane. Brown-fluorescing material, with some traces of blue-fluorescing impurities, moved rapidly off the column, leaving the major portion of the blue-fluorescing substances on the column. The eluates containing the brown-fluorescing mixture were then further purified by extended paper chromatography, using in order the solvent systems 60% acetic acid–water, 15% acetic acid–water, and nitromethane–benzene–water (2:3:5 v./v. upper layer) for purification of the quercetin-3-methyl ether. For obtaining pure quercetin-3,7-dimethyl ether, the 60% acetic acid–water, nitromethane-benzene–water, and finally 60% acetic acid–water systems were used. R_f values in the 15% acetic acid and 60% acetic acid systems were respectively: quercetin-3-methyl ether, 0.17 and 0.63 and quercetin-3,7-dimethyl ether, 0.19 and 0.72. Each of these compounds was eluted from its final chromatogram with 50% methanol–water. The purified quercetin-3-methyl ether checked in every respect (fluorescence, R_f values, color tests, and spectral studies) with authentic quercetin-3-methyl ether kindly furnished by Dr. R. M. Horowitz, USDA Fruit and Vegetable Laboratory, Pasadena, Calif. The identity of the purified, synthetic quercetin-3,7-dimethyl quercetin was checked by procedures similar to those described above for the determination of the structure of the tobacco quercetin-3,3′-dimethyl ether isolated from tobacco.

CHEMISTRY DEPARTMENT
UNIVERSITY OF OKLAHOMA
NORMAN, OKLA.
AND
DIVISION OF BIOLOGICAL AND MEDICAL RESEARCH
ARGONNE NATIONAL LABORATORY
ARGONNE, ILL.

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Fluoro Analogs of Prostigmine

SEYMOUR L. SHAPIRO, THEODORE BAZGA, AND LOUIS FREEDMAN

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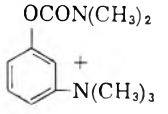
The useful physiological properties of prostigmine,[1] I, and its analogs suggested exploration of

(1) A. Stempel and J. A. Aeschlimann, *Medicinal Chemistry*, Vol. III, John Wiley & Sons, New York, N. Y., 1956. p. 239 (see pp. 270–274).

trifluoromethylphenyl carbamates, and related compounds, II.



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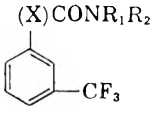


II

X = O, NH
R_1R_2 = H, alkyl, aryl

In particular, employment of a strongly *meta* orienting trifluoromethyl group[2] evaluated replacement of the electronically similar trimethylammonium group[3,4] of I. The steric effects of the trifluoromethyl group[5] and its incorporation into biologically active agents[6] have been recently described. The *meta* relationship of the oxy function in II was indicated on pharmacological[7] and chemical[2,8–12] bases.

The compounds were conveniently prepared by reaction of the appropriate isocyanate ester with *m*-trifluoromethylphenol or *m*-trifluoromethylaniline and are described in Table I.

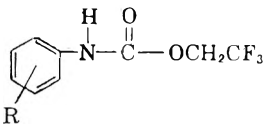
TABLE I

m-TRIFLUOROMETHYLPHENYL CARBAMATES AND UREAS, II

No.	R_1[a]	M.P.[b,c]	Formula	Nitrogen,[d] % Calcd.	Found
		X = —O—			
1	CH_3—[e]	[f]	$C_{10}H_{10}F_3NO_2$	[g]	
2	C_2H_5—	52–53	$C_{10}H_{10}F_3NO_2$	6.0	6.1
3	*n*-C_4H_9—	43–44	$C_{12}H_{14}F_3NO_2$	5.4	5.0
4[h]	C_6H_5—	142[c1]	$C_{14}H_{10}F_3NO_2$	5.0	5.0
5	*p*-$C_2H_5OC_6H_4$—	137–138	$C_{16}H_{14}F_3NO_3$	4.3	4.7
		X = —NH—			
6	C_2H_5—	119–120[c2]	$C_{10}H_{11}F_3N_2O$	12.1	12.0
7	C_4H_9—	[i]	$C_{12}H_{15}F_3N_2O$	10.8	10.5
8	$C_2H_5OOCH_2$—	112–114	$C_{12}H_{13}F_3N_2O_3$	9.7	9.8

[a] R_2 is hydrogen unless otherwise indicated. [b] Melting points are not corrected (capillary). [c] Recrystallizing solvent is hexane unless otherwise shown; [c1]ethanol;[c2]acetonitrile. [d] Analyses by Weiler and Strauss, Oxford, England. [e] R_2 is methyl. [f] B.p. 84–86° (0.2 mm.). [g] *Anal.* Calcd. C, 51.5; H, 4.3. Found: C, 51.7; H, 4.2. [h] Reported by M. T. Leffler and E. J. Matson, *J. Am. Chem. Soc.*, **70**, 3439 (1948), m.p. 138–140°. [i] B.p. 184–192° (2 mm.).

On testing[13] compound 1, the trifluoromethyl analog of I, gave complete ganglionic block at 5 mg./kg., although it was without anticholinesterase activity.[1] Other noted effects were tranquilizing activity with compound 2, anti-tremorine effects with compound 3, and anti-inflammatory activity with compounds 6–8. Compound 6 showed anesthetic activity somewhat better than procaine. The noted tranquilizing activity of compound 2 suggested examination of β,β,β-trifluoroethylcarbanilate analogs, III,[14] which proved to be inactive.



III

R = *p*-CH_3O— (m.p. 81–83°)
R = *p*-Cl— (m.p. 70–71°)

EXPERIMENTAL[15]

N,N-Dimethyl-(m-trifluoromethyl)phenyl carbamate (Compound 1). To a stirred refluxing solution of 8.1 g. (0.05 mole) of *m*-trifluoromethylphenol in 30 ml. of benzene and 10 ml. of triethylamine there was added dropwise 6.0 g. (0.056 mole) of dimethylcarbamyl chloride over 75 min. Stirring and refluxing was continued for 3 hr. When cool, the formed triethylamine hydrochloride was separated and washed with benzene. The filtrate and the benzene washings were combined, the benzene was removed, and the residue distilled to give 8.36 g. (72%) of product, b.p. 84–86° (0.2 mm.).

N-Ethyl-(m-trifluoromethyl)phenyl carbamate (Compound 2). A mixture of 3.24 g. (0.02 mole) of *m*-trifluoromethylphenol, 1.36 g. (0.02 mole) of ethyl isocyanate, and 1 drop of pyridine was warmed under reflux in an oil bath maintained at 100° for 1 hr. When cool, the reaction mixture crystallized and upon trituration with cold hexane gave 2 g. (43%) of product.

Compounds 3–5 were similarly prepared.

N-Ethyl,N'-(m-trifluoromethyl)phenylurea (Compound 6). A mixture of 3.2 g. (0.02 mole) of *m*-aminobenzotrifluoride and 1.36 g. (0.02 mole) of ethyl isocyanate reacted at 20° and solidified. Upon trituration with hexane 2.8 g. (61%) of product was obtained.

Compounds 7 and 8 were similarly prepared.

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(15) Data shown in Table I are not reproduced. Representative examples are shown for the general procedures used.

Acknowledgment. The authors wish to thank Dr. G. Ungar and his staff for the pharmacological screening of the compounds, and Dr. I. Rose for the preparation of compound 1.

ORGANIC RESEARCH DIVISION
U. S. VITAMIN & PHARMACEUTICAL CORP.
YONKERS 1, N. Y.

Mescaline Analogs. X. 3,4-Dimethyl-, 3,4-Dichloro-, and 3,5-Dimethoxy-4-methyl-β-phenethylamines[1]

F. BENINGTON,[2] R. D. MORIN,[2] AND LELAND C. CLARK, JR.[3]

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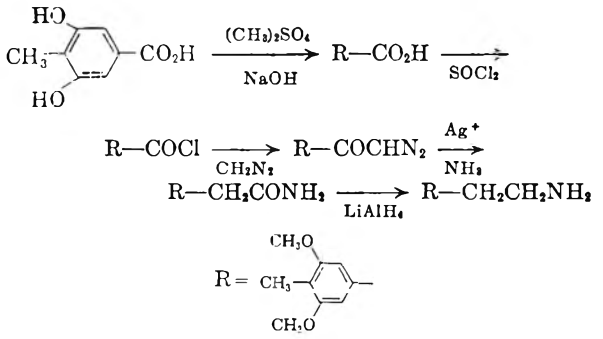
In a continuation of a long-range study of the influence of ring substituents on β-phenethylamines on psychopharmacological activity,[4] three new β-phenethylamines substituted in the 3-, 4-, or 5-positions of the ring were synthesized, and the effect of these compounds on normal cat behavior was examined. The sham rage response[5] induced by 3,4,5-trimethyl-, 4-methyl-, 4-chloro-, and 3,5-dimethyl-4-methoxy-β-phenethylamines[4] prompted investigation of other β-phenethylamines with these ring substituents.

The three new β-phenethylamines described in this communication, 3,4-dimethyl-, 3,4-dichloro-, and 3,5-dimethoxy-4-methyl-, all induced a strong rage response in cats. These findings confirmed previous observations that the substitution of methyl or chloro groups in the 3- and 4-positions of the β-phenethylamine molecule results in compounds which produce a rage syndrome in cats. Replacement of just the 4-methoxy group in mescaline (3,4,5-trimethoxy-β-phenethylamine) with methyl is sufficient to impart rage-producing properties to the compound, whereas mescaline itself does not induce rage.

3,4-Dimethyl-β-phenethylamine was synthesized from 3,4-dimethylbenzyl chloride by conversion to 3,4-dimethylphenylacetonitrile and reduction with lithium aluminum hydride. 3,4-Dichloro-β-phenethylamine was obtained in a similar manner.

3,5-Dimethoxy-4-methyl-β-phenethylamine was synthesized from 3,5-dihydroxy-*p*-toluic acid[6] by the following steps:



Details of the pyschopharmacological properties of these compounds will be published elsewhere.

EXPERIMENTAL[7]

3,4-Dimethylbenzyl chloride. A rapid stream of dry hydrogen chloride gas was passed into a stirred mixture of 106 g. of *o*-xylene, 84 g. of 35% aqueous formaldehyde solution, and 450 ml. of concd. hydrochloric acid kept at 65 ± 5° for 6 hr. The organic layer was separated, the aqueous layer extracted with ether, and the combined organic layer was washed thoroughly with water and aqueous sodium bicarbonate, dried over anhydrous magnesium sulfate, and distilled through a 12-in. Vigreux column. After removal of unchanged *o*-xylene and a small intermediate fraction, 3,4-dimethylbenzyl chloride was collected as the fraction boiling at 113–116°/22 mm.; yield, 98.4 g. (64%). The structure of this chloromethyl compound has been demonstrated.[8]

3,4-Dimethylphenylacetonitrile. To a stirred solution of 26 g. of sodium cyanide in 30 ml. of water was added a solution of 62 g. of 3,4-dimethylbenzyl chloride in 100 ml. of alcohol, and the resulting mixture was stirred and refluxed for 4 hr. The dark reaction mixture was filtered from inorganic salts, and most of the alcohol was removed from the filtrate by evaporation under reduced pressure. The residue was treated with water, and the crude oily product extracted with ether. The ether solution was washed three times with 50-ml. portions of 1:1 hydrochloric acid to remove foul-smelling isonitrile, then several times with water, and finally dried over anhydrous magnesium sulfate. After removal of ether, the residue was distilled under reduced pressure through a 12 in.-Vigreux column; b.p. 147–150°/22 mm.; yield, 44.6 g. (77%).

Anal. Calcd. for $C_{10}H_{11}N$: C, 82.7; H, 7.6. Found: C, 82.4; H, 7.5.

3,4-Dimethyl-β-phenylethylamine. To a stirred solution of 11.7 g. of lithium aluminum hydride in 250 ml. of dry absolute ether was added slowly a solution of 29 g. of 3,4-dimethylphenylacetonitrile at a rate which caused the ether to reflux. The mixture was then stirred and heated under reflux for 0.5 hr., cooled in an ice bath, and hydrolyzed by slow and cautious addition of water until decomposition of the reaction complex was complete. Inorganic matter was removed by filtration, the filtrate was dried (anhydrous magnesium sulfate), filtered again, and treated with alcoholic hydrogen chloride to precipitate the 3,4-dimethyl-β-phenethylamine as its hydrochloride salt; yield, 21 g. (57%); recrystallization from hot alcohol afforded colorless plates, m.p. 222–223°.

Anal. Calcd. for $C_{10}H_{15}ClN$: Cl, 19.1; N, 7.55. Found: Cl, 19.0; N, 7.47.

3,4-Dichlorophenylacetonitrile. A mixture of 100 g. of α,3,4-trichlorotoluene,[9] 130 ml. of ethanol, 33.4 g. of sodium cyanide, and 40 ml. of water was stirred and heated under

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(3) The University of Alabama Medical School.
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(7) Melting points are uncorrected.
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(9) From Eastman Organic Chemicals.

reflux for 3.5 hr. Most of the ethanol was distilled under reduced pressure, and the dark residue was added to 500 ml. of water. The crude nitrile was extracted with ether, washed with 1:1 hydrochloric acid and water, dried (anhydrous magnesium sulfate), ether removed, and distilled under reduced pressure; b.p. 115–130°/0.5 mm. (reported,[10] b.p. 170°/12 mm.); yield, 71.5 g. (76%). The distillate gradually solidified, and melted at 45–46° after recrystallization from petroleum ether.

Anal. Calcd. for $C_8H_5Cl_2N$: Cl, 38.2; N, 7.53. Found: Cl, 37.8; N, 7.34.

3,4-Dichloro-β-phenethylamine. To a stirred solution of 16.9 g. of lithium aluminum hydride in 300 ml. of dry absolute ether was added gradually a solution of 37.2 g. of 3,4-dichlorophenylacetonitrile in 100 ml. of dry ether. The reaction mixture was then refluxed for an additional hour, cooled, hydrolyzed cautiously with water, and filtered from inorganic matter. The dried ether solution was treated with dry hydrogen chloride to precipitate 3,4-dichloro-β-phenethylamine hydrochloride, which was recrystallized from methanol-ether; yield, 7.5 g. (17%); m.p. 178–179°.

Anal. Calcd. for $C_8H_{10}Cl_3N$: Cl, 47.0; N, 6.18. Found: Cl, 46.9; N, 6.14.

3,5-Dimethoxy-4-methylbenzoic acid. To a stirred solution of 40 g. of 3,5-dihydroxy-p-toluic acid in 57 g. of sodium hydroxide and 250 ml. of water were added three 33-ml. portions of methyl sulfate at such a rate that the temperature remained below 30° during addition of the first portion, at 30 to 35° during the second, and at 40 to 45° during the third.[11] The mixture was then boiled under reflux for 2 hr., treated with a solution of 20 g. of sodium hydroxide in 30 ml. of water, and boiled for an additional 2 hr. Acidification with dilute hydrochloric acid precipitated the crude product, which was purified by recrystallization from acetone; yield, 30.5 g. (65%); m.p. 216–217°; (reported[12] m.p., 213–214°).

ω-Diazo-3,5-dimethoxy-4-methylacetophenone. A mixture of 30 g. of 3,5-dimethoxy-4-methylbenzoic acid, 30 ml. of dry benzene, and 22 ml. of thionyl chloride was refluxed for 2 hr. After removal of benzene and excess thionyl chloride, the residue was distilled under reduced pressure to yield 21 g. (64%) of 3,5-dimethoxy-4-methylbenzoyl chloride, b.p. 107–110°/0.5 mm. A solution of this acid chloride was added to a cooled (ice bath) and stirred solution of 0.316 mole of diazomethane (generated from *N*-nitroso-*N*-methylurea and 45% potassium hydroxide and assayed against benzoic acid) in 680 ml. of dry ether. After stirring for 20 hr. at room temperature, the diazoketone had separated as a yellow solid. Collection of this solid and concentration of the filtrate by evaporation yielded a total of 19.6 g. (90%) of the pure diazoketone; m.p. 138–139° dec.

Anal. Calcd. for $C_{11}H_{12}N_2O_3$: C, 60.0; H, 5.5. Found: C, 59.7; H, 5.7.

3,5-Dimethoxy-4-methylphenylacetamide. To a mixture of 19 g. of ω-diazo-3,5-dimethoxy-4-methylacetophenone and 100 ml. of dioxane was added 200 ml. of concd. ammonium hydroxide and 20 ml. of 10% aqueous silver nitrate. The mixture was heated on a steam bath under a reflux condenser for 16 hr. when evolution of nitrogen, brisk at first, was complete. The hot reaction mixture was treated with Norite, filtered, and concentrated by evaporation whereupon the crude solid amide crystallized on cooling. Recrystallization of the crude product from alcohol-water yielded 10.5 g. (58%) of pure 3,5-dimethoxy-4-methylphenylacetamide, m.p. 166–167°.

Anal. Calcd. for $C_{11}H_{15}NO_3$: C, 63.2; H, 7.2. Found: C, 63.2; H, 7.4.

3,5-Dimethoxy-4-methyl-β-phenethylamine. To a stirred solution of 6.8 g. of lithium aluminum hydride in 200 ml. of dry absolute ether was added a slurry of 10 g. of 3,5-dimethoxy-4-methylphenylacetamide in 125 ml. of hot dry reagent benzene, using part of the benzene to rinse in the last of the amide. The resulting mixture was stirred and refluxed for 1 hr., cooled in an ice bath, and hydrolyzed by slow and cautious addition of water. The ether solution of the amine obtained after filtration from inorganic matter and drying (anhydrous magnesium sulfate) was treated with dry hydrogen chloride to precipitate the product as its hydrochloride salt; yield, 8.9 g. (80%); m.p. 233–235°. Recrystallization from ethanol–ethyl acetate raised the melting point to 244–245°.

Anal. Calcd. for $C_{11}H_{18}ClNO_2$: C, 57.0; H, 7.8; Cl, 15.3. Found: C, 56.2; H, 8.0; Cl, 15.2.

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COLUMBUS 1, OHIO

THE UNIVERSITY OF ALABAMA MEDICAL SCHOOL
BIRMINGHAM 3, ALA.

(10) C. E. Kwartler and P. Lucas, *J. Am. Chem. Soc.*, **68**, 2395 (1946) reported this compound as an oil rather than the crystalline solid which we obtained.

(11) See F. Mauthner, *Org. Syntheses*, Coll. Vol. I, 537 (1943) for methylation of gallic acid.

(12) K. Yamaguchi, *J. Chem. Pharm. Soc. (Japan)*, **62**, 491 (1952).

Nobiletin from the Peel of the Valencia Orange (*Citrus sinensis* L.)[1]

LYLE JAMES SWIFT

Received March 28, 1960

During an investigation of the constituents of orange peel, a substance was isolated which was identified as nobiletin by physical and chemical properties, elemental analysis, and degradation products.

Nobiletin was first isolated by Tseng[2] from the Chinese drug chen-pi which, in turn, was made from the peel of a variety of mandarin (*Citrus nobilis*, Lour.). In the original work the isolation was made by a rather tedious process from a cold methanolic extract of the drug but in the present study the juice of fresh orange peel was utilized.

The structural formula for nobiletin was partly elucidated by Tseng[2] and Robinson and Tseng,[3] who isolated veratric acid and acetoveratrone (as the oxime) from the alkaline hydrolysis mixture. On the basis of this and other evidence, Robinson and Tseng came to the conclusion that nobiletin was 3′, 4′, 5, 6, 7, 8-hexamethoxyflavone. This view was supported later by syntheses carried out by Horii,[4] Sreerama Murti and Seshadri,[5]

(1) Presented before the Symposium on Chemistry of the Citrus Fruit Industry at the Miami meeting of the American Chemical Society, April, 1957.

(2) K. Tseng, *J. Chem. Soc.*, 1003 (1938).

(3) R. Robinson and K. Tseng, *J. Chem. Soc.*, 1004 (1938).

(4) Z. Horii, *J. Pharm. Soc. Japan*, **60**, 614, Abstracts 246 (1940); *Chem. Abstr.* **35**, 7964 (1941).

(5) V. V. Sreerama Murti and T. R. Seshadri, *Proc. Indian Acad. Sci.*, 27-A, 217 (1948).

and by Oliverio and Casinovi.[6] Thus there is no doubt about the proposed structural formula.

EXPERIMENTAL

Isolation of nobiletin. Orange peel juice was obtained from the peel oil centrifugals which were operated in connection with a frozen concentrate plant. Peel from the orange juice extractors passed directly through grooved rolls which expressed an emulsion of peel oil and the aqueous peel juice. After screening to remove peel fragments, the emulsion was fed directly to the centrifugals which separated part of the oil.

Juice so obtained was filtered in the laboratory with a diatomaceous filter aid on precoated Büchner funnels. The filtrate was extracted once with petroleum ether (b.p. 60–68°) to remove any remaining peel oil and adjusted to *p*H 8.0 with sodium hydroxide pellets. The alkaline mixture was then extracted batchwise with carbon tetrachloride, using two 50-ml. portions to each 1.5-l. portion of juice. The combined extracts were then concentrated *in vacuo* nearly to dryness and the residue was dissolved in hot methanol. After treatment with a small quantity of decolorizing carbon, the hot solution was filtered and allowed to crystallize. The precipitate was repeatedly recrystallized from methanol to a constant melting point of 137–138° cor. The yield was quite small, 4.7 g. nobiletin being obtained from about 250 l. of peel juice.

The ultraviolet spectrum was determined in 95% ethanol solution. The locations of the maxima and corresponding log ϵ values were as follows: 210 mμ (4.627), 248 mμ (4.341), 271 mμ (4.283), 333 mμ (4.449).

Anal. Calcd. for $C_{21}H_{22}O_8$: C, 62.68; H, 5.51; —OCH_3, 46.28. Found: C, 62.95, 63.05; H, 5.67, 5.72; —OCH_3, 46.34, 46.29. Nobiletin is tasteless in the crystalline form, probably because of its slight solubility. Alcoholic solutions diluted with water are quite bitter.

Hydrolysis of nobiletin. A 2.0-g. portion of nobiletin was refluxed with a mixture of 100 ml. of ethanol and 100 ml. of 20% aqueous potassium hydroxide for 6 hr. The mixture was concentrated at atmospheric pressure to half its volume and 100 ml. of water were added. Carbon dioxide was bubbled into the mixture until it was saturated. An ether extraction of the neutral products of hydrolysis was then made and reserved for the isolation of acetoveratrone. The aqueous residue was also retained for the isolation of the acidic hydrolysis products.

Isolation of acetoveratrone oxime. The ethereal extract of the neutral hydrolysis products was evaporated nearly to dryness. To this was added a mixture containing 0.5 g. of hydroxylamine hydrochloride and 4 ml. of 5% sodium hydroxide and enough ethanol to give a clear solution. After heating for 10 min. in a hot water bath, the mixture was cooled and placed in a cold room at 4°. A yield of 0.23 g. of crystals melting at 141° cor. was obtained which agrees with that reported by Robinson and Tseng[3] for acetoveratrone oxime.

Anal. Calcd. for $C_{10}H_{13}O_3N$: C, 61.55; H, 6.66; —OCH_3, 31.80; N, 7.18. Found: C, 61.98, 61.74; H, 6.65, 6.72; —OCH_3, 31.24, 31.09; N, 6.76, 6.80.

Acidic hydrolysis products. Veratric acid. The aqueous residue remaining after the extraction of the neutral hydrolysis products was acidified with dilute sulfuric acid and extracted again with ether. The ether was removed by evaporation and the residue weighing 1.4 g. was twice crystallized from about 70 ml. water. After drying, the melting point was found to be 182° cor. A mixture with anisic acid gave a melting-point depression of 30°, thus excluding this as a possibility. Analysis and a neutral equivalent determination were in agreement with those of veratric acid. The yield was 0.4 g. The amide melted at 164–166°, which is in agreement with the values given in the literature for veratric acid.

Anal. Calcd. for $C_9H_{10}O_4$: C, 59.33; H, 5.53; —OCH_3, 34.07; Neut. equiv., 182.2. Found: C, 59.56, 59.67; H, 5.70, 5.68; —OCH_3, 34.26, 34.34; Neut. equiv., 185.1.

Acknowledgment. The author is indebted to L. E. Brown of the Southern Regional Research Branch, ARS, for the elemental analyses.

FRUIT AND VEGETABLE PRODUCTS LABORATORY
SOUTHERN UTILIZATION RESEARCH AND DEVELOPMENT DIVISION
AGRICULTURAL RESEARCH SERVICE
U. S. DEPARTMENT OF AGRICULTURE
WINTER HAVEN, FLA.

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Reaction of Cyclic Sulfites of 1,3-Glycols with Sodium Iodide

STANLEY WAWZONEK AND J. T. LOFT[1]

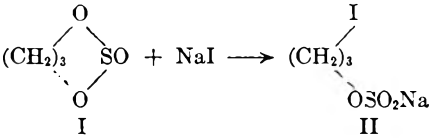
Received February 22, 1960

Alkyl sulfites have not been studied extensively as alkylating agents because of the ease of preparation and reactivity of the corresponding sulfates and sulfonates.

Cyclic sulfites of 1,3-glycols which are much more readily available than the cyclic sulfates have not been studied in this respect. Their behavior as alkylating agents would offer a convenient route to 3-monosubstituted derivatives of 1-propanol.

In this work the reaction of sodium iodide with the sulfites of trimethylene glycol, 3,3-bishydroxymethyloxetane, pentaerythritol, 3,3-dimethyl-1,3-propanediol, and 3-methyl-3-hydroxymethyl-1,3-propanediol has been studied and found to proceed normally with the first three compounds; 3-iodo-1-propanol, 3-hydroxymethyl-3-iodomethyloxetane, and 2,2-bisiodomethyl-1,3-propanediol were obtained, respectively.

The reaction was carried out in methyl ethyl ketone and found to proceed in a similar fashion to that found by others[2] for the reaction of sodium



I II

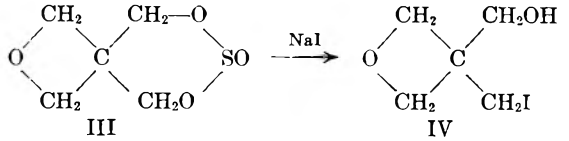
iodide with alkyl sulfites in acetone. Simultaneous condensation of methyl ethyl ketone apparently occurs with the liberation of water and subsequent hydrolysis of the intermediate sulfite. The methyl ethyl ketone bisulfite addition compound in contrast to the findings of Foster, *et al.*[2] coprecipitated

(1) Abstracted in part from the Ph.D. thesis of J. T. Loft, August 1959.

(2) A. B. Foster, E. B. Hancock, W. G. Overend, and J. C. Robb, *J. Chem. Soc.*, 2589 (1956).

with sodium iodide during the reaction. The alkylation in the presence of water was found to cause the precipitation of sodium bisulfite instead and to increase the yield of 3-iodo-1-propanol in the reaction of trimethylene sulfite (I) with sodium iodide. A similar addition of water to a solution of pentaerythrityl disulfite and sodium iodide in methyl ethyl ketone was deleterious, as the alkylation reaction was slower and hydrolysis of the sulfite to pentaerythritol occurred.

The structure of 3-hydroxymethyl-3-iodomethyloxetane (IV) obtained from 2,4,8,3-trioxathiaspiro[5,3]nonane-3-oxide (III)[3] was indicated by its elemental analysis and its infrared spectra.



III IV

The sulfite of 2-methyl-2-hydroxymethyl-1,3-propane-diol[3] required methyl isopropyl ketone as a solvent to effect a reaction. The reaction proceeded normally but the product, 2-methyl-2-hydroxymethyl-3-iodo-1-propanol was isolated as a 1:1 complex with 2-methyl-2-hydroxymethyl-1,3-propanediol. Dissociation of the complex occurs in acetone since after five crystallizations from this solvent 2-methyl-2-hydroxymethyl-1,3-propanediol could be obtained in pure condition.

The sulfite of 2,2-dimethyl-1,3-propanediol was resistant to alkylation and after refluxing with sodium iodide in methyl isopropyl ketone for forty-eight hours gave very little product. The stability of this cyclic sulfite is no doubt brought on by the *gem* methyl groups.

EXPERIMENTAL[4]

3-Iodo-1-propanol. A solution of 1,3,2-dioxanthiane-2-oxide[5] (24.4 g.), sodium iodide (30 g.), and water (3.6 g.) in methyl ethyl ketone (300 ml.) was refluxed for 24 hr. and formed a light yellow precipitate. The entire mixture was dried with anhydrous sodium sulfate and filtered. Fractional distillation under nitrogen gave 24.5 g. of 3-iodo-1-propanol boiling at 112° (31 mm.); n_D^{20} 1.5515; d_4^{25} 2.014. The literature[6] reports a boiling point of 115° (38 mm.) and a refractive index of n_D^{20} 1.5585.

Anal. Calcd. for C_3H_7OI: C, 19.38; H, 3.79. Found: C, 19.42; H, 3.58.

3-Hydroxymethyl-3-iodomethyloxetane (IV). 2,4,8,3-Trioxathiaspiro[5,3]nonane-3-oxide[3] (III) (10 g.) and sodium iodide (14.2 g.) were refluxed in methyl ethyl ketone for 20 hr. The solution was filtered, then acidified with dilute hydrochloric acid and separated from the water layer. Removal of the methyl ethyl ketone gave an oil which distilled at 128° (2 mm.); yield, 2.6 g.; n_D^{24} 1.5603.

Anal. Calcd. for $C_5H_9O_2I$: C, 26.31, H, 3.95. Found: C, 25.8; H, 3.80.

The infrared spectra of 3-hydroxymethyl-3-iodomethyloxetane had the characteristic oxetane absorption peak at 970 cm.$^{-1}$[7] and hydroxyl peaks at 2850 and 3400 cm.$^{-1}$

2,2-Bisiodomethyl-1,3-propanediol. A mixture of sodium iodide (30 g.) and 2,4,8,10-tetraoxa-3,9-dithia[5,5]undecane-3,9-oxide[8] (22.8 g.) in dry methyl ethyl ketone (300 ml.) was refluxed for 36 hr. with constant stirring. Removal of the solvent gave a heavy oil which was extracted twice with methylene chloride (150 ml.). The solid which remained proved to be the starting material (2.7 g.).

The combined methylene chloride extracts were dried with calcium sulfate and upon removal of the solvent gave an oil (17 g.). Trituration with ethanol gave additional starting material (1 g.). Removal of the ethanol gave an oil which was crystallized from water and gave 2,2-bisiodomethyl-1,3-propanediol (11 g.) melting at 129–130°. The literature[9] reports a similar melting point.

Anal. Calcd. for $C_5H_{10}O_2I_2$: C, 16.86; H, 2.81. Found: C, 16.65; H, 3.02.

Reaction of sodium iodide with 5-methyl-5-hydroxymethyl-1,3,2-dioxathiane-2-oxide. A solution of sodium iodide (60 g.) and 5-methyl-5-hydroxymethyl-1,3,2-dioxathiane-2-oxide[3] (64 g.) in methyl isopropyl ketone (500 ml.) protected from light was refluxed with stirring for 48 hr. Removal of the solvent gave an oil which was separated by distillation into two fractions. The first fraction boiling at 110–140° (7 mm.) proved to be mainly starting materials (35 g.). The second fraction, which distilled at 160° (7 mm.), gave an oil which upon crystallization from chloroform gave 13.4 g. of a white solid melting at 70–71°. Analysis and a molecular weight determination in camphor indicated that this solid was a molecular complex of 2-methyl-2-hydroxymethyl-1,3-propanediol and 2-methyl-2-hydroxymethyl-3-iodo-1-propanol.

Anal. Calcd. for $C_{10}H_{22}O_5I$: C, 32.35; H, 6.76; I, 37.33. Found: C, 32.67; H, 6.58; I, 37.24. Mol. wt. 349.9. Found: 354.4, 350.8 (Rast) (Acetone, b.p. el.) 184, 145.

Five fractional crystallizations of the complex (3 g.) from acetone at −70° gave 0.05 g. of 2-methyl-2-hydroxymethyl-1,3-propanediol melting at 199–200°.

Reaction of 5,5-dimethyl-1,3,2-dioxathiane-2-oxide with sodium iodide. 5,5-Dimethyl-1,3,2-dioxathiane-2-oxide[10] (30 g.) and sodium iodide (30 g.) were refluxed in methyl isopropyl ketone (600 ml.) with stirring and protected against light for 48 hr. Removal of the solvent gave a dark residue which was fractionally distilled. Starting material (17.6 g.) was obtained together with 2.0 g. of a liquid which boiled at 106–110° (35 mm.). Two further distillations gave a sample which had an approximate analysis for 2,2-dimethyl-3-iodo-1-propanol.

DEPARTMENT OF CHEMISTRY
STATE UNIVERSITY OF IOWA
IOWA CITY, IOWA

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(4) Melting points and boiling points are not corrected.

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Preparation of 2,2,2-Trinitroethanol[1]

HENRY FEUER AND THOMAS J. KUCERA

Received April 4, 1960

The synthesis of trinitroethanol (I) has been reported from the reaction of trinitromethane with

(1) From the Ph.D. Thesis of Thomas J. Kucera, Purdue University, August 1953.

an excess of paraformaldehyde.[2] The experimental procedure involved distillation of I and the authors reported that explosions were encountered during this operation. In addition, compound I made by this method was very low melting (30°) and unstable.

An investigation of this reaction in this laboratory by G. Leston[3] showed that compound I could be obtained with a much higher melting point (65–66°), but that it was still hygroscopic and decomposed in the presence of moisture.

We now wish to report a more efficient preparation of I which eliminates the explosion hazard and affords in 80% yield pure I, m.p. 72°, directly from the reaction solution.

Pure I was found to be nonhygroscopic and stable. The presence of small amounts of water and formaldehyde was found to decrease the melting point and to cause I to react with the absorbed atmospheric moisture. The ready dissociation of I to trinitromethane and formaldehyde in water has recently been studied.[4]

EXPERIMENTAL

2,2,2-Trinitroethanol. In a three-necked flask which was provided with a stirrer, reflux condenser, and thermometer were placed 100 ml. of carbon tetrachloride, 2.12 g. (1.4 mmoles) of trinitromethane and 0.45 g. of paraformaldehyde (14.3 mmoles of formaldehyde assuming 95% formaldehyde). The turbid solution was heated with stirring for 3 hr. at 60–65° and then at reflux for 30 min. Concentrating the solution to 30 ml. and cooling in the refrigerator gave trinitroethanol in the form of long needles. Further concentration of the filtrate gave additional crops of crystals, m.p. 72°. The overall yield was 80%.

Anal. Calcd. for $C_2H_3O_7N_3$: C, 13.26; H, 1.66; N, 23.20. Found: C, 13.22; H, 1.62; N, 23.02.

Acknowledgment. We are indebted to the Office of Naval Research for the financial support of this work.

DEPARTMENT OF CHEMISTRY
PURDUE UNIVERSITY
LAFAYETTE, IND.

(2) N. S. Marans and R. P. Zelinski, *J. Am. Chem. Soc.*, **72**, 5329 (1950).

(3) Unpublished results from the M.S. dissertation of G. Leston, Purdue, 1949.

(4) J. Reinhart, J. G. Meitner, and R. W. Van Dolah, *J. Am. Chem. Soc.*, **77**, 496 (1955).

Polymerizable Esters of Trinitroethanol[1]

HENRY FEUER, HENRY B. HASS, AND R. D. LOWREY

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The preparation of polymerizable mononitroalcohol esters of acrylic acid was described by D'Alelio.[2] Marans and Zelinski[3] showed that trinitroethanol (I) reacts readily with acetyl chloride and propionyl chloride to give the expected esters of I in high yields. We now wish to report the preparation of esters of I with unsaturated acids which are enumerated in Table I. In all cases the acid chlorides were employed and with the monobasic acids the highest yields were obtained in the absence of a solvent. This was also the case with fumaryl chloride, but the reaction temperature had to be raised to 130°. In the preparation of ditrinitroethyl itaconate the reaction was performed in petroleum ether. On heating, trinitroethyl acrylate and trinitroethyl methacrylate (II) were converted to high melting translucent solids of high softening range. Ester II was also copolymerized with ditrinitroethyl fumarate.

Attempts to prepare a monomer from isopropenyl isocyanate and compound I were unsuccessful. Reactions which were carried out in the presence of a polymerization inhibitor such as trinitrobenzene led to a viscous oil which turned to a solid during distillation at low pressure. It had the correct analysis for a polymer of trinitroethyl *N*-isopropenylcarbamate.

EXPERIMENTAL

Trinitroethyl methacrylate (II). Three grams (0.019 mole) of trinitroethanol and 10 ml. of methacrylyl chloride were agitated with a stream of dry nitrogen while the temperature was raised to 80° and kept there for 3 hr. The excess acid chloride was removed *in vacuo*, the residue dissolved in ether, washed successively with water, 1.5*N* potassium carbonate, and again with water, and the ether solution was dried with calcium sulfate. Distillation at 95° and 5 mm. caused the ester to crystallize in the condenser. Recrystallization from petroleum ether (b.p. 60–70°) at −60° gave *trinitroethyl methacrylate*, m.p. 26°.

Trinitroethyl acrylate. The procedure was the same as described above, except that the reaction was carried out at 28° for 2 hr.

Ditrinitroethyl fumarate. The reaction was conducted at 100° for 4 hr. and then at 130° for 3 more hr. After work-up as described above, a solid, m.p. 119°, remained. It was recrystallized from dibutyl ether to give *ditrinitroethyl fumarate*, m.p. 150°.

Ditrinitroethyl itaconate. The procedure was the same as described for the preparation of ester II except that petroleum ether (b.p. 60–70°) was employed as a solvent and the reaction mixture was refluxed for 16 hr. Removal of the solvent gave an oil which solidified on adding ethanol. Recrystallization from ethanol gave *ditrinitroethyl itaconate*, m.p. 97°.

Polymerization experiments. Heating ester II at 70° in an airtight flask for 6 days gave a yellow translucent solid which softened at 250–280°.

Similar treatment of trinitroethyl acrylate gave a solid of softening range 170–210°.

Heating an equimolar mixture consisting of ester II and ditrinitroethyl fumarate in a sealed flask at 70° for 6 days gave a translucent solid softening at 150–190°.

(1) From the Ph.D. Thesis of Robert D. Lowrey, Purdue University, February 1950.

(2) G. F. D'Alelio, U. S. Patent **2,499,804** (Sept. 21, 1948).

(3) N. S. Marans and R. P. Zelinski, *J. Am. Chem. Soc.*, **72**, 5329 (1950).

TABLE I

UNSATURATED ESTERS OF TRINITROETHANOL

Compound	B.P.	M.P.	Yield, %	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Trinitroethyl acrylate	80/2 mm.	...	41	$C_5H_5N_3O_8$	25.53	2.21	17.87	25.25	2.18	17.90
Trinitroethyl methacrylate	95/5 mm.	26	54	$C_6H_7N_3O_8$	28.92	2.83	16.87	28.60	2.76	16.78
Trinitroethyl crotonate	97/5 mm.	...	60	$C_6H_7N_3O_8$	28.92	2.83	16.85	29.90	2.88	16.32
Ditrinitroethyl fumarate	...	150	18	$C_8H_6N_6O_{16}$	21.71	1.35	19.00	22.05	...	18.45
Ditrinitroethyl itaconate	...	97	9	$C_9H_8N_6O_{16}$	23.68	1.75	18.42	...	...	18.00

Polytrinitroethyl N-isopropenylcarbamate. Three grams (0.019 mole) of trinitroethanol, 0.85 g. (0.01 mole) of isopropenyl isocyanate[4] and 0.005 g. of trinitrobenzene were allowed to stand 1 week at 24°, and the mixture was then diluted with ether. A small amount of material which did not dissolve was discarded. Washing the solution with water until the water layer was colorless, drying with anhydrous calcium sulfate, and distilling *in vacuo*, left a dark semisolid which did not distill at 100° and 2 mm. It was purified by washing with hot petroleum ether (b.p. 60–70°).

Anal. Calcd. for $C_6H_8N_4O_8$: C, 27.28; H, 3.05, N, 21.21. Found: C, 27.35; H, 3.38; N, 21.18.

Acknowledgment. We are indebted to the Office of Naval Research for the financial support of this work.

DEPARTMENT OF CHEMISTRY
PURDUE UNIVERSITY
LAFAYETTE, IND.

(4) D. D. Coffmann, U. S. Patent, 2,334,476 (Nov. 16, 1943).

Polymerization of Perfluorobutyne-2[1]

HENRY C. BROWN AND HERMAN L. GEWANTER

Received March 18, 1960

High molecular weight polymers of perfluorobutyne-2 have not been previously reported although recent publications[2-4] have described the thermal and catalytic preparation of trimers and tetramers of this bis(perfluoroalkyl)acetylene.

It has now been found that perfluorobutyne-2 forms a new, thermally stable, high molecular weight polymer under the influence of γ-radiation. Exposure of perfluorobutyne-2 to a Co^{60} source for sixty-seven hours at a rate of 3.6×10^5 r./hr. produced, in quantitative yield, a white, inert, solid polymer that is not attacked or wetted by boiling concentrated sulfuric acid, concentrated nitric acid or 50% sodium hydroxide solution. The polymer is insoluble in ether, carbon tetrachloride, methyl alcohol, benzene, and all other common laboratory solvents.

Preliminary data indicate that the thermal behavior of this polymer, polyperfluorobutyne, is quite different from that of polytetrafluoroethylene. The decomposition curve obtained from a thermogravimetric analysis in nitrogen showed an initiation point at 425°, approximately the same temperature as was found for polytetrafluoroethylene; at the 50% decomposition point, however, the curve for polyperfluorobutyne was about 75° above that of polytetrafluoroethylene.

Pyrolysis of polyperfluorobutyne and polytetrafluoroethylene in an evacuated system showed a more marked difference in behavior. Production of gaseous products from polytetrafluoroethylene began at 430°; the temperature was raised to 550°, and after six hours, one-half of the polytetrafluoroethylene had formed gaseous products; three hours at 630° completed the decomposition of this polymer sample. In contrast, with the same heating schedule, polyperfluorobutyne did not form gaseous products until a temperature of 550° had been reached, and after four hours at 630° only about 40% of the weight of the sample was converted to gaseous products. This pyrolysis does not necessarily indicate greater thermal stability in polyperfluorobutyne but does show a type of decomposition different from that of polytetrafluoroethylene.

The infrared spectrum of polyperfluorobutyne resembled that of polytetrafluoroethylene in the position of its major absorption peaks; there was a shift, however, to somewhat higher frequencies than those found for polytetrafluoroethylene.

Elemental analysis confirmed the assumption that this new product is a polymer of perfluorobutyne and that neither carbon nor fluorine was lost by fragmentation in the irradiation process. An empirical formula of C_4F_6 was obtained from the analysis.

Assumptions of the structure of this new polymer are at the present only speculative. As perfluorobutadiene is known to polymerize rather easily,[5] the possibility that perfluorobutyne-2

(1) This work was supported in part by the Office of Naval Research, Chemistry Branch, under Contract N-onr 580(03); NR 356-333 with the University of Florida. Reproduction in whole or in part is permitted for any purpose of the United States Government.

(2) H. C. Brown, H. L. Gewanter, D. M. White, and W. G. Woods, *J. Org. Chem.*, 25, 634 (1960).

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(4) J. F. Harris, Jr., U. S. Patent 2,923,746, February 2, 1960.

(5) C. Slesser and S. R. Schram, *The Preparation, Properties, and Technology of Fluorine and Organic Fluorine Compounds*, McGraw-Hill Book Company, New York, New York, 1951, pp. 624–626.

might isomerize to perfluorobutadiene and subsequently polymerize was considered. A 1,4-linear polymerization of perfluorobutadiene would leave one carbon-carbon double bond in each monomer unit and this should be detectable in the infrared spectrum. The spectra of the new polymer showed no absorption in this region. The known homopolymers of perfluorobutadiene decompose at approximately 300° and thus do not resemble the polymer obtained in the present work.

There was no apparent phase change when polyperfluorobutyne was heated in a melting point tube to 500°. This fact and the lack of unsaturation seem to indicate a highly branched and highly cross-linked structure.

Small yields of polyperfluorobutyne (*ca.* 7%) have been obtained also in the thermal preparation of hexa(trifluoromethyl)benzene from perfluorobutyne-2.[2]

EXPERIMENTAL

Polyperfluorobutyne. Hexafluorobutyne-2 (2.25 g., 0.0139 mole) was condensed in a previously evacuated heavy-wall Pyrex tube 40 cm. × 1.3 cm. (*ca.* 50 ml. capacity). The reaction tube was then sealed and placed in the Co^{60} irradiation tank for 67 hr. to receive γ-radiation at a rate of 3.6×10^5 r./hr. (total dosage 2.4×10^7 r.).

The polymerization tube was then opened and 0.24 g. of unchanged perfluorobutyne-2 recovered. Remaining in the tube was 2.0 g. of a white, solid polymer. This polymer was refluxed with concd. sulfuric acid, with concd. nitric acid and with 50% sodium hydroxide solution with no apparent degradation. It was insoluble in ethyl ether, carbon tetrachloride, methyl alcohol, benzene, and a variety of other common laboratory solvents.

The infrared spectra of solid polyperfluorobutyne shows strong absorption peaks at 8.05, 8.36, and 8.50 μ; a weak absorption peak was found at 8.80 μ. These peaks are in the same region as the major peaks for polytetrafluoroethylene but at slightly higher frequencies.

Anal. Calcd. for C_4F_6: C, 29.63; F, 70.37. Found: C, 29.14; F, 70.27.

Comparative pyrolysis of polyperfluorobutyne and polytetrafluoroethylene. Polyperfluorobutyne, 2.0 g. and polytetrafluoroethylene, 2.0 g. were placed in individual heavy-wall Pyrex tubes and each tube was connected by Tygon pressure tubing to its own liquid-air cooled trap for condensation of gaseous pyrolysis products. The pyrolysis tubes were then bound together, placed in a vertical tube furnace, and the system evacuated.

The temperature of the furnace was raised to 100° and held at this temperature for 1 hr. while the system was pumped to remove residual moisture or air from the polymer samples. The furnace temperature was then raised to 524°, to 550°, and to 630° in steps as shown in Table I. Moles of gaseous products were determined in following the course of the reaction.

TABLE I

PYROLYSIS OF POLYPERFLUOROBUTYNE AND POLYTETRAFLUOROETHYLENE

Temp.	Time, Hr.	Moles, gaseous product, × 10^3	
		Polytetrafluoroethylene	Polyperfluorobutyne
524–550	5.5	10.1	0.0
550	5.5	14.9	0.0
550	11.5	17.4	0.0
550–630	13.3	—	3.1[a]
330	14.5	20.0	—
330	16.3	(Completely pyrolyzed)	6.9[b]

[a] Av. mol. wt., 116. [b] Av. mol. wt., 123.

Pyrolysis of polytetrafluoroethylene resulted in an almost quantitative decomposition to tetrafluoroethylene. The infrared spectra of the polyperfluorobutyne gaseous decomposition products indicated that it was largely hexafluoroethane, though other compounds, at least one of which showed C—C unsaturation, were also present.

In addition to the volatile products, the pyrolysis of polyperfluorobutyne produced 0.95 g. of a tan powder, collected from the upper part of the pyrolysis tube and the connecting tubing that evidently contained unsaturation as it decolorized an acetone solution of potassium permanganate. Further investigation of this pyrolysis product will be reported in a subsequent publication.

Acknowledgment. The authors wish to thank the Materials Laboratory, Wright Air Development Division, U. S. Air Force, for the thermogravimetric analysis data.

DEPARTMENT OF CHEMISTRY
DEPARTMENT OF CHEMICAL ENGINEERING
UNIVERSITY OF FLORIDA
GAINESVILLE, FLA.

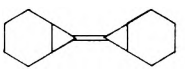
Communications TO THE EDITOR

Reactions of *gem*-Dibromocyclopropanes with Alkyllithium Reagents. Formation of Allenes, Spiropentanes, and a Derivative of Bicyclopropylidene[1]

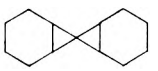
Sir:

We have found that treatment of *gem*-dibromocyclopropanes with methyl- or butyllithium in ether at 0 to −80° presents a general method for the synthesis of allenes[2]; 1,2-undecadiene (*Anal.* Found: C, 86.77; H, 13.04), 2,3-heptadiene (*Anal.* Found: C, 87.52; H, 12.60), 1,2-cyclodecadiene (*Anal.* Found: C, 88.13; H, 11.96), and 1,2-cycloundecadiene (*Anal.* Found: C, 87.81; H, 12.12) have been obtained in 70–90% yields.

In these reactions, no evidence of carbene intermediates[3] has been found in experiments employing cyclohexene as a trapping agent. However, treatment of 7,7-dibromobicyclo [4.1.0]heptane (I) with methyllithium in ether-cyclohexene at −80° gave a mixture of products from which a white solid (II) (30%), m.p. 120.5–121°, $C_{14}H_{20}$ (*Anal.* Found: C, 89.56; H, 10.54; mol. wt.,[4] 188) and liquids (III) (10%; *Anal.* Found: C, 88.43; H, 11.53; mol. wt.,[4] 176) and IV (5%; *Anal.* Found: C, 88.68; H, 11.45; mol. wt.,[4] 176), both $C_{13}H_{20}$, were isolated by gas chromatography.[5] In the absence of cyclohexene, II was obtained but III and IV were not formed.



II

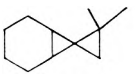


III

Structure II has been assigned on the basis of the following data: reaction with bromine, high end absorption in the ultraviolet ($\lambda^{C_2H_5OH}$ 206 mμ, $\epsilon \sim 13{,}000$), NMR[6] absorption in the region τ = 8 − 9 only (no olefinic protons), $\nu_{max}^{CCl_4}$ 2977 cm.$^{-1}$ (cyclopropane C—H). Hydrogenation of II (platinum, acetic acid, 25°, 1 atm.) has given mixtures of dihydro-II ($\nu_{max}^{CCl_4}$ 3000 cm.$^{-1}$; *Anal.* Found: C, 88.31; H, 11.55), tetrahydro-II ($\nu_{max}^{CCl_4}$ 3000 cm.$^{-1}$; *Anal.* Found: C, 87.08; H, 12.51) and 1,2-dicyclohexylethane (hexahydro-II). At higher temperatures, both di- and tetrahydro-II are slowly hydrogenated to give 1,2-dicyclohexylethane.

Structure III has been assigned on the basis of the following data: no reaction with bromine, essentially no end absorption in the ultraviolet ($\lambda^{C_2H_5OH}$ 206 mμ, $\epsilon < 300$), NMR[6] absorption in the region τ = 8 − 9 only, $\nu_{max}^{CCl_4}$ 2988 cm.$^{-1}$ Hydrogenation of III (platinum, acetic acid, 120°, 34 atm.) gave only cyclohexylcycloheptane (identified by gas chromatography on three columns and comparison of infrared spectra. *Anal.* Found: C, 86.61; H, 13.49). Less vigorous conditions (platinum, propionic acid, 100°, 1 atm.) gave 74% of cyclohexylcycloheptane, 1% of a compound with retention times (four columns) identical to those of dicyclohexylmethane, and 24% of dihydro-III (mol. wt.[4] 178; $\nu_{max}^{CCl_4}$ 2996 cm.$^{-1}$).

Present results indicate that the formation of spiropentanes related to III may be general. A liquid, $C_{11}H_{18}$ (*Anal.* Found: C, 87.91; H, 12.04; mol. wt.[4] 150), assigned structure V on the basis of evidence similar to that presented for III, has been obtained from the reaction of I with methyllithium in the presence of isobutylene.



V

VI

The formation of spiropentanes III[7] and V[7] must involve a common intermediate which may be carbene VI, or the highly strained 1,2-cycloheptadiene, or a species which is intermediate in structure between carbene and allene. The formation of bicyclopropylidene II[7] may also involve this intermediate. We hope that work in progress may shed some light on these questions.

DEPARTMENT OF CHEMISTRY
MASSACHUSETTS INSTITUTE OF TECHNOLOGY
CAMBRIDGE 39, MASS.

WILLIAM R. MOORE
HAROLD R. WARD[8]

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(1) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

(2) W. von E. Doering and P. M. LaFlamme, *Tetrahedron*, **2**, 75 (1958) have reported related reactions.

(3) Certain polyhalomethylenes produce carbenes when treated with alkyllithium reagents. (a) G. L. Closs and L. E. Closs, *J. Am. Chem. Soc.*, **81**, 4996 (1959). (b) W. T. Miller, Jr., and C. S. Y. Kim, *J. Am. Chem. Soc.*, **81**, 5008 (1959).

(4) Determined by mass spectrometry. We thank Prof. K. Biemann for measuring the mass spectra.

(5) (a) Relative retention times: Carbowax 20 M (142°) t_{II}/t_{III} = 2.70, t_{IV}/t_{III} = 1.00; silver nitrate (15%) − tetraethylene glycol (115°), t_{IV}/t_{III} = 1.41. (b) The structure of IV (an olefin) and the structures of lower boiling products will be discussed in the future.

(6) (a) $\tau = 10.00 - \delta^{int}_{Me_4Si}$. (b) Tertiary cyclopropane protons in certain fused-ring systems (*e.g.*, norcarane) show signals below τ = 9. (c) We thank Dr. G. E. Maciel for measuring NMR spectra.

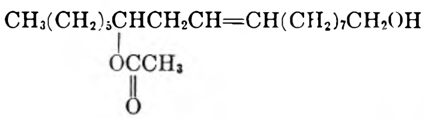
(7) Consistent names: II, 7,7′-{bicyclo[4.1.0]heptylidene}; III, 7,7′-spirobi{bicyclo[4.1.0]heptane}; IV, spiro{bicyclo[4.1.0]heptane-7,1′-(2′,2′-dimethylcyclopropane)}.

(8) National Science Foundation Summer Fellow, 1959.

Synthesis of a Highly Potent Gypsy Moth Sex Attractant

Sir:

The gypsy moth (*Porthetria dispar* L.) is one of the most serious pests of fruit, shade, and woodland trees in New England and eastern New York State, causing extensive loss by defoliation. The male is attracted to the virgin female by means of a substance secreted by her abdominal glands, and the use of traps baited with a crude extract of these glands is the best known means of detecting infestations of the insect.[1] Collection of the necessary insects and preparation of the extract are extremely costly and a practical, efficient synthetic attractant is needed as a substitute. 12-Acetoxy-1-hydroxy-*cis*-9-octadecene (I), prepared as a model compound for oxidation studies during the chemical investigation of the natural lure,[2] has now been found to be a highly potent attractant for the male gypsy moth.



I

Lithium aluminum hydride reduction of ricinoleic acid (Kahlbaum) gave a quantitative yield of rincinoleyl alcohol [b.p. 175°/0.5 mm., n_D^{25} 1.4704, $[\alpha]_D^{30}$ +5.3° (chloroform); reported[3] b.p. 178°/0.5 mm., n_D^{25} 1.4700, $[\alpha]_D^{24}$ +5.7° (undiluted). *Anal.* Found: C, 75.83; H, 12.67], which was acetylated in 62% yield with acetyl chloride in refluxing benzene (containing pyridine) to the 1,12-diacetate [b.p. 180°/1.3 mm., n_D^{25} 1.4519, $[\alpha]_D^{30}$ +8.7° (chloroform). *Anal.* Found: C, 71.52; H, 11.06]. Saponification with refluxing ethanolic potassium hydroxide removed only the primary acetyl group,[4] giving a 90% yield of I [b.p. 182°/0.5 mm., n_D^{25} 1.4607, $[\alpha]_D^{30}$ +7.4° (chloroform). *Anal.* Found: C, 73.36; H, 11.70]. The compound shows blue fluorescence in ultraviolet light, is remarkably stable to heat, and does not appear to decompose on storage at room temperature.

Male gypsy moths in large numbers were lured to field traps containing as little as one microgram of I,[5,6] and the compound was attractive at one ten-millionth of a microgram in laboratory bioassay tests.[7] These figures compare very favorably with the activity of the natural attractant. The use of the synthetic lure in U. S. Department of Agriculture survey traps should result in substantial monetary savings in the conduct of current programs, and the product may provide a new means of control.

The effect of isomerization of the double bond of I and its optical isomers on activity is being investigated.

ENTOMOLOGY RESEARCH DIVISION
AGRICULTURAL RESEARCH SERVICE
U. S. DEPARTMENT OF AGRICULTURE
BELTSVILLE, MD.
MARTIN JACOBSON

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(1) F. Acree, Jr., M. Beroza, R. F. Holbrook, and H. L. Haller, *J. Econ. Entomol.*, 52, 82 (1959).

(2) M. Jacobson, M. Beroza, and W. A. Jones, *Science*, October 1960.

(3) S. P. Ligthelm, E. von Rudloff, and D. A. Sutton, *J. Chem. Soc.*, 3187 (1950).

(4) The secondary acetyl group was extremely resistant to saponification with refluxing ethanolic alkali, and it was necessary to use diethylene glycol-potassium hydroxide mixture at 120° to break this linkage.

(5) Field tests were carried out as described by J. M. Corliss, *Yearbook of Agriculture (Insects)*, 694 (1952). The assistance of Mr. E. C. Paszek, U. S. Department of Agriculture, Nashua, N. H., in carrying out these tests is gratefully acknowledged.

(6) The only lures previously reported, 1,2-epoxyhexadecane and 1,2-hexadecanediol [*cf.* M. Jacobson, U. S. Patent **2,900,756** (Aug. 25, 1959)] were considerably less attractive in the field when tested at 0.5 g. per trap.

(7) Bioassay tests were carried out by the method of B. C. Block, *J. Econ. Entomol.*, **53**, 172 (1960).