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Preparation of Alkyl Azides from Hydrazine Derivatives[1]

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N-Alkyl-*N*-acylhydrazines have been found to give alkyl azides in poor to satisfactory yields by treatment with nitrous acid. Isobutyl and hexahydrobenzyl azides were prepared by this method from the corresponding 2-alkylsemicarbazides, and the adducts of these azides with acetylenedicarboxylic acid, dicyclopentadiene, or bicycloheptadiene were prepared as characterizing derivatives. *N*-*tert*-Butyl-*N*-benzoylhydrazine has been prepared by benzoylation of acetone *N*-*tert*-butylhydrazone followed by selective hydrolysis; nitrosation converts it in small part to *tert*-butyl azide.

The reaction of arylhydrazines with nitrous acid has been recognized for a long time as a useful method for the synthesis of aryl azides.[2] The nitrogen atom from the nitrous acid has been shown to become the outer, terminal atom of the azide chain,[3] and the initial attack by nitrous acid is therefore presumably on the unsubstituted amino group.

$$\mathrm{Ar{-}NH{-}NH_2 + HNO_2 \longrightarrow [Ar{-}NH{-}NH{-}NO] \longrightarrow Ar{-}N_3 + H_2O}$$

Alkyl hydrazines, due to their more difficult accessibility, have been much less studied regarding their behavior on nitrosation. The available information shows that their nitrosation is not a useful synthesis of alkyl azides and that, indeed, azides are rarely formed at all. The primary nitrosation products that have been isolated appear to be 1-nitroso-1-alkylhydrazines,[4] which obviously cannot give rise to azides without rearrangement, and not surprisingly they decompose in other ways.

$$\mathrm{R{-}NH{-}NH_2 + HNO_2 \longrightarrow R{-}\underset{\underset{NO}{|}}{N}{-}NH_2 \xrightarrow{//} R{-}N_3}$$

The explanation for this difference in behavior between aryl- and alkylhydrazines appears to be in the effect of the substituents on the relative basicity of the two hydrazine nitrogens. Inasmuch as aryl groups are base-weakening and alkyl groups are base-strengthening when attached to an amine nitrogen, one might reasonably expect the substituted nitrogen of alkylhydrazines to be more basic than the unsubstituted one, and the reverse to be true for arylhydrazines. The very reasonable assumption that nitrosation occurs on the more basic nitrogen then explains the observed behavior.

In order to bring about nitrosation on the unsubstituted nitrogen of alkylhydrazines, we prepared 1-alkyl-1-acylhydrazines. The base-weakening acyl group would be expected to prevent nitrosation at the alkylated nitrogen, but would be removable hydrolytically at a suitable time. Nitrosation on the unsubstituted nitrogen would then give rise to the three-nitrogen chain of the azide system, and subsequent elimination of the acyl group should produce an alkyl azide. A solitary exemplification of this is the reported formation of a keto azide from a fused-ring *N*-aminoimidazolidone or a related oxime.[5]

1-Alkyl-1-acylhydrazines might be prepared by acylation of an alkylhydrazine, or by nitrosation of an *N*-alkyl amide followed by reduction of of the *N*-nitroso group. The latter was investigated first, because of the more readily accessible starting

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(2) J. H. Boyer and F. Canter, *Chem. Revs.*, **54**, 1 (1954).

(3) K. Clusius and H. R. Weisser, *Helv. Chim. Acta*, **35**, 1548 (1952); *Naturwissenschaften*, **39**, 42 (1952).

(4) J. Thiele, *Ann.*, **376**, 239 (1910).

(5) M. O. Forster and H. E. Fierz, *J. Chem. Soc.*, **87**, 826 (1905); **91**, 867 (1907).

materials. Alkylurethans and alkylureas were chosen, since their nitrosation behavior has been fairly well studied. Difficulty was encountered in converting the urethans to 1-alkyl-1-carboalkoxyhydrazines, so attention was concentrated on the ureas, which could be converted to 1-alkyl-1-carbamylhydrazines in satisfactory yield. The difference in behavior between the urethans and the ureas may be due either to an intrinsic difference in the ease of reductive cleavage of the N=N bond, or may perhaps be due to the greater ease of handling the urea derivatives, which were all solids in contrast to the liquid urethan derivatives.

Nitrosation of the 2-alkylsemicarbazides obtained gave rise to azides without isolation of intermediates; the reactions were not clean-cut, as shown by the somewhat low yields, but elimination of the carbamyl group was spontaneous under the conditions used. The two successful examples both involved primary alkyl groups (isobutyl and hexahydrobenzyl).

$$H_2N{-}NR{-}CO{-}NH_2 \xrightarrow{HNO_2} R{-}N_3 - CO_2 + N_2$$

Attempts to extend the reaction to the secondary and tertiary class, represented by cyclohexyl- and *tert*-butyl-semicarbazides, were at first thwarted by our failure to obtain the required semicarbazides by the nitrosation and reduction route. However, 2-substituted semicarbazides can also be prepared by a different route, the key step of which is the reaction of a carbamyl chloride with the magnesium derivative of a benzophenone *N*-alkylhydrazone, obtained by the addition of a Grignard reagent to diphenyldiazomethane.[6] We found that *tert*-butylmagnesium chloride added readily to diphenyldiazomethane, but the resulting salt could not be made to react with acid chlorides.

Since it appeared probable that the unreactivity was steric in origin, and in part due to the size of the phenyl groups as well as the *tert*-butyl, we next investigated acetone *tert*-butylhydrazone, which was prepared from *tert*-butylhydrazine. We were able to benzoylate this compound successfully, and to hydrolyze the product selectively to *N*-benzoyl-*N*-*tert*-butylhydrazine. Treatment of this with nitrous acid then brought about some conversion to *tert*-butyl azide, but the yields were too low to permit its isolation in pure form.

$$(CH_3)_2C{=}N{-}NH{-}C_4H_9\text{-}t \longrightarrow (CH_3)_2C{=}N{-}N(COC_6H_5){-}C_4H_9\text{-}t \xrightarrow[H_2O]{HCl} C_6H_5CO{-}N(NH_2){-}C_4H_9\text{-}t$$

tert-Butylhydrazine was required in quantity for these experiments. Since previously published syntheses of this compound[7,8] did not seem satisfactory, we explored most of the synthetic methods that have been used for other alkylhydrazines. Most failed altogether or gave only negligible yields, but the seldom used method discovered by Zerner[9] and developed by Coleman, Gilman, Adams, and Pratt,[6] utilizing the reaction of Grignard reagents with diphenyldiazomethane, worked well, and we were able to carry it out on a scale of several moles and to characterize pure *tert*-butylhydrazine for the first time. However, the hydrolysis of the intermediate benzophenone *tert*-butylhydrazone had to be carried out at room temperature for success; hot acid caused elimination of the *tert*-butyl group.

$$(C_6H_5)_2C{=}N_2 \xrightarrow{t\text{-}C_4H_9MgCl} (C_6H_5)_2C{=}N{-}NH{-}C_4H_9\text{-}t \xrightarrow[H_2O]{HCl} (C_6H_5)_2CO + H_2N{-}NH{-}C_4H_9\text{-}t$$

Although the route to alkyl azides developed here is not a generally useful synthetic method, it has the potentially important characteristic of allowing the aliphatic azide group to be built up one atom at a time. This makes it in principle possible to prepare aliphatic azides with a specific nitrogen atom isotopically tagged, a feat hitherto possible only for aryl azides.

In the course of this work, the need to characterize liquid azides by conversion to a solid derivative arose. Three reagents were investigated: acetylenedicarboxylic acid, which gives rise to 1-alkyltriazole-4,5-dicarboxylic acids; and bicyclo[2.2.1]-heptadiene and dicyclopentadiene, which would be expected to give bicyclic fused-ring triazolines. All three reagents were successful in giving crystalline derivatives readily. The triazoledicarboxylic acids were rather unsatisfactory in that they readily form hydrates, which may have indefinite melting points. The bicycloheptadiene adducts showed addition at both double bonds, giving products which are presumably bis(triazolino)-bicycloheptanes, the positions of substitution on the two triazoline rings relative to each other being unknown. These are high-melting, crystalline substances which appear to be stable to storage, and make suitable derivatives for characterization. *tert*-Butyl azide, however, did not form such derivatives satisfactorily. It was therefore characterized by rearrangement to acetone *N*-methylimine with concentrated sulfuric acid, and isolating acetone dinitrophenylhydrazone.

EXPERIMENTAL

2-Isobutylsemicarbazide was prepared in 54% yield by reduction of *N*-nitroso-*N*-isobutylurea[8] with zinc and acetic acid; it had m.p. 89–91° (reported[10] 91.5–92°).

(6) G. H. Coleman, H. Gilman, C. E. Adams, and P. E. Pratt, *J. Org. Chem.*, **3**, 99 (1938).

(7) F. Klages, *Ann.*, **547**, 25 (1941).

(8) L. F. Audrieth and K. H. Diamond, *J. Am. Chem. Soc.*, **76**, 4869 (1954).

(9) E. Zerner, *Monatsh.*, **34**, 1609 (1913).

(10) K. Taipale, *J. Russ. Phys. Chem. Soc.*, **56**, 81 (1925); *Chem. Zentr.*, 1926, I, 872.

Isobutyl azide. A solution of 26.2 g. (0.2 mole) of 2-isobutylsemicarbazide in 50 ml. of concentrated hydrochloric acid and 50 ml. of water was cooled to 0° and a solution of 19.3 g. (0.28 mole) of sodium nitrite in 35 ml. of water was added dropwise; the solution became bright green. It was stirred an additional hour and then urea was added to destroy the excess nitrous acid; the green color disappeared. The solution was made basic, causing the separation of a second layer, and the mixture was then distilled, the product being codistilled with the water. The distillate was extracted with ether and the extracts were dried over calcium chloride. The solution was fractionally distilled at 752.5 mm., giving 7.59 g. of b.p. 40–53°, 3.40 g. of b.p. 53–93°, 5.53 g. of b.p. 93–95°, and 3.08 g. of b.p. >95°. The 93–95° fraction was taken up in petroleum ether (b.p. 30–37°) and washed twice with 5% hydrochloric acid, once with water, dried and redistilled at 751.5 mm., giving 1.50 g., b.p. 45–53°; 2.90 g., b.p. 93–94°; and 0.62 g., b.p. >94°. The middle fraction, which reacted vigorously with concentrated sulfuric acid and flashed in a flame, was taken as isobutyl azide (it is not clear whether the small discrepancy in the carbon analysis should be attributed to impurity in the azide or to its immoderate behavior on combustion).

Anal. Calcd. for $C_4H_9N_3$: C, 48.46; H, 9.15. Found: C, 49.18; H, 9.06.

1-Isobutyl-1,2,3-triazole-4,5-dicarboxylic acid. The foregoing isobutyl azide, 2.80 g., was taken up in petroleum ether (b.p. 30–60°), washed with two portions of 10% hydrochloric acid, once with water, and dried over magnesium sulfate. To this was added 4.55 g. (0.034 mole) of acetylenedicarboxylic acid hydrate and 20 ml. of dry ether, and the solution was refluxed for one hour, cooled, and petroleum ether was added until a white solid precipitated; yield 5.94 g. (74.7%), m.p. 50–95°.

Recrystallization from ether–petroleum ether mixture gave white needles which lost water at 121° and melted at 136–137°. The neutral equivalent was 109.3 (calcd. 106.5). The sample was allowed to stand open to the air until the weight was constant. The neutral equivalent was then found to be 118 (calcd. for the monohydrate 115.5).

Anal. Calcd. for $C_8H_{11}O_4N_3 \cdot H_2O$: C, 41.56; H, 5.67. Found: C, 41.92; H, 5.62.

Isobutyl azide–bicycloheptadiene adduct. A mixture of 1.50 g. (0.015 mole) of isobutyl azide and 0.70 g. (0.0076 mole) of bicycloheptadiene was allowed to stand at room temperature for several days. The addition of a small amount of methylene chloride and sufficient petroleum ether (b.p. 40–60°) to cause some precipitation gave 0.16 g. (7.3%) of colorless crystals, m.p. 186–188°; presumably, more could have been obtained from the mother liquors. Recrystallization from the same solvents gave an analytical sample, m.p. 188–191°.

Anal. Calcd. for $C_{15}H_{26}N_6$: C, 62.02; H, 9.02. Found: C, 62.05; H, 9.18.

Nitrosohexahydrobenzylurea (1-cyclohexanemethyl-1-nitrosourea). A mixture of 78 g. (0.5 mole) of hexahydrobenzylurea,[11] 150 ml. of ether, 50 g. of ice, and 160 g. (2.25 moles) of sodium nitrite in 250 ml. water was acidified by dropwise addition of 150 g. of concentrated nitric acid and 150 g. of ice. More ice was added as needed, to keep the temperature below 5°. The product which precipitated was filtered off and washed with cold water, and the mother liquors were extracted with ether. The ethereal solution was dried and evaporated. The total yield was 47.1 g. (51%), m.p. 118–121°. Recrystallization from ethanol-water mixture gave an analytical sample, m.p. 120–123° dec.

Anal. Calcd. for $C_8H_{15}O_2N_3$: C, 51.87; H, 8.16. Found: C, 52.00; H, 8.14.

2-Hexahydrobenzylsemicarbazide (2-cyclohexanemethylsemicarbazide). A solution of 18.5 g. (0.1 mole) of nitrosohexahydrobenzylurea in 100 ml. of glacial acetic acid and 50 ml. of water was added dropwise to 30 g. of zinc dust and 100 ml. of 50% acetic acid, while the temperature was kept below 20°. After the addition was completed, the mixture was allowed to warm to room temperature and was then filtered. The filtrate was made basic and the product was filtered and washed with water. The filtrate was extracted with ether, which was then dried and evaporated. The combined yield of 2-hexahydrobenzylsemicarbazide was 11 g. (64.5%), m.p. 154–162°. Recrystallization twice from absolute alcohol gave an analytical sample, m.p. 160.5–163°.

Anal. Calcd. for $C_8H_{16}ON_3$: C, 56.11; H, 10.01. Found: C, 56.28; H, 10.04.

Hexahydrobenzyl azide (cyclohexanemethyl azide). One-fifth mole (34.2 g.) of 2-hexahydrobenzylsemicarbazide was triturated with 50 ml. of concentrated hydrochloric acid and heated on a steam bath. To the hot suspension was added 50 ml. of water, and the mixture was cooled to 0°. The solution was stirred mechanically while a solution of 20.7 g. (0.3 mole) of sodium nitrite in 35 ml. of water was added dropwise. Stirring was continued for an additional hour, and the solution was made basic and then filtered to remove a small amount of solid material.

The filtrate was steam-distilled and the distillate was extracted with ether. The extracts were dried over calcium chloride, the ether was removed at the aspirator and the residue distilled at 0.15-mm. pressure; the entire amount distilled at 30–34°/0.15 mm. The distillate, wt. 14.5 g. (48.6%), gave a very vigorous reaction with concentrated sulfuric acid.

Anal. Calcd. for $C_7H_{13}N_3$: C, 60.40; H, 9.41. Found: C, 60.58; H, 9.64.

The solid which had been filtered from the basic solution weighed 2.62 g. and melted at 100–120°. Two recrystallizations from absolute alcohol gave 1.08 g. (4.3%), m.p. 144–147°, of *sym*-dihexahydrobenzylurea.

Anal. Calcd. for $C_{15}H_{28}ON_2$: C, 71.38; H, 11.18. Found: C, 71.21; H, 11.41.

Upon the addition of water to the mother liquors, a second solid was obtained. This material was recrystallized from ethanol-water to give a yellowish solid, m.p. 94° dec., weight 1.38 g. (3.5%), which gave a Liebermann nitroso test. Repeated recrystallization did not give an apparently pure sample.

Anal. Found: C, 55.35; H, 9.08; N, 21.64.

Hexahydrobenzyl azide–bicycloheptadiene adduct. This material was prepared in the same manner as the isobutyl azide adduct; the yield was 53%, m.p. 208–212°.

Anal. Calcd. for $C_{21}H_{34}N_6$: C, 68.07; H, 9.37. Found: C, 68.15; H, 9.37.

Hexahydrobenzyl azide–dicyclopentadiene adduct. A mixture of 5.0 g. (0.036 mole) of hexahydrobenzyl azide, 2.38 g. (0.018 mole) of dicyclopentadiene and 10 ml. of ether was allowed to stand for several days. Evaporation of the ether caused a white solid (2.30 g., 31.2%) to separate, m.p. 108–114° after washing with petroleum ether (b.p. 40–60°).

Anal. Calcd. for $C_{17}H_{25}N_3$: C, 75.23; H, 9.28. Found: C, 75.35; H, 9.17.

sym-Dihexahydrobenzylurea (1,3-biscyclohexanemethylurea). To a stirred suspension of 33.9 g. (0.3 mole) of hexahydrobenzylamine and 16.8 g. (0.3 mole) of potassium hydroxide in 100 ml. of water, was slowly added 17 g. (0.15 mole) of phosgene in 100 ml. of reagent benzene. The white solid which formed was filtered off, and a small additional amount was obtained by evaporating the benzene solution. The total yield of crude *sym*-dihexahydrobenzylurea was 21.2 g. (56.2%), m.p. 117–124°. Recrystallization from ethanol-water gave fine white platelets, m.p. 148–150°, undepressed when mixed with the *sym*-dihexahydrobenzylurea obtained from the hexahydrobenzyl azide preparation.

2-Ethylsemicarbazide. To a stirred suspension of 20 g. of zinc dust in 70 ml. of 50% acetic acid there was added dropwise a solution of 10 g. (0.085 mole) of *N*-nitroso-*N*-methylurea in 50 ml. of glacial acetic acid and 25 ml. of water. The temperature of the reaction was kept at about 20°

(11) O. Wallach, *Ann.*, **353**, 299 (1907).

during the addition, and then raised to 50–60° for 1 hr. The zinc dust was filtered from the hot solution, and the filtrate was made basic (dissolving all the zinc hydroxide) and extracted continuously with ether. After several days, the ether extract had precipitated 0.57 g. of a substance which melted at 97–103°. Recrystallization of 0.47 g. from ethylene glycol dimethyl ether gave 0.15 g., m.p. 105.5–107.5°, and a second crop weighing 0.05 g. By continuing the ether extraction, a total of 2.73 g. (31%) was obtained.

Anal. Calcd. for $C_3H_9ON_3$: C, 34.94; H, 8.80. Found: C, 35.02; H, 8.70.

Because of the difficulties of preparing sufficient quantities, this semicarbazide was not investigated further than the preparation of derivatives.

1-(p-Chlorobenzylidene-2-ethylsemicarbazide). A mixture of 0.1 g. (0.0085 mole) of 2-ethylsemicarbazide and 0.14 g. (0.001 mole) of *p*-chlorobenzaldehyde with 10 ml. of absolute alcohol was refluxed for 10 min., allowed to cool, and slowly diluted with water until needles formed. The crude, colorless product weighed 0.12 g. (63%), m.p. 153–154°. Recrystallization from the same solvents gave an analytical sample, m.p. 153.5–154°.

Anal. Calcd. for $C_{10}H_{12}ON_3Cl$: C, 53.20; H, 5.76. Found: C, 53.19; H, 5.48.

1-Benzylidene-2-ethylsemicarbazide. Ten grams of *N*-nitroso-*N*-ethylurea was reduced in the same manner as described above. Instead of the usual work-up, 10 g. of benzaldehyde was added to the filtered mixture and the flask was shaken on a mechanical shaker overnight. The solid which formed was filtered off and washed with water and a very small portion of ether; wt. 7.14 (44%), m.p. 135–139°. Recrystallization from alcohol-water gave fine white needles, m.p. 137.5–139°.

Anal. Calcd. for $C_{10}H_{13}ON_3$: C, 62.80; H, 6.85. Found: C, 62.80; H, 6.75.

1-Ethyl-1,2,3-triazole-4,5-dicarboxylic acid. A mixture of 4 g. (0.0565 mole) of ethyl azide,[12] 6.4 g. (0.0565 mole) of acetylenedicarboxylic acid and 10 ml. of ether was allowed to reflux under the heat of the reaction, and then heated on a steam bath for about 15 min. longer. Upon evaporation of the solvent, the hydrated triazole was obtained as a white solid, 7.57 g. (66%), which started to soften at 85° when heated slowly. Recrystallization from ether–petroleum ether mixture gave the anhydrous material, m.p. 106–109° (reported[13] 108–110°).

Benzophenone tert-butylhydrazone. A solution of 814 g. (4.18 moles) of diphenyldiazomethane[14] in 2 lb. of ether was slowly added with stirring to a solution of *tert*-butylmagnesium chloride, cooled by ice, prepared from 585 g. (6 moles) of *tert*-butyl chloride. Upon completion of the addition, the mixture was allowed to stand overnight; the red solution became nearly colorless and a yellow precipitate formed. The mixture was hydrolyzed with ammonium chloride and ice, the ether layer was separated, and the water layer was extracted twice with more ether. The combined ethereal layers were dried over calcium chloride and then evaporated. There remained 948 g. (87.5%) of benzophenone *tert*-butylhydrazone as a yellow solid, m.p. 68–72°. Recrystallization of a portion from alcohol gave light yellow needles, m.p. 73.5–75°.

Anal. Calcd. for $C_{17}H_{20}N_2$: C, 80.91; H, 7.99; N, 11.10. Found: C, 81.02; H, 7.79; N, 11.17.

tert-Butylhydrazine. Initial attempts to hydrolyze benzophenone *tert*-butylhydrazone with refluxing 20% or 50% hydrochloric acid gave only hydrazine hydrochloride, while distillation from 10% sodium hydroxide solution produced no volatile base of any kind.

A mixture of 7.0 g. of benzophenone *tert*-butylhydrazone, 10 ml. of concd. hydrochloric acid and 15 ml. of alcohol was allowed to stand at room temperature overnight. The alcohol was then evaporated in a stream of air, and the remainder was extracted twice with ether, diluted with 10 ml. of water, and again extracted twice with ether. The combined extracts were washed twice with water, and the washings were added to the ether-insoluble residue. Evaporation of the ethereal extracts gave 3.94 g. (78%) of benzophenone. The aqueous layers on evaporation left 2.07 g. (60%) of *tert*-butylhydrazine hydrochloride; recrystallization of a portion from alcohol gave colorless plates, m.p. 189° (reported m.p. 187°;[8] 191–192°[7]).

Free *tert*-butylhydrazine was obtained in 94% yield by distilling larger quantities of the hydrochloride from 25% sodium hydroxide solution, treating the distillate with successive portions of solid sodium hydroxide until a water layer no longer appeared, and distilling the dried material from barium oxide through a Podbielniak column. The colorless, pungent *tert*-butylhydrazine so obtained had b.p. 109°/749 mm., n_D^{25} 1.4270, and density 0.82264 at 25°, and evolved gas slowly when in contact with impurities. A boiling point of 129–134° has been reported[7] for alleged *tert*-butylhydrazine whose identity was not supported by analysis.

Anal. Calcd. for $C_4H_{12}N_2$: C, 54.50; H, 13.72; N, 31.78. Found: C, 54.31, 54.27; H, 13.73, 13.77; N, 31.55, 31.66.

Acetone tert-butylhydrazone. A mixture of 5.0 g. of *tert*-butylhydrazine and 6.6 g. of acetone, prepared with cooling, was allowed to stand for a short time, and ether and potassium hydroxide pellets were then added. The lower, aqueous layer was removed and fresh potassium hydroxide pellets were added; the procedure was repeated until no more water could be removed. The ethereal layer was then distilled from barium oxide to yield 5.41 g. (74%) of a colorless strong-smelling liquid, b.p. 132–134°.

Anal. Calcd. for $C_7H_{16}N_2$: C, 65.57; H, 12.58. Found: C, 65.68; H, 12.66.

Acetone N-tert-butyl-N-benzoylhydrazone. A mixture of 2.0 g. of acetone *tert*-butylhydrazone with 4.4 g. of benzoyl chloride was agitated with 15 ml. of 10% sodium hydroxide solution until the odor of benzoyl chloride was gone. The product was taken up in ether and dried over magnesium sulfate. Evaporation left 3.65 g. (100%) of a viscous, light yellow oil. Distillation at 0.1 to 0.15-mm. pressure gave without appreciable loss a colorless product, b.p. 100–103°, which soon crystallized. After recrystallization from aqueous methanol it had m.p. 70–70.5°.

Anal. Calcd. for $C_{14}H_{20}N_2O$: C, 72.30; H, 8.68. Found: C, 72.28; H, 8.90.

N-Benzoyl-N-tert-butylhydrazine. A solution of 0.5 g. of acetone *N-tert*-butyl-*N*-benzoylhydrazone in 3 ml. of 10% hydrochloric acid and 3 ml. of alcohol was allowed to stand at room temperature for 11 hr., and was then made basic with dilute sodium hydroxide. The alcohol was evaporated in an air stream, and the solid which separated was filtered off. It weighed 0.35 g. (85%), and had m.p. 117–123°. Recrystallization from aqueous alcohol gave an analytical sample, m.p. 131–132°.

Anal. Calcd. for $C_{11}H_{16}N_2O$: C, 68.72; H, 8.39. Found: C, 68.67; H, 8.34.

Nitrosation of N-benzoyl-N-tert-butylhydrazine. A solution of 1.33 g. of nitrogen tetroxide in 15 ml. of dioxane was chilled in a Dry Ice–alcohol bath, 2.4 g. of anhydrous sodium acetate was added and the mixture was allowed to warm to 0°. While this solution was being stirred, 0.8 g. of *N*-benzoyl-*N-tert*-butylhydrazine was added in portions, after which the mixture was kept at room temperature for 34 hr.

Distillation of the mixture then gave a 10-ml. fraction of b.p. 85–95° before dioxane began to distill. This fraction, which should have contained any *tert*-butyl azide, was added dropwise to 10 ml. of concd. sulfuric acid with stirring; gas

(12) E. Oliveri-Mandalá and G. Caronna, *Gazz. chim. ital.*, **71**, 182 (1941); H. Staudinger and E. Hauser, *Helv. Chim. Acta*, **4**, 861 (1921).

(13) F. von Bruckhausen and H. Hoffmann, *Ber.*, **74**, 1593 (1941).

(14) L. I. Smith and K. L. Howard, *Org. Syntheses*, Coll. Vol. III, 352 (1955).

was evolved. The mixture was then diluted with 30 ml. of water and distilled. Treatment of the distillate with 2,4-dinitrophenylhydrazine reagent solution gave an orange precipitate, which was purified by chromatography on an alumina column. Elution with benzene gave 0.08 g. (8.5%) of acetone dinitrophenylhydrazone, m.p. 115–120°, undepressed by mixture with an authentic sample. Furthermore, the infrared spectrum of this product was identical with that of an authentic sample.

Benzoic acid (0.33 g., 65%) was isolated from the higher boiling part of the dioxane solution and from the undistilled part of the sulfuric acid reaction mixture.

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Investigation of Some Dialkylamino Isocyanides[1]

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Some 3-dialkylaminopropylamines and 2-dialkylaminoethylamines have been converted to the corresponding isocyanides by the Hofmann synthesis. Neither hydroxyalkylamines nor *N,N*-dialkylhydrazines could be converted to isocyanides. In several Hofmann syntheses formamides were formed. *N*-Dialkylaminoalkylcarbonimidyl chlorides and 1-dialkylaminoalkyltetrazoles were prepared by treating the corresponding isocyanides with chlorine or hydrogen azide.

Isocyanides have been known for 90 years due to their discovery independently by Hofmann[2] and Gautier.[3] In that time two general syntheses have been developed: the action of silver cyanide on alkyl iodides,[2–5] and the action of alkali on a mixture of chloroform and an amine.[2,5–8] Aryl isocyanides with various functional groups on the benzene nucleus have been prepared, but no aliphatic isocyanides with other functional groups have yet been reported. This paper reports the synthesis and properties of a group of dialkylaminoalkyl isocyanides, and the attempted preparation of some hydroxyalkyl isocyanides and isocyanoamines by the known general methods.

The Hofmann synthesis was used successfully to prepare 3-diethylaminopropyl isocyanide (IIa), 3-dimethylaminopropyl isocyanide (IIb), and 2-diethylaminoethyl isocyanide (IIc) from the corresponding amines (Ia, b, c). The adaptation described by Malatesta[8] was found to be the most convenient for carrying out the reaction. The yields were low, and the products were accompanied by unreacted amine and tar.

$$\underset{\text{(I)}}{\text{R—NH}_2} \xrightarrow[\text{KOH}]{\text{CHCl}_3} \underset{\text{(II)}}{\text{R—NC}}$$

a, R = $(C_2H_5)_2NCH_2CH_2CH_2$—;
b, R = $(CH_3)_2NCH_2CH_2CH_2$—;
c, R = $(C_2H_5)_2NCH_2CH_2$—.

A black, tarry mass remained after the isocyanides and unreacted amines were distilled from the reaction mixtures. Attempts to remove any higher boiling component from the tar by further distillation resulted, in the case of IIa, only in extensive decomposition. However, from the tar obtained in the preparation of IIb there was obtained a small amount of impure carbonyl compound. Cuprous chloride successfully freed it from an isocyanide impurity by complex formation.[9] Comparison of the boiling point and infrared spectrum with those of 3-dimethylaminopropylformamide suggests that they are the same substance. Analysis, however, indicated an impurity low in nitrogen. This is also indicated by a comparison of the relative intensities of the C—H bond N—H stretching bands in the infrared with those of an authentic sample.

The Hofmann synthesis with 3-diethylaminopropylamine (Ia) and methanolic potassium hydroxide produced no isocyanide. Besides unreacted amine, there was isolated a small amount of high-boiling material, identified as 3-diethylaminopropylformamide (III) by analysis, infrared spectrum and comparison with an authentic sample.

$$\underset{\text{(Ia)}}{(C_2H_5)_2N(CH_2)_3NH_2} \xrightarrow{\text{CHCl}_3\ \text{KOH}} \underset{\text{(III)}}{(C_2H_5)_2N(CH_2)_3NHCHO}$$

No isocyanides were isolated when 1-amino-2-propanol or 3-aminopropanol were subjected to the Hofmann synthesis. In the latter case, however,

(1) This work was supported by the Chemical Corps, U. S. Army, under Prime Contract No. DA18-108-CML-5271, Subcontract 7, at the University of Michigan.

(2) A. Hofmann, *Ann.*, **144**, 114 (1867); **146**, 107 (1868).

(3) A. Gautier, *Ann. chim. et Phys.*, [4] **17**, 103 (1869).

(4) W. Schneidewind, *Ber.*, **21**, 1329 (1888); H. Guillemard, *Ann. chim. et phys.*, [8] **14**, 408 (1908).

(5) H. Lindemann and L. Wiegrebe, *Ber.*, **63B**, 1650 (1930).

(6) J. U. Nef, *Ann.*, **270**, 267 (1892).

(7) M. Passerini, *Gazz. chim. ital.*, **50II**, 340 (1920); M. Passerini and G. Banti, *Gazz. chim. ital.*, **58**, 636 (1928); D. Hammick, R. New, N. V. Sidgwick, and L. Sutton, *J. Chem. Soc.*, 1876 (1930); R. New and L. Sutton, *J. Chem. Soc.*, 1415 (1932); H. Dreyfus, U. S. Patent **2,347,772** (*Chem. Abstr.*, **39**, 89 (1945)).

(8) L. Malatesta, *Gazz. chim. ital.*, **77**, 238 (1947).

(9) F. Klages, K. Monkemeyer, and R. Heinle, *Ber.*, **85**, 109 (1952).

traces of an isocyanide were detected by infrared spectrum.

When methanolic potassium hydroxide was added to a chloroform solution of 3-aminopropanol, there was obtained a high-boiling compound tentatively identified as 3-hydroxypropylformamide (IV). The structural assignment is based on infrared data and the results of the analogous reaction of 3-diethylaminopropylamine. The Compound IV had only an amide carbonyl bond, at 1660 cm.$^{-1}$ (6.02 μ). An attempt to prepare an authentic sample of 3-

$$HO{-}(CH_2)_3{-}NH_2 \xrightarrow{CHCl_3,\ KOH} HO{-}(CH_2)_3{-}NHCHO \quad (IV)$$

hydroxypropylformamide (IV) by heating 3-aminopropanol with formic acid gave only 3-formamidopropyl formate. The infrared spectrum of the latter compound showed absorption due to both ester and amide carbonyl. Further investigation was precluded by the minute amount obtained and by our inability to repeat its preparation.

The formation of formamides during the Hofmann isocyanide synthesis must be parallel with and not subsequent to isocyanide formation, since isocyanides, once formed, are inert to alkaline conditions. If Nef's hypothesis is correct[10] that the formation of isocyanides proceeds through initial formation of dichlorocarbene, CCl_2, from chloroform, followed by addition to the amino group and hydrogen migration to give the structure R—NH—$CHCl_2$, the formation of formamides as side products can be accounted for by hydrolysis of the intermediate competing with dehydrohalogenation.

Neither *N*-aminopiperidine nor 1,1-bis(*p*-chlorophenyl)hydrazine gave isolable isocyanides when subjected to the Hofmann synthesis. This result is contrary to the report that *N*-aminopiperidine gives "the isocyanide reaction" with chloroform and potassium hydroxide.[11]

The preparation of *N*-aminopiperidine was accomplished by reducing *N*-nitrosopiperidine with lithium aluminum hydride according to the method reported by Poirier and Benington[12] for the reduction of *N*-nitrosodiphenylamine, and found to be superior to the reduction with zinc and acetic acid customarily used. The preparation of 1,1-bis(*p*-chlorophenyl)hydrazine followed the same path. *p,p'*-Dichlorodiphenylamine, required for its synthesis, was prepared by the Chapman rearrangement.[13]

Efforts to convert 2-iodoethanol and 3-iodopropanol to isocyanides by reaction with silver cyanide resulted only in tars.

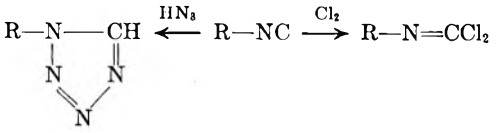
For detecting the presence of isocyanides in reaction mixtures, we found the color test of Pertusi and Gastaldi[14] useful, in which benzidine is oxidized to benzidine blue by cupric acetate when a suitable complexing agent is added. Since the test is not specific for the isocyanide function, confirmatory evidence was obtained by an examination of the infrared spectrum when possible; all of the isocyanides which we have prepared showed characteristic absorption at 2150 cm.$^{-1}$ (4.65 μ).

Samples of both 3-diethylaminopropyl and 3-dimethylaminopropyl isocyanides have been stored for weeks at room temperature in sealed ampoules without discoloring, but under identical conditions samples of 2-diethylaminoethyl isocyanide turned light yellow after one week.

Aromatic "isocyano dichlorides" (carbonimidyl chlorides) were prepared by Nef[6] by treating aromatic isocyanides with chlorine in cold chloroform solution. These compounds have been more conveniently prepared by the reaction of isothiocyanates with chlorine.[15] No aliphatic carbonimidyl chlorides have been reported before.

Passing a stream of chlorine through chloroform solutions of IIb and IIc resulted in the precipitation of rather pure *N*-(3-dimethylaminopropyl)carbonimidyl chloride and *N*-(2-diethylaminoethyl)carbonimidyl chloride. Both compounds are very hygroscopic. Treatment of 3-diethylaminopropyl isocyanide with either chlorine or bromine gave by contrast only gummy substances that could not be purified.

Isocyanides are known to give tetrazoles when treated with hydrogen azide.[16] Under such conditions, IIa, IIb, and IIc gave the corresponding 1-dialkylaminoalkyltetrazoles smoothly.



Tetrazoles are reported to have characteristic absorption in the 9 to 10 μ region of the infrared,[17] where they may have from one to three bands. The foregoing tetrazoles (as films) also absorb in this region, and each showed a band at 1100 cm.$^{-1}$ (9.08 μ), which is found in the spectra of the corresponding isocyanides. In addition, the tetrazoles showed absorption at 3100–3130 cm.$^{-1}$, which most

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(11) L. Knorr, *Ann.*, **221**, 299 (1883).

(12) R. Poirier and F. Benington, *J. Am. Chem. Soc.*, **74**, 3192 (1952).

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(16) (a) E. Oliveri-Mandalá, *Atti acad. Lincei*, **19I**, 228 (1910), *Chem. Abstr.*, **4**, 2455 (1910). (b) E. Oliveri-Mandalá, and B. Alagna, *Gazz. chim. ital.*, **40II**, 441 (1910). (c) F. G. Fallon and R. M. Herbst, *J. Org. Chem.*, **22**, 933 (1957). (d) F. G. Fallon, Ph.D. Thesis, Michigan State University, 1956.

(17) E. Lieber, D. Levering, and L. Patterson, *Anal. Chem.*, **23**, 1594 (1951).

likely is due to the C—H stretching frequency of the ring carbon (the usual C—H absorption was also present, at 2800–3000 cm.$^{-1}$). Somewhat similar observations have been reported by Herbst and Fallon.[16d]

Most samples of the foregoing tetrazoles also showed puzzling absorption at 2040 cm.$^{-1}$, although the samples were repeatedly distilled and gave correct analyses. These bands are undoubtedly due to impurities, however, for in one case the sample was obtained free of such absorption by careful cleaning of the distillation column immediately prior to collecting the reference cut; this technique was not successful with all samples. During the distillation of some of the crude samples of 1-(3-diethylaminopropyl)tetrazole, decomposition became evident at a bath temperature of 140° and a pressure of 0.3 mm., with concomitant distillation of a small amount of yellow, foamy, viscous liquid, prior to the actual distillation of the tetrazole fraction. The tetrazole which afterwards distilled was identical in all respects to the other samples, except for the absence of the 2040 cm.$^{-1}$ infrared absorption. This band is thus presumably due to an azide contaminant that can decompose during distillation.

EXPERIMENTAL[18]

Preparation of isocyanides. (*a*) *3-Diethylaminopropyl isocyanide* (IIa). A mixture of 40 g. of powdered potassium hydroxide and 100 ml. of benzene was placed in a 1-l. round-bottom flask equipped with a reflux condenser, drying tube, stirrer, and dropping funnel. The mixture was stirred and heated under reflux, and gradually a solution of 15.8 g. of 3-diethylaminopropylamine in 29 ml. of chloroform was added. At a point during the addition the reaction became violently exothermic. Heating was immediately discontinued, and the reaction was moderated but not quenched by cooling the mixture externally with ice water. The remainder of the chloroform solution was added at a rate to maintain vigorous refluxing, and the mixture was then allowed to stand until cool. It was then filtered, the brown, tarry precipitate was washed with benzene, and the washings were added to the filtrate. Solvent was removed, and further distillation gave a fraction of b.p. 87–107°/45 mm., and a tarry residue. Attempted further distillation of this residue at 1.0 mm. resulted only in decomposition. The distillate was redistilled to give 2.49 g. of 3-diethylaminopropylamine, 2.37 g. of mixture of b.p. 86–105°/45 mm., and 2.99 g. (20.5%) of 3-diethylaminopropyl isocyanide, b.p. 105–107°/45 mm. This product was a clear, colorless liquid having the typical isocyanide infrared absorption band at 2150 cm.$^{-1}$ (4.65 μ).

Anal. Calcd. for $C_8H_{16}N_2$: C, 68.51; H, 11.51; N, 19.98. Found: C, 68.67; H, 11.64; N, 20.06.

(*b*) *3-Dimethylaminopropyl isocyanide* (IIb). The reaction of a solution of 14.9 g. of 3-dimethylaminopropylamine in 29 ml. of chloroform with a mixture of 40 g. of powdered potassium hydroxide and 100 ml. of benzene was carried out as in (*a*) to give 2.10 of 3-dimethylaminopropylamine, 1.89 g. of mixture of b.p. 65–86°/55 mm., and 1.80 g. (11%) of 3-dimethylaminopropyl isocyanide, b.p. 86–88°/55 mm. This product was a clear, colorless liquid showing infrared absorption at 2150 cm.$^{-1}$

Anal. Calcd. for $C_6H_{12}N_2$: C, 64.23; H, 10.80; N, 24.97. Found: C, 64.19; H, 10.84; N, 25.04.

(*c*) *2-Diethylaminoethyl isocyanide* (IIc). A solution of 17.9 g. of 2-diethylaminoethylamine in 40 ml. of chloroform was treated with a mixture of 55 g. of powdered potassium hydroxide and 140 ml. of benzene as in (*a*), and gave 4.05 g. of 2-diethylaminoethylamine, 1.60 g. of fraction of b.p. 64–94°/45 mm., and 2.90 g. (14.8%) of diethylaminoethyl isocyanide, b.p. 94–95°/45 mm. The clear, colorless product gradually became yellow when stored at room temperature, even in a sealed ampoule; it showed infrared absorption at 2150 cm.$^{-1}$

Anal. Calcd. for $C_7H_{14}N_2$: C, 66.62; H, 11.18; N, 22.20. Found: C, 66.72; H, 11.20; N, 22.18.

3-Diethylaminopropylformamide. A solution of 11.2 g. of 3-diethylaminopropylamine in 20 ml. of chloroform and 20 ml. of methanol was prepared, and 40 g. of potassium hydroxide in 90 ml. of methanol was added over 0.5 hr.; the vigorous reaction which took place caused rapid refluxing. The mixture was then cooled and filtered, and the solid was washed with fresh methanol. The combined filtrates were concentrated by distillation until two layers became evident. The bottom layer was discarded, and the top layer was distilled to give 2.79 g. of recovered amine and 2.93 g. (22%) of 3-diethylaminopropylformamide, b.p. 110–114°/1.3–1.6 mm. A sample prepared for analysis had b.p. 116–118°/2 mm., and showed infrared absorption at 3250 cm.$^{-1}$ (N—H), 1540 cm.$^{-1}$ (N—H), and 1670 cm.$^{-1}$ (amide carbonyl).

Anal. Calcd. for $C_8H_{18}N_2O$: C, 60.72; H, 11.46; N, 17.71. Found: C 60.97; H, 10.84; N, 17.87.

This substance was identical in boiling point and infrared spectrum with a sample prepared by heating and distilling a mixture of 3-diethylaminopropylamine and excess formic acid, stirring the viscous distillate with ether and solid potassium hydroxide until the initially two liquid phases had become one, filtering, and redistilling.

Anal. Found: C, 60.77; H, 11.61; N, 17.74.

3-Dimethylaminopropylformamide. A mixture of 3-dimethylaminopropylamine and excess formic acid was heated for 1.5 hr., water and formic acid were removed by distillation, and the residue was mixed with ether (two phases) and stirred with powdered potassium hydroxide. Filtration and distillation gave a colorless liquid, b.p. 92–95° at 0.7 mm., showing infrared absorption at 3275, 1540, and 1665 cm.$^{-1}$

Anal. Calcd. for $C_6H_{14}N_2O$: C, 55.35; H, 10.84; N, 21.52. Found: C, 55.40; H, 10.67; N, 21.58.

A substance of identical boiling point was obtained from distillation of the pot-residue from the preparation of 3-dimethylaminopropyl isocyanide described herein. The crude distillate from an experiment with 26.8 g. of amine weighed 1.18 g., b.p. 84–88° at 0.3 mm. It was diluted with ether, stirred with cuprous chloride to remove isocyanide contamination, dried over sodium hydroxide, and distilled at 92–94° at 0.7 mm. for comparison. Although the infrared spectrum was identical with that of 3-dimethylaminopropylformamide, except for a difference in the relative intensities of the C—H and N—H stretching bands, the analysis was not in agreement; it was not further investigated.

Anal. Found: C, 57.30, 57.39; H, 10.39, 10.35.

Hofmann synthesis with 3-aminopropanol. When 11.0 g. of 3-aminopropanol was treated with chloroform and methanolic potassium hydroxide in the usual manner, there was recovered 1.86 g. of unreacted 3-aminopropanol-1, b.p. 112–113° at 40 mm. Further distillation gave a mixture showing spectral characteristics of both amide and isocyanide, wt. 0.8 g., b.p. 70° at 0.6 mm., and 1.90 g. of an oil, b.p. 142–146° at 0.7 mm., showing infrared absorption typical of amides at 1540 and 1660 cm.$^{-1}$ and O—H absorption at 3280 cm.$^{-1}$ The last substance may be 3-hydroxypropyl-

(18) All melting points are corrected. Infrared spectra of solids are of Nujol mulls, and of liquids are of thin films. Analyses are by Spang Microanalytical Laboratory, Ann Arbor.

formamide. Additional attempts to obtain more of these substances led only to recovered amino alcohol.

3-Formamidopropyl formate. A solution of 3-aminopropanol in excess formic acid was refluxed for 2 hr. and then distilled to remove water and formic acid. Further distillation gave a colorless, viscous distillate of b.p. 132–134°/0.7 mm. and showing infrared absorption at 3280, 1665, and 1720 cm.$^{-1}$, consistent with the presence of N—H, ester carbonyl, and amide carbonyl.

Anal. Calcd. for $C_5H_9NO_3$: C, 45.79; H, 6.92; N, 10.86. Found: C, 46.05; H, 7.15; N, 10.67.

N-Formamidopiperidine. A solution of 23.5 g. of *N*-aminopiperidine[11] in excess formic acid was refluxed for 2 hr., and formic acid and water were removed by distillation. Further distillation gave 19.9 g. (70%) of an oil, b.p. 111–114°/1 mm., which soon solidified to a white solid, m.p. 75–77.5°. An analytical sample, m.p. 77–78°, was obtained by several recrystallizations from petroleum ether.

Anal. Calcd. for $C_6H_{12}N_2O$: C, 56.22; H, 9.45; N, 21.86. Found: C, 56.28; H, 9.42; N, 21.79.

Attempts to convert *N*-formamidopiperidine to an isocyanide by dehydration *via* the imidyl chloride, using phosphoryl chloride with excess pyridine or triethylamine, were completely unsuccessful.

N-p-Chlorophenylbenzimidyl chloride.[19] This compound was prepared according to a procedure reported for *N*-phenylbenzimidyl chloride.[20] The crude product was a pale green oil which solidified when chilled in an ice bath. It was dissolved in ether and used directly for the preparation of its *p*-chlorophenyl ester.

p-Chlorophenyl N-p-Chlorophenylbenzimidate. To 20 ml. of absolute alcohol was added 1.21 g. of sodium. The solution was cooled and 6.8 g. of *p*-chlorophenol was added. An ethereal solution of the imidyl chloride prepared from 4.5 g. of benz-*p*-chloroanilide was then added. The mixture was stirred for several hours after the initial boiling had subsided, and was then filtered. Distilling the ether from the filtrate and chilling the residue gave 4.3 g. (64%) of pale yellow rods, m.p. 70–72°; Chapman[13] reports 68–69°.

N,N-Bis(p-chlorophenyl)benzamide and p,p'-Dichlorodiphenylamine. By the general method of Chapman,[21] 13.9 g. of *p*-chlorophenyl *N-p*-chlorophenylbenzimidate was rearranged to the diarylbenzamide, which on recrystallization from ethanol gave 10.8 g. (78%) of product, m.p. 155–156°. Claus and Schaare[22] prepared this compound by chlorination of *N,N*-diphenylbenzamide, and reported m.p. 153–154°; in our hands their method was unsuccessful.

Hydrolysis of 16.6 g. of the foregoing *N,N*-bis(*p*-chlorophenyl)benzamide by the method of Chapman[23] and recrystallization of the crude product from petroleum ether gave 10.8 g. (94%) of long, straw colored needles, m.p. 79–81°. Chapman reports 78–79°.[13]

N-Nitrosobis(p-chlorophenyl)amine. Dichlorodiphenylamine was nitrosated by the procedure reported by Fischer for nitrosating diphenylamine.[24] The initially oily product solidified when agitated and chilled; dilution of the reaction mixture with water caused a further amount to precipitate. The yellow solid was collected, washed with water, dried in air, and crystallized from petroleum ether (b.p. 60–75°) to give yellow plates, m.p. 81–82°, in yields of about 95% in several trials.

Anal. Calcd. for $C_{12}H_8N_2OCl_2$: C, 53.96; H, 3.02. Found: C, 54.19; H, 3.09.

1,1-Bis(p-chlorophenyl)hydrazine. *N*-Nitroso-*p,p'*-dichlorodiphenylamine was reduced by the procedure used by Poirier and Benington[12] with *N*-nitrosodiphenylamine. From 10 g. of nitroso compound in 50 ml. of dry ether and a slurry of 2.0 g. of lithium aluminum hydride in 75 ml. of ether, the desired hydrazine was obtained and isolated as its hydrochloride, dec. 158°. The free hydrazine was obtained by stirring a mixture of the hydrochloride, aqueous sodium hydroxide, and ether until no more undissolved hydrochloride was present, extracting the aqueous layer with ether, and evaporating the combined extracts on a steam bath. A white, crystalline mass was obtained on cooling. Recrystallization from petroleum ether (60–75°) gave white needles, m.p. 92.5–94°, in yields of about 70% in several trials. Infrared absorption occurred at 3200 and 3500 cm.$^{-1}$

Anal. Calcd. for $C_{12}H_{10}N_2Cl_2$: C, 56.94; H, 4.27; N, 11.07. Found: C, 57.21; H, 4.05; N, 11.26.

The compound formed a *benzoyl derivative*, m.p. 219–219.5° from benzene; decomposition, as evidenced by a pink discoloration, began shortly after preparation, and may have affected the analysis.

Anal. Calcd. for $C_{15}H_{14}N_2Cl_2$: C, 63.87; H, 3.95. Found C, 63.36; H, 3.82.

With acetone, the hydrazine gave *acetone bis-(p-chlorophenyl)hydrazone*, m.p. 79–79.5° from petroleum ether (b.p. 60–75°).

Anal. Calcd. for $C_{15}H_{14}N_2Cl_2$: C, 61.45; H, 4.81; N, 9.56. Found: C, 61.74; H, 4.82; N, 9.55.

2,2-Bis(p-chlorophenyl)formhydrazide. A mixture of 1,1-bis(*p*-chlorophenyl)hydrazine and excess 98% formic acid was refluxed for 2 hr. Cooling caused precipitation of the product, which was washed with water, air-dried, and recrystallized from benzene to give a fluffy matted mass of white rods, m.p. 212.5–213°. Attempts to convert this compound to an isocyanide *via* the imidyl chloride by reaction with phosphoryl chloride and pyridine or triethylamine were unsuccessful.

Anal. Calcd. for $C_{13}H_{10}N_2OCl_2$: C, 55.54; H, 3.59; N, 9.97. Found: C, 55.53; H, 3.50; N, 10.00.

N-(3-Dimethylaminopropyl)carbonimidyl dichloride. A solution of 1.44 g. of 3-dimethylaminopropyl isocyanide in 11 ml. of chloroform was well cooled in an ice bath, and a stream of chlorine was bubbled through until the solution was yellow. The resulting precipitate was filtered off, dried in air for an hour, and then *in vacuo*, to give 1.45 g. (62%) of a white, electrostatically charged powder, m.p. 130.5–132°. It was very hygroscopic.

Anal. Calcd. for $C_6H_{12}N_2Cl_2$: C, 39.36; H, 6.61; N, 15.30. Found: C, 39.48; H, 6.76; N, 15.41.

N-(2-Diethylaminoethyl)carbonimidyl dichloride. A solution of 4.10 g. of 2-diethylaminoethyl isocyanide in 30 ml. of chloroform was well cooled in an ice bath, and a stream of chlorine was passed through until saturation. The resulting precipitate was collected, washed with cold chloroform, dried in air for an hour and then *in vacuo* to give 4.06 g. (64%) of a white solid, m.p. 117–119°. After recrystallization from chloroform it had m.p. 120–122° and was very hygroscopic.

Anal. Calcd. for $C_7H_{14}N_2Cl_2$: C, 42.65; H, 7.15; N, 14.22. Found: C, 42.71; H, 7.31; N, 14.26.

1-(3-Diethylaminopropyl)tetrazole. A solution of 6.7 g. of 3-diethylaminopropyl isocyanide in 40 ml. of benzene was cooled in an ice bath, and 60 ml. of a 10% solution of hydrogen azide in benzene was added gradually. After standing overnight, the mixture had separated into two layers. The upper layer was decanted and discarded, and the lower was distilled to give 4.8 g. (55%) of a yellow liquid, b.p. 150–153° at 0.8 mm. Redistillation gave a colorless sample, b.p. 135–138° at 0.3 mm., that burned in a flame with sputtering.

Anal. Calcd. for $C_8H_{17}N_5$: C, 52.43; H, 9.35; N, 38.22. Found: C, 52.47; H, 9.22; N, 38.26.

1-(3-Dimethylaminopropyl)tetrazole. In the manner just described, 5.0 g. of 3-dimethylaminopropyl isocyanide gave 4.2 g. (61%) of tetrazole in the form of a colorless liquid, b.p. 116–120° at 0.2 mm., that burned in a flame with sputtering.

(19) H. Lev, *Ber.*, **31**, 241 (1898).

(20) O. Wallach and M. Hoffmann, *Ann.*, **184**, 79 (1877).

(21) A. W. Chapman, *J. Chem. Soc.*, 1743 (1927).

(22) A. Claus and H. Schaare, *Ber.*, **15**, 1285 (1882).

(23) A. W. Chapman, *J. Chem. Soc.*, 569 (1929).

(24) E. Fischer. *Ann.*, **190**, 174 (1878); A. Lachman, *Ber.*, **33**, 1022 (1900).

Anal. Calcd. for $C_6H_{13}N_5$: C, 46.43; H, 8.44; N, 45.13. Found: C, 46.36; H, 8.51; N, 45.17.

1-(2-Diethylaminoethyl)tetrazole. In the manner just described, 12.2 g. of 2-diethylaminoethyl isocyanide was treated with hydrogen azide; the reaction mixture stayed as one phase. The benzene and excess hydrogen azide were distilled off, and further distillation gave 11.2 g. (69%) of a pale yellow liquid, b.p. 128–132° at 0.3 mm.

Anal. Calcd. for $C_7H_{15}N_5$: C, 49.68; H, 8.93; N, 41.39. Found: C, 49.43; H, 8.67; N, 41.53.

ANN ARBOR, MICH.

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

Some Diazine-*N*-oxides[1]

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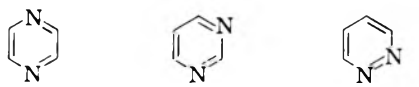
Preparations of mono- and di-*N*-oxides of pyrazine, 2-methylpyrazine, and 2,5-dimethylpyrazine, and of mono-*N*-oxides of pyrimidine and pyridazine are described. The oxides of methylated pyrazines undergo normal Boekelheide rearrangement with acetic anhydride, forming acetoxymethylpyrazines, but all of the oxides were resistant to nitration. A strong absorption at 1230–1325 cm.$^{-1}$ appears to be characteristic of the *N*-oxide function.

Heteroaromatic *N*-oxides have been studied extensively in recent years,[2] but little is known about the *N*-oxides of simple diazines.[3] Preparations and a few reactions of some of these substances are described in the present paper.



I II III

Pyrazine (I), 2-methylpyrazine, and 2,5-dimethylpyrazine yielded mainly mono-oxides when treated with one equivalent of hydrogen peroxide in hot acetic acid. As expected, two isomeric mono-oxides of 2-methylpyrazine were formed. In each preparation, small amounts of the corresponding dioxides were also produced, and these compounds were obtained in good yields when excess hydrogen peroxide was used.

Pyrimidine (II) was destroyed by hydrogen peroxide in hot acetic acid, but at room temperature it furnished 6.5% of its mono-oxide (m.p. 95–96°) together with 2.5% of 4(3) pyrimidone; a di-oxide could not be obtained. The yield (11%) and m.p. (85–88°) of pyrimidine mono-oxide reported recently[3j] were not duplicated, but the product obtained in the present work had the same infrared absorption as that described.

Pyridazine (III) gave only a mono-oxide, the best yield being obtained by oxidation at room temperature

2,5-Dimethylpyrazine mono-oxide formed 1:1 addition products with hydrogen chloride, methyl iodide, or benzyl chloride. Spectral studies did not permit a definite decision as to the point of attachment of the electrophilic reagent, but basification of the benzyl chloride adduct gave no benzaldehyde, indicating that salt formation had involved the unoxidized nitrogen atom. A similar conclusion regarding salt formation was reached by Landquist[3h] in his study of quinoxaline mono-oxide.

2,5-Dimethylpyrazine mono-oxide reacted with acetic anhydride to form 2-acetoxymethyl-5-methylpyrazine, the product expected by analogy with Boekelheide's work in the pyridine series.[4] The same substance, together with 2,5-bisacetoxymethylpyrazine was obtained from 2,5-dimethylpyrazine dioxide. 2-Acetoxymethyl-5-methylpyrazine dioxide was partly deoxidized by acetic anhydride giving 2,5-bisacetoxymethylpyrazine and its mono-oxide and 2-acetoxymethyl-5-methylpyrazine mono-oxide.

Assignment of structures to the two isomeric mono-oxides of 2-methylpyrazine was based on reactions with acetic anhydride. 2-Methylpyrazine-1-oxide (m.p. 43–45°) gave an acetate saponified to 2-hydroxymethylpyrazine, which showed strong broad —OH absorption at 3300 cm.$^{-1}$ 2-Methylpyrazine-4-oxide (m.p. 91–92°) gave an acetate saponified to 5-methyl-2(1)-pyrazinone, showing weak absorption at 1660 cm.$^{-1}$

Corresponding to observations of Adams and Miyano[5] in the pyridine series, 2,5-dimethylpyra-

(1) From the Ph.D. thesis of W. H. Gunprecht, July 1957.

(2) C. C. J. Culvenor, *Revs. Pure and Appl. Chem.* (*Australia*), **3**, 83 (1953); E. Ochiai, *J. Org. Chem.*, **18**, 534 (1953); A. R. Katritzky, *Quart. Revs.*, **10**, 395 (1956); M. Colonna, *Bull. sci. soc. chim. ind. Bologna*, **15**, 1 (1957).

(3) (a) E. Ochiai, M. Ishikawa, and S. Zai-Ren, *J. Pharm. Soc. Japan*, **65**, 73 (1945); (b) G. T. Newbold and F. S. Spring, *J. Chem. Soc.*, 1183 (1947); (c) R. A. Baxter, G. T. Newbold, and F. S. Spring, *J. Chem. Soc.*, 1859 (1948); (d) W. Sharp and F. S. Spring, *J. Chem. Soc.*, 932 (1951); (e) G. T. Newbold, W. Sharp, and F. S. Spring, *J. Chem. Soc.*, 2679 (1951); (f) E. Ochiai and H. Yamonaka, *Pharm. Bull.* (*Tokyo*), **3**, 175 (1955); (g) W. F. Beech, *J. Chem. Soc.*, 3094 (1955); (h) J. K. Landquist, *J. Chem. Soc.*, 1885 (1956); (i) G. Karmas and P. E. Spoeri, *J. Am. Chem. Soc.*, **78**, 4071 (1956); (j) R. H. Wiley and S. C. Slaymaker, *J. Am. Chem. Soc.*, **79**, 2233 (1957).

(4) V. Boekelheide and W. J. Linn, *J. Am. Chem. Soc.*, **76**, 1286 (1954).

(5) R. Adams and S. Miyano, *J. Am. Chem. Soc.*, **76**, 3168 (1954).

zine dioxide reacted with benzaldehyde in presence of sodium hydroxide, whereas dimethylpyrazine itself was not affected; the product was 2,5-distyrylpyrazine dioxide. Strangely, 2,5-dimethylpyrazine mono-oxide yielded 2,5-distyrylpyrazine mono-oxide, and no evidence for superior reactivity of one of the methyl groups was obtained.

Nitration of 2,5-dimethylpyrazine dioxide could not be accomplished. The compound was recovered quantitatively after it had been kept for one hour at 50° with sodium nitrate in excess sulfuric acid; and 75% of it was recovered after 16 hr. at 70° with the same reagent.

Infrared absorption of *N*-oxides has been found by Clemo and Daglish[6] in the regions 1350–1390 and 1040–1090 cm.$^{-1}$, whereas Sartori, Costa, and Blasina[7] found it in the region 1240–1310 cm.$^{-1}$ Observations in the present work agree with the latter assignment only. All of the oxides examined showed an absorption band, usually strong, at 1230–1325 cm.$^{-1}$, which was absent in the spectrum of the parent diazine.

EXPERIMENTAL

Pyrazine mono-oxide. A solution of 14.2 g. of 30% hydrogen peroxide in 100 ml. of acetic acid was added dropwise during 2.5 hr. to a solution of 10 g. of pyrazine in 125 ml. of acetic acid at 70–80°. Heating was continued for about 5 hr. or until starch-iodide showed no peroxide. Acetic acid was then removed by distilling at 100° under reduced pressure, adding 200 ml. of water, and repeating the distillation. The residue was dissolved in 500 ml. of hot chloroform and dried with a mixture of sodium sulfate and sodium carbonate. Concentration of the solution to 150 ml. gave a small amount of crude dioxide, and more of this (0.6 g.) was obtained by exhaustive extraction of the drying agents.

Evaporation of the chloroform left 8.6 g. of crude mono-oxide, and recrystallization from benzene gave the pure compound; colorless needles, m.p. 113–114°; strong absorption at 1305 cm.$^{-1}$ ($CHCl_3$).

Anal. Calcd. for $C_4H_4N_2O$: C, 50.0; H, 4.2; N, 29.16. Found: C, 50.3; H, 4.2; N, 28.4.

Pyrazine dioxide. Oxidation of 5 g. of pyrazine in 40 ml. of acetic acid with 14.3 g. of 30% hydrogen peroxide at 70° for 24 hr. gave 6.3 g. of crude solid product. Soxhlet extraction with 60–68° ligroin removed 2.76 g. of mono-oxide, and crystallization of the residue gave 2.97 g. of pure dioxide, colorless needles from methanol, m.p. 285–295°; strong absorption at 1270 cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_4H_4N_2O_2$: C, 42.8; H, 3.6; N, 25.0. Found: C, 42.7; H, 3.7; N, 24.6.

2-Methylpyrazine oxides. Oxidation of 22.5 g. of 2-methylpyrazine in 275 ml. of acetic acid with 26 g. of 35% hydrogen peroxide at 70–80° for 8 hr. gave 24 g. of yellow oil which slowly crystallized. Soxhlet extraction with 30–40° ligroin left 2.2 g. of crude 2-methylpyrazine dioxide which was purified by sublimation at 140° and 0.1 mm. It formed colorless needles, m.p. 230–231°; strong absorption at 1260 cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_5H_6N_2O_2$: C, 47.6; H, 4.8; N, 22.2. Found: C, 47.8; H, 4.8; N, 22.1.

Evaporation of the ligroin extract left 18.7 g. of mixed mono-oxides. These were separated by fractional distillation followed by crystallization from ether. The first fraction (9.15 g., b.p. 114–116° at 7 mm.) gave 4.85 g. of *2-methylpyrazine-4-oxide;* large colorless prisms, m.p. 91–92°; strong absorption at 1300 cm.$^{-1}$ ($CHCl_3$).

Anal. Calcd. for $C_5H_6N_2O$: C, 54.5; H, 5.5. Found: C, 54.5; H, 5.6.

The second fraction (4.9 g., b.p. 109–110° at 5 mm.) was combined with the material in the mother liquor from the 4-oxide and crystallized several times, giving 5.7 g. of *2-methylpyrazine-1-oxide,* fine needles, m.p. 43–45°; strong absorption at 1305 cm.$^{-1}$ ($CHCl_3$). A mixture of the isomeric mono-oxides had m.p. 41–85°.

Anal. Calcd. for $C_5H_6N_2O$: C, 54.5; H, 5.5; N, 25.4. Found: C, 54.5; H, 5.4; N, 25.2.

Reaction of 2-methylpyrazine-1-oxide with acetic anhydride. A mixture of 3.6 g. of the oxide with 10 ml. of acetic anhydride was boiled for 30 min. and then kept at room temperature for 3 days. Evaporation at 100° under reduced pressure left a viscous black residue which was distilled at 10 mm., giving 2.9 g. of an orange oil. A solution of this crude acetate in 30 ml. of 10% sodium hydroxide was kept under nitrogen for three days, then neutralized with carbon dioxide and evaporated. Extraction with chloroform and distillation gave 1.7 g. of 2-hydroxymethylpyrazine, a colorless oil, b.p. 64–66° at 0.3 mm. The ultraviolet spectrum (95% alcohol) had bands at 2200 Å, ϵ = 4200, and 2650 A, ϵ = 7300, with a shoulder at about 3000 Å, ϵ = 1100.

Anal. Calcd. for $C_5H_6N_2O$: C, 54.5; H, 5.5. Found: C, 54.7; H, 5.7.

Reaction of 2-methylpyrazine-4-oxide with acetic anhydride. A mixture of 4.5 g. of the oxide with 10 ml. of acetic anhydride was processed as described for the isomeric oxide. There was obtained 3.0 g. of crude distilled acetate, and hydrolysis of this gave 1.9 g. of 5-methyl-2(1)-pyrazinone, colorless needles from ether, m.p. 68–69°. The compound gave no color with ferric chloride; its ultraviolet spectrum (95% alcohol) had bands at 2220 Å, ϵ = 13000, and 2700 Å, ϵ = 12600.

Anal. Calcd. for $C_5H_6N_2O$: C, 54.5; H, 5.5. Found: C, 54.6; H, 5.7.

2,5-Dimethylpyrazine mono-oxide. A solution of 132 g. of 2,5-dimethylpyrazine and 132 ml. of 30% hydrogen peroxide in 3 liters of acetic acid was kept at 70–80° for 9 hr. and then evaporated under reduced pressure. Soxhlet extraction of the residue with 60–68° ligroin left a small amount of insoluble dioxide; the soluble part was recrystallized from 2-propanol giving 90 g. of the mono-oxide, colorless needles, m.p. 105–106° (reported[3b] 105–108°); strong absorption at 1285 cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_6H_8N_2O$: C, 58.0; H, 6.5; N, 22.6. Found: C, 58.1; H, 6.6; N, 22.5.

Evaporation of a solution of the mono-oxide in concentrated hydrochloric acid left 2,5-dimethylpyrazinium chloride *N*-oxide, which had m.p. 166–168° after repeated crystallization from alcohol. The spectrum (Nujol) had strong bands at 1900, 2000, 2200, and 2300 cm.$^{-1}$ similar to those of 2,5-dimethylpyrazinium chloride, and one at 1800 cm.$^{-1}$

Anal. Calcd. for $C_6H_9ClN_2O$: C, 44.9; H, 5.7; N, 17.4. Found: C, 45.4; H, 5.9; N, 17.3.

The spectrum of *N*-hydroxy-4-picolinium chloride (colorless needles from alcohol; m.p. 120–122°; found: C, 49.7; H, 5.5; N, 9.4; C_6H_8ClNO requires: C, 49.5; H, 5.5; N, 9.6) had a broad strong band at 1700–2500 cm.$^{-1}$, not at all similar to the two spectra referred to above.

1,2,5-Trimethylpyrazinium iodide N-oxide, obtained in 71% yield from 18 g. of the mono-oxide and 21 g. of methyl iodide in 30 ml. of dimethylformamide, formed yellow plates from alcohol, dec. 234–237°.

Anal. Calcd. for $C_7H_{11}INO_2$: C, 31.6; H, 4.2; N, 10.6. Found: C, 31.8; H, 4.4; N, 10.8.

1,2,5-Trimethylpyrazinium chloride N-oxide, from the iodide with silver chloride in water, formed colorless plates from alcohol-ether, dec. 190°.

(6) G. R. Clemo and A. F. Daglish, *J. Chem. Soc.,* 1481 (1950).

(7) G. Sartori, G. Costa, and P. Blasina, *Gazz. chim. ital.,* 85, 1085 (1955).

Anal. Calcd. for $C_7H_{11}ClN_2O$: C, 48.2; H, 6.4; N, 16.0. Found: C, 48.0; H, 6.7; N, 15.9.

The methochloride-oxide was recovered unchanged after 8 hr. treatment with excess hydrogen peroxide in acetic acid at 80°.

1-Benzyl-2,5-dimethylpyrazinium chloride N-oxide, from the mono-oxide and excess benzyl chloride, kept at 60° for one week, formed colorless plates from alcohol, dec. 210–220°. No benzaldehyde was formed when this salt was warmed with aqueous alkali.

Anal. Calcd. for $C_{13}H_{15}ClN_2O$: C, 62.2; H, 6.0; N, 11.2. Found: C, 62.3; H, 6.1; N, 11.2.

Attempted nitration of 1 g. of 2,5-dimethylpyrazine mono-*N*-oxide in 5 ml. of sulfuric acid containing 0.7 g. of sodium nitrate by heating for 1 hr. at 70° gave back 0.92 g. of unchanged oxide. Using 1.4 g. of sodium nitrate and prolonging the heating to 14 hr. gave back 0.7 g. of oxide.

2,5-Distyrylpyrazine mono-N-oxide was obtained in a yield of 20% when a mixture of 5 g. of 2,5-dimethylpyrazine mono-oxide, 4.3 g. of benzaldehyde, one ml. of 5% sodium hydroxide, and 50 ml. of alcohol was kept at 60–70° for one week under nitrogen. It formed yellow needles from acetic acid, m.p. 243–245°. A mono-styryl derivative could not be isolated from this or several other experiment using piperidine or triethylamine as catalysts.

Anal. Calcd. for $C_{20}H_{16}N_2O$: C, 80.0; H, 5.4; N, 9.3. Found: C, 79.7; H, 5.5; N, 9.2.

Reaction of 2,5-dimethylpyrazine mono-N-oxide with acetic anhydride. A mixture of 50 g. of the oxide with 100 ml. of acetic anhydride was warmed under reflux until vigorous reaction started, and after this was over the black mixture was boiled for 1 hr. Acetic acid and anhydride were then removed under reduced pressure and the residue was distilled, giving 24 g. of light yellow oil and a carbonaceous residue. Redistillation gave mainly 2-acetoxymethyl-5-methylpyrazine, b.p. 70–71°, at 0.4 mm.; n_D^{25} 1.5057.

Anal. Calcd. for $C_8H_{10}N_2O_2$: C, 57.8; H, 6.1; N, 16.9. Found: C, 57.5; H, 6.1; N, 17.0.

Saponification of 1 g. of the ester with 10 ml. of 10% sodium hydroxide under nitrogen at room temperature for two days, and exhaustive extraction with ether gave 2-hydroxymethyl-5-methylpyrazine; purified by microdistillation at 0.5 mm., the compound had m.p. 36–39°.

Anal. Calcd. for $C_6H_8N_2O$: C, 58.0; H, 6.5; N, 22.6. Found: C, 58.0; H, 6.6; N, 22.6.

2-Acetoxymethyl-5-methylpyrazine di-N-oxide was obtained in 80% yield when a solution of 3 g. of 2-acetoxymethyl-5-methylpyrazine and 5 ml. of 30% hydrogen peroxide in 30 ml. of acetic acid was kept at 80° for 10 hr. It formed colorless plates from alcohol, m.p. 242–243°.

Anal. Calcd. for $C_8H_{10}N_2O_4$: C, 48.5; H, 5.1; N, 14.1. Found: C, 48.3; H, 5.3; N, 141.1

Hydrolysis of the ester with 0.1% sulfuric acid by keeping under nitrogen for one month gave 55% of 2-hydroxymethylpyrazine di-*N*-oxide, colorless plates from alcohol, m.p. 226–228°.

Anal. Calcd. for $C_6H_8N_2O_3$: C, 46.2; H, 5.2; N, 17.9. Found: C, 46.6; H, 5.2; N, 17.9.

Reaction of 2-acetoxymethyl-5-methylpyrazine di-N-oxide with acetic anhydride. A mixture of 31.5 g. of the dioxide with 53 ml. of acetic anhydride was treated in the same way as described for the mono-oxide acetylation. The crude distillate (23.7 g.) crystallized when it was cooled. Recrystallization from alcohol gave 5.3 g. of *2,5-diacetoxymethylpyrazine mono-N-oxide*, colorless needles, m.p. 113–114°.

Anal. Calcd. for $C_{10}H_{12}N_2O_5$: C, 50.0; H, 5.0; N, 11.7. Found: C, 50.0; H, 5.3; N, 11.9.

Redistillation of the material in the alcoholic mother liquor followed by chromatography on alumina gave 1.2 g. of 2,5-diacetoxymethylpyrazine, m.p. 80–81° (see below) and 1.1 g. of a *mono-N-oxide of 2-acetoxymethyl-5-methylpyrazine*, colorless needles from ether, m.p. 96–97°.

Anal. Calcd. for $C_8H_{10}N_2O_3$: C, 52.7; H, 5.5; N, 15.4. Found: C, 53.4; H, 5.7; N, 15.2.

Confirmation for the structure as a mono-oxide was found in the observation that oxidation with hydrogen peroxide in hot acetic acid gave the dioxide m.p. 242–243° also obtained in a different way as described above.

2,5-Dimethylpyrazine di-N-oxide. This substance was obtained in 90% yield by the method of Newbold and Spring.[3b] It was not changed when it was kept at 70° for one week with methyl iodide alone or in dimethyl formamide. It did not react with phenylmagnesium bromide even in hot anisole. It was recovered nearly quantitatively when attempts to nitrate it were made.

When a mixture of 5 g. of the dioxide, 7.6 g. of benzaldehyde, 1 ml. of 5% sodium hydroxide, and 50 ml. of alcohol was kept under nitrogen for three days, there was formed 7.5 g. of *2,5-distyrylpyrazine* di-*N*-oxide, yellow needles from acetic acid, dec. 284–287°.

Anal. Calcd. for $C_{20}H_{16}N_2O_2$: C, 75.9; H, 5.1; N, 8.9. Found: C, 75.8; H, 5.2; N, 8.6.

Distyrylpyrazine dioxide (0.5 g.) boiled in chloroform with 2 ml. of phosphorus trichloride gave 0.3 g. of distyrylpyrazine, yellow plates from benzene, m.p. 218–219° (reported[8] 218–219°). It was found that the compound was converted into a colorless insoluble polymer (?) dec. 331–333° when the solid was exposed for a few hours to ultraviolet light. The polymer was analyzed without purification.

Anal. Calcd. for $(C_{20}H_{16}N_2O_2)$: C, 75.9; H, 5.1; N, 8.9. Found: C, 75.8; H, 5.2; N, 8.6.

Reaction of 2,5-dimethylpyrazine di-N-oxide with acetic anhydride. A mixture of 20 g. of the dioxide with 48 g. of acetic anhydride reacted vigorously and became black when it was heated. It was boiled for 1 hr. and then distilled, giving 15.2 g. of light yellow oil and a carbonaceous residue. Fractionation of the oil gave 3.25 g. of 2-acetoxymethyl-5-methylpyrazine, b.p. 70–72° at 0.3 mm., and 4.92 g. of *2,5-diacetoxymethylpyrazine*, b.p. 123–124° at 0.5 mm., the latter formed colorless plates from ether, m.p. 80–81°.

Anal. Calcd. for $C_{10}H_{12}N_2O_4$: C, 53.6; H, 5.4; N, 12.5. Found: C, 53.5; H, 5.4; N, 12.7.

The diacetoxy compound was saponified when its solution in 10% sodium hydroxide was kept under nitrogen for one week. Exhaustive extraction with ether gave *2,5-dihydroxymethylpyrazine*, colorless needles from chloroform, m.p. 88–89°.

Anal. Calcd. for $C_6H_8N_2O_2$: C, 51.4; H, 5.8; N, 20.0. Found: C, 51.5; H, 6.0; N, 19.9.

Pyrimidine mono-N-oxide. A solution of 6.5 g. of pyrimidine and 9.3 g. of 30% hydrogen peroxide in 150 ml. of acetic acid was kept at room temperature for 15 days and then evaporated under reduced pressure. The oily residue was basified with dilute sodium carbonate (ammonia evolution), evaporated again, and extracted with chloroform in a Soxhlet. Evaporation of the chloroform left a partly crystalline residue which was extracted with hot cyclohexane. The insoluble part (0.2 g.) was 4(3) pyrimidone, m.p. 165–166° (reported[9] 163–165°) and showed an infrared spectrum identical with that reported[10] for this substance. The soluble part (0.5 g.), was pyrimidine mono-*N*-oxide, colorless needles from cyclohexane, m.p. 95–96°; strong absorption at 1260 cm.$^{-1}$ ($CHCl_3$).

Anal. Calcd. for $C_4H_4N_2O$: C, 50.0; H, 4.2; N, 29.2. Found: C, 49.7; H, 4.2; N, 28.9.

Pyridazine mono-N-oxide. A solution of 10.2 g. of pyridazine and 14.5 g. of 30% hydrogen peroxide in 250 ml. of acetic acid was kept at room temperature for four weeks and then evaporated. The residual oil was dissolved in 100 ml. of water, made strongly basic with solid potassium hy-

(8) R. Franke, *Ber.*, **38**, 3726 (1905).

(9) D. J. Brown, *J. Soc. Chem. Ind.*, **69**, 353 (1950).

(10) L. N. Short and H. W. Thompson, *J. Chem. Soc.*, 168 (1952).

droxide, and extracted with ether. Distillation at 0.3 mm. gave 9.7 g. of mono-oxide, m.p. 38–39°. Experiments using two equivalents of hydrogen peroxide, or at higher temperatures gave the same mono-oxide in poorer yields. A solution in chloroform showed strong absorption at 1325 cm.$^{-1}$

Anal. Calcd. for $C_4H_4N_2O$: C, 50.0; H, 4.2; N, 29.2. Found: C, 50.4; H, 4.1; N, 29.0.

Pyridazine mono-oxide reacted vigorously with phosphorus oxychloride, but no pure product could be isolated.

MINNEAPOLIS, MINN.

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

Condensation of 3-Acetylcoumarin with Acetone and Amines[1]

C. F. KOELSCH AND HARLAN D. EMBREE

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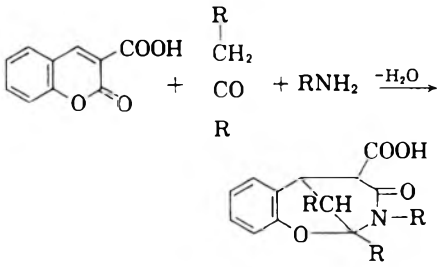
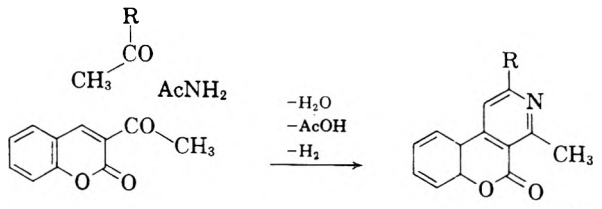
3-Acetylcoumarin reacts with acetone and certain primary amines to form *N*-substituted derivatives of 9-amino-7-methyl-6-dibenzo[*bd*]pyrone, I, in yields of 10–47%.

It has been shown that condensation of 3-coumarincarboxylic acid with ketones and amines yields bridged 8-membered ring compounds.[2]



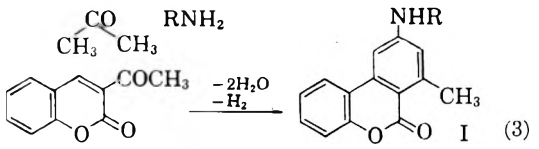
(1)

Further, the reaction of 3-acetylcoumarin with ketones and amides yields pyridocoumarins.[3]



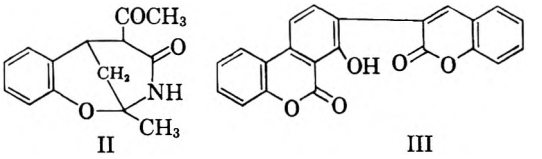
(2)

It has now been found that 3-acetylcoumarin reacts with acetone and amines to form aminobenzocoumarins, I.



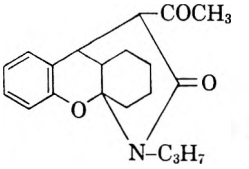
I (3)

The amines used were aniline (yield 12.6%), *p*-chloroaniline (15.8%), *n*-butylamine (10.5%), isopropylamine (47%), and cyclohexylamine (40%). Other bases, *t*-butyl, benzyl, and hydroxyethylamine, gave no crystalline products. Ammonia reacted according to (1) forming II, and piperidine yielded III, the self-condensation product of 3-acetylcoumarin.[4]



II III

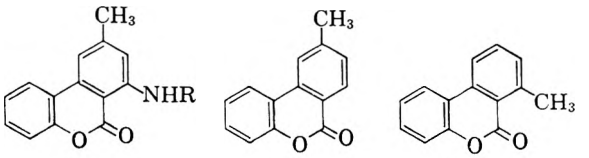
Ketones other than acetone were not thoroughly studied. Diethylketone with isopropylamine gave no crystalline product, whereas cyclohexanone, sterically prevented from forming a compound like I, reacted according to (1) forming IV.



IV

The structures of the products were established by analysis and chemical properties. Although the substances were generally insoluble in dilute aqueous hydrochloric acid, crystalline hydrobromides and acetyl derivatives were formed. The lactone ring in I (R = C_6H_5) was opened when the compound was boiled with alcoholic alkali; acidification of the resulting solution regenerated I, whereas treatment with methyl sulfate gave a methoxy acid and a methoxy ester. Saponification of the ester was difficult but led to the methoxy acid.

That the products were secondary amines of structure I rather than V was proved by degrada-



V VI VII

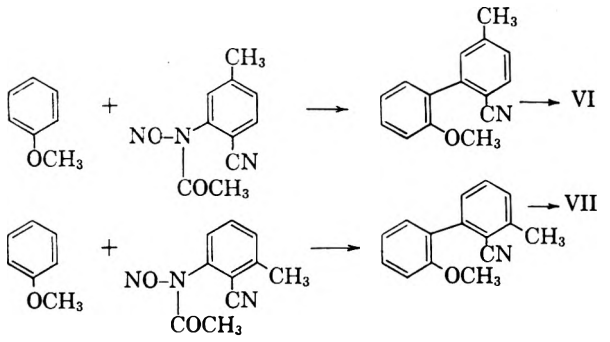
(1) From the Ph.D. Thesis of H. D. Embree, July 1952.

(2) C. F. Koelsch and M. C. Freerks, *J. Org. Chem.*, **18**, 1538 (1953).

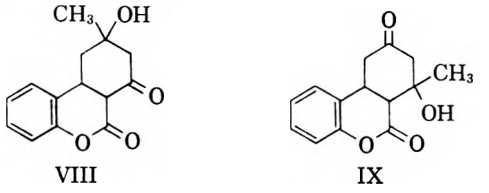
(3) C. F. Koelsch and S. A. Sundet, *J. Am. Chem. Soc.*, **72**, 168 (1950).

(4) C. F. Koelsch and S. A. Sundet, *J. Am. Chem. Soc.*, **72**, 1844 (1950).

tion to VII. This was accomplished by pyrolysis of the hydrobromide of I (R = C_3H_7 and C_6H_{11}), giving I (R = H). The primary amine was then deaminated (HNO_2, H_3PO_2) to VII. For comparison VI and VII were synthesized by standard methods.



In a previous study[4] it was shown that reaction of acetone with 3-acetocoumarin involved a Michael reaction and an aldol cyclization, and the product was formulated as VIII. This product has now been found to react with isopropylamine to form I. R = C_3H_7. Although not conclusive evidence against VIII, this indicates that the aldol cyclization took place in a different way, and that the compound formerly represented as VIII is actually IX.



EXPERIMENTAL

9-Anilino-7-methyl-6-dibenzo[bd]pyrone. I, R = C_6H_5. A mixture of 94 g. of 3-acetylcoumarin, 91 ml. of aniline, 57 ml. of acetic acid, and 500 ml. of acetone was stirred at room temperature for 24 hr. The orange precipitate was then removed, washed with acetone and alcohol, and dried. This material, 25 g., m.p. 220–246°, could not be purified. To convert it into I, 5 g. of it was stirred with 20 ml. of acetic acid at 80–100° for 3 hr. while a slow stream of air was passed through. Cooling to room temperature then gave 3.8 g. of product, m.p. 266–270°. A sample distilled (b.p. 318–320° at 9 mm.) and recrystallized from pyridine had m.p. 271.5–272.5°.

Anal. Calcd. for $C_{20}H_{15}NO_2$: C, 79.8; H, 5.0; N, 4.65. Found: C, 79.7; H, 5.3; N, 4.4.

The compound was nearly insoluble in common organic solvents, in hot aqueous alkali or 10% hydrochloric acid. It was moderately soluble in chloroform or ethyl acetate, and quite soluble in hot dioxan, acetic acid, or pyridine. It dissolved in alcoholic sodium hydroxide giving a water-soluble salt from which the original compound was precipitated by acids.

9-(p-Chloroanilino)-7-methyl-6-dibenzo[bd]pyrone was obtained from 9.4 g. of acetylcoumarin, 12.8 g. of *p*-chloroaniline, 5.7 ml. of acetic acid, and 50 ml. of acetone. The intermediate dihydro compound (3.4 g., m.p. 296–310°) was aerated in hot acetic acid. The product formed colorless needles from pyridine, m.p. 314–316° with darkening.

Anal. Calcd. for $C_{20}H_{14}ClNO_2$: C, 71.6; H, 4.2; N, 4.2. Found: C, 71.3; H, 4.1; N, 4.2.

9-n-Butylamino-7-methyl-6-dibenzo[bd]pyrone. I, R = C_4H_9. A mixture of 9.4 g. of 3-acetylcoumarin, 7.3 g. of butylamine, 5.7 ml. of acetic acid, and 50 ml. of acetone kept for 24 hr. gave 1.8 g. of solid product. Extraction of this with 100 ml. of warm acetone left 0.1 g. of III, the self-condensation product of acetylcoumarin, and concentration of the extract gave 1.63 g., m.p. 163–167°. A portion of this (0.56 g.) in 7 ml. of alcohol containing 0.23 g. of quinone was boiled for 30 min. Cooling gave 0.51 g. of nearly pure product, crystals from dilute acetic acid, m.p. 169–170°.

Anal. Calcd. for $C_{18}H_{19}NO_2$: C, 76.8; H, 6.8; N, 5.0. Found: C, 76.5; H, 6.5; N, 4.9.

The compound was insoluble in 10% sodium hydroxide or 10% hydrochloric acid.

9-Isopropylamino-7-methyl-6-dibenzo[bd]pyrone. I, R = C_3H_7. A mixture of 9.4 g. of 3-acetylcoumarin 5.9 g. of isopropylamine, 5.7 ml. of acetic acid, and 50 ml. of acetone gave 6.8 g. of solid, m.p. 186–193°; concentration of the mother liquor gave 0.8 g. more. The melting point of this material often varied in similar experiments sometimes being as low as 175–181°. This had little significance in the ultimate quantity of product, and probably depended on the proportion of aromatized substance formed by accidental dehydrogenation. Two grams of the solid and 0.84 g. of quinone heated in 60 ml. of alcohol for 1 hr. gave 1.65 g. of product, colorless needles from alcohol, m.p. 196–197°.

Anal. Calcd. for $C_{17}H_{17}NO_2$: C, 76.4; H, 6.4; N, 5.2. Found: C, 76.3; H, 6.4; N, 5.6.

Although the amine was insoluble in aqueous hydrochloric acid, treatment of an alcoholic solution with hydrogen bromide and ether converted it quantitatively into its *hydrobromide*, colorless needles, m.p. 251–252° dec.

Anal. Calcd. for $C_{17}H_{18}BrNO_2$: Br, 23.0. Found: Br, 23.3.

When the amine was warmed with acetic anhydride containing potassium acetate it was converted into its *acetyl derivative*, colorless prisms from benzene-ligroin, m.p. 188–189°.

Anal. Calcd. for $C_{19}H_{19}NO_3$: C, 73.8; H, 6.2; N, 4.5. Found: C, 74.0; H, 6.2; N, 4.6.

9-Cyclohexylamino-7-methyl-6-dibenzo[bd]pyrone. I, R = C_6H_{11}. When acetic acid was used as in the previous condensations, only about 4% of product was obtained. The low yield was due mainly to insolubility of cyclohexylamine acetate, and was greatly improved by use of butyric acid. Use of butyric acid in the previous condensations gave results no better, and in some cases worse than acetic acid.

A mixture of 9.4 g. of 3-acetylcoumarin, 9.9 g. of cyclohexylamine, 8.8 g. of butyric acid, and 50 ml. of acetone kept for 22 hr. gave 9.2 g., m.p. 190–197°. Two grams of this and 0.7 g. of quinone in 50 ml. of alcohol heated for 30 min. gave 1.33 g., m.p. 168–169° (dehydrogenation by aeration in hot acetic acid or benzene was not effective). Recrystallized from alcohol, the product had m.p. 168.5–169.3°.

Anal. Calcd. for $C_{20}H_{20}NO_2$: C, 78.4; H, 6.6; N, 4.6. Found: C, 78.2; H, 7.0; N, 4.8.

The compound was insoluble in aqueous hydrochloric acid; but alcoholic hydrogen bromide gave the *hydrobromide*, fine colorless needles from alcohol-ether, m.p. 238–239.5° dec.

Anal. Calcd. for $C_{20}H_{21}BrNO_2$: Br, 20.6. Found: Br, 21.1.

The *acetyl derivative* formed colorless prisms from benzene-ligroin or alcohol, m.p. 182–183°.

Anal. Calcd. for $C_{22}H_{23}NO_3$: C, 75.7; H, 6.6; N, 4.0. Found: C, 75.4; H, 6.9; N, 4.2.

Methylation of I, R = C_6H_5. A solution of 2 g. of sodium hydroxide and 3.25 g. of I, R = C_6H_5 in 90 ml. of alcohol was heated for 45 min. and then diluted with 30 ml. of water and distilled. The residue was dissolved in 20 ml. of water, treated with 3.2 g. of methyl sulfate, and stirred for 1 hr. The mixture was centrifuged to remove ester, and then acidified. The precipitate (2.7 g.) was extracted with 10% sodium bicarbonate, leaving 1.3 g. of I. Acidification of the extract gave 1.7 g. of crude *5-anilino-3-methyl 2'-methoxybiphenyl-2-carboxylic acid*, m.p. 174–176° dec. Recrystallization from dilute alcohol and then dilute acetic acid gave colorless needles, m.p. 181–182° dec.

Anal. Calcd. for $C_{21}H_{19}NO_3$: C, 75.6; H, 5.8; N, 4.2; N.E. 333. Found: C, 75.4; H, 5.8; N, 4.4; Neut. Equiv. 335.

When the methylation was carried out in alcohol using a 3-fold excess of methyl sulfate the product was the *methyl ester*, colorless needles from alcohol or benzene—ligroin, m.p. 127–128°.

Anal. Calcd. for $C_{22}H_{21}NO_3$: C, 76.0; H, 6.1; N, 4.0. Found: C, 75.8; H, 6.3; N, 4.4.

The ester was resistant to saponification; 0.4 g. of it heated for 8 hr. with excess 10% alcoholic potash gave only 0.1 g. of the acid.

Dealkylation of I, R = cyclohexyl or isopropyl. When 2 g. of the hydrobromide of I, R = C_6H_{11} was heated for 1 hr. in a bath at 255–260°, cyclohexene was evolved. The residue was dissolved in 60 ml. of hot alcohol, filtered, and treated with aqueous sodium carbonate, giving 1.1 g. of *9-amino-7-methyl-6-dibenzo[b.d]pyrone, I, R=H*, faintly tan needles from alcohol, m.p. 192–193°.

Anal. Calcd. for $C_{14}H_{11}NO_2$: C, 74.7; H, 4.9; N, 6.2. Found: C, 75.0; H, 5.0; N, 6.5.

Pyrolysis of the iso-propyl analog gave the same product in a yield of 95%.

Deamination of I, R = H. A suspension of 3.7 g. of the hydrobromide of I, R = H in 30 ml. of 18% hydrochloric acid was stirred at 0° and treated with 0.83 g. of sodium nitrite in a little water. The diazonium salt separated and the mixture became pasty. After 30 min., 16 g. of 50% hypophosphorus acid in an equal volume of water was added. Nitrogen evolution caused severe foaming requiring the use of a large flask for the preparation. After 12 hr. at 0°, the mixture was diluted and extracted with chloroform. Colored impurities were removed by passing the chloroform solution through a short column of alumina. Crystallization from benzene-ligroin gave 1.7 g. of 7-methyl-6-dibenzo (b,d) pyrone (VII), m.p. 101–102° alone or mixed with a sample synthesized as described below.

Anal. Calcd. for $C_{14}H_{10}O_2$: C, 80.0; H, 4.8. Found: C, 80.1; 80.4; H, 4.7, 5.1.

7-Methyl-6-dibenzo[bd]pyrone (VII). A mixture of 16.3 of 3-amino-2-cyanotoluene,[5] 145 ml. of acetic acid, 70 ml. of acetic anhydride, and 11 g. of potassium acetate was boiled for 20 min. and then cooled to 0°. One gram of phosphorus pentoxide was added, followed by a solution of 8.5 g. of nitrosyl chloride in 50 ml. of acetic anhydride. The mixture was kept at 0° for 30 min., then poured into one liter of ice water. The oily nitroso compound was extracted with 250 + 150 ml. of anisole. The anisole extract was washed with water, 75 ml. of anisole being used to rinse the funnel. Addition of 40 g. of sodium sulfate and 20 g. of potassium carbonate brought about evolution of nitrogen and change to a deep red color. The mixture was kept for 12 hr. at room temperature, then filtered and distilled. After anisole had been removed, the main fraction came over at 133–136° at 0.15 mm. as a pale yellow oil. When a solution of this oil in ether-ligroin was kept for two days at room temperature, it deposited colorless prisms, 1.5 g., m.p. 152–153° or 154–155° after sublimation and recrystallization. This was a by-product of unknown structure that gave only resins when treated with hot hydrobromic acid.

Anal. Calcd. for $C_{14}H_{15}N_3O$: C, 69.7; H, 6.24; N, 17.4. Found: C, 69.7; H, 6.1; N, 16.3.

The main product was a yellow oil. A mixture of 1.5 g. of it with 20 ml. of concentrated hydrochloric acid was heated at 180° for 3 hr. Dilution with water, extraction with chloroform, and distillation gave 0.7 g., b.p. 170–174° at 1 mm. Crystallization from alcohol and then benzene-ligroin gave colorless needles (0.4 g.), m.p. 101–102°, identical with the previously described substance.

9-Methyl-6-dibenzo[bd]pyrone (VI). A mixture of 28.5 g. of 3-amino-4-cyanotoluene,[6] 250 ml. of acetic acid, 120 ml. of acetic anhydride, and 20 g. of potassium acetate was boiled for 20 min., then cooled to 5°. One gram of phosphorus pentoxide was added, followed by 15.4 g. of nitrosyl chloride in 90 ml. of cold acetic anhydride. After one hour, the mixture was poured into 2.5 liters of ice water. The crystalline nitroso compound was collected, washed with water, and pressed as dry as possible (35 g., m.p. 70–72° dec.). It was then dissolved in 800 ml. of anisole containing a little potassium carbonate, and kept at room temperature for 12 hr. or until nitrogen evolution ceased. Filtration and distillation gave anisole and then 21 g. of crude product, b.p. 150–155° at 0.6 mm. Crystallization from ether-ligroin and then alcohol gave 7.7 g., m.p. 94–95°. Sublimation and recrystallization from alcohol gave pure *2-cyano-2'-methoxy-3-methylbiphenyl*, m.p. 96–97°.

Anal. Calcd. for $C_{15}H_{13}NO$: C, 80.7; H, 5.9; N, 6.3. Found: C, 80.7; H, 6.1; N, 6.3.

A mixture of 4 ml. of acetic acid, 4 ml. of 48% hydrobromic acid, and 0.75 g. of the cyano compound was boiled for 4 hr. and then diluted with water, giving 0.54 g. of crude product, m.p. 101–102°. The material was dissolved in hot alcoholic sodium hydroxide, treated with charcoal, precipitated by acidification, and recrystallized from alcohol giving colorless needles, m.p. 102.5–103°. A mixture with the isomeric 7-methyl derivative had m.p. 62–65°.

Anal. Calcd. for $C_{14}H_{10}O_2$: C, 80.0; H, 4.8. Found: C, 80.2; H, 4.8.

Condensation of acetylcoumarin with acetone and ammonia. A mixture of 9.4 g. of acetylcoumarin, 7.7 g. of ammonium acetate, and 50 ml. of acetone was stirred at room temperature for 16 hr. The white precipitate was removed, washed with acetone, alcohol, and water and then dried; yield 7.2 g., m.p. 222–226°. In another preparation 7.0 g. of product was obtained after only 4 hr. Again, 7 g. of product was obtained when only 7.3 ml. of acetone was used and the mixture was heated on a water bath for 20 min. Crystallization from acetic acid gave colorless prisms, m.p. 226–227°. The compound gave a deep purple color with alcoholic ferric chloride; it was not affected by aeration in hot acetic acid. It was insoluble in 10% hydrochloric acid or 20% sulfuric acid. Hot 10% sodium hydroxide slowly dissolved it. These properties suggest that the compound is II, *2-amino-2-methylchroman-4,α-acetoacetic acid lactam.*

Anal. Calcd. for $C_{14}H_{15}NO_3$: C, 68.6; H, 6.1; N, 5.7. Found: C, 68.6; H, 6.4; N, 5.4.

Condensation of acetylcoumarin with cyclohexanone and isopropylamine. A mixture of 9.4 g. of 3-acetylcoumarin, 5.9 g. of isopropylamine, 8.8 g. of butyric acid, and 50 ml. of cyclohexanone was stirred at room temperature for 24 hr. About 10 mg. of III was removed by filtration and most of the cyclohexanone by distillation under reduced pressure. The residue was dissolved in ether, washed with bicarbonate, concentrated and cooled for six days, giving 5.7 g. of crude crystalline product. Recrystallization from alcohol gave nearly colorless plates, m.p. 137.5–138.5°. The properties of the compound, insolubility in dilute acid and deep green color with alcoholic ferric chloride, indicate structure IV, *2-isopropylamino-2,3-tetramethylenechroman-4,α-acetoacetic acid lactam.*

Anal. Calcd. for $C_{20}H_{24}NO_3$: C, 73.6: H, 7.4: N, 4.3. Found: C, 73.6: H, 7.7: N, 4.4.

Reaction of the aldol IX *with Isopropylamine.* A mixture of 0.5 g. of the aldol prepared by Sundet,[4] 1 g. of isopropylamine, 1 ml. of acetic acid, and 15 ml. of acetone was stirred at room temperature for 22 hr., then filtered and concentrated. The resulting crystals were boiled in 6 ml. of alcohol with 0.2 g. of quinone for 30 min. The crystalline product was washed with alcohol, giving 0.3 g. of 7-methyl-9-isopropylamino-6-dibenzo[bd]pyrone, m.p. 195–196.5°.

MINNEAPOLIS, MINN.

(5) S. Gabriel and A. Thieme, *Ber.*, **52**, 1079 (1919); J. Kenner and E. Witham, *J. Chem. Soc.*, **119**, 1458 (1921).

(6) S. Niementowski, *Ber.*, **21**, 1535 (1888); G. Glock, *Ber.*, **21**, 2662 (1888); G. T. Morgan and E. A. Coulson, *J. Chem. Soc.*, 2551 (1929).

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NORTHWESTERN UNIVERSITY]

Reactions of Pyridine-Type Bases with Iodine and Certain Quinolines or Isoquinolines Containing a Reactive Methyl Group

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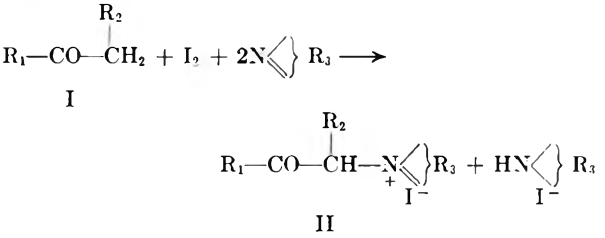
Quinoline-type bases with a methyl group in the 2 or 4 position and isoquinoline-type bases with a methyl group in the 1 position undergo reaction with iodine and pyridine, or certain bases related to pyridine, to give quaternary salts. The preparation and structure of a number of these quaternary salts is described herein.

A number of authors have recorded the preparation of quaternary salts of Type II when compounds containing an active methyl or methylene group, such as I react with iodine and heterocyclic tertiary amines.[2] Quaternary salts were reported wherein R_1 was aryl,[2a] substituted aryl,[2b-e] thienyl,[2c] 2-nitrocyclopropyl,[2f] or a substituted cyclopentanoperhydrophenanthrene derivative,[2a,g] where R_2 was alkyl, phenyl or hydrogen,[2c] and where R_3  was any of a number of heterocyclic nitro-



I II

geneous bases of the pyridine type.[2d] Recently Sapper and Southwick,[3] prepared 1(1,4-diphenyl-2-keto-3-butenyl)pyridinium iodide from benzyl styryl ketone, iodine, and pyridine, thus extending the reaction to an active methylene group adjacent to an α,β unsaturated system. Using the reaction with iodine and pyridine, Reid and Bender[4] prepared pyridinium salts from 2-methylbenzothiazole, 2-methylbenzoxazole, and from 2-methylquinazoline. This reaction has been used for the preparation of pyridinium salts from 2-methyl-γ-chromone,[5a] and from *N*-methyl-2-picolinium iodide.[5b]

In the present paper we show that quinoline type bases with a methyl group in the 2, or 4 position and isoquinoline type bases with a methyl group in the 1 position undergo reaction with iodine and pyridine, and certain bases related to pyridine to give quaternary salts.

When quinaldine reacts with iodine and the various pyridine like bases, the quaternary salts are formulated as III. The structures of the products obtained in these reactions were established in detail by means of the following lines of evidence.

1. The presence of an active methylene group in the molecule was established in each case by means of the picryl chloride test of Krohnke.[6]

2. In the case of 1-(2-quinolylmethyl)pyridinium iodide (IIIa), the methylene group was further established by conversion to 2-quinolyl-*N*-(*p*-dimethylaminophenyl) nitrone (IV) using the method of Krohnke[7] and subsequently converting IV to the known 2-quinolinecarboxaldehyde-2,4-dinitrophenylhydrazone.[8]

3. The structure of each of the quaternary salts prepared from quinaldine, was established in detail by independent synthesis and conversion to a common derivative. Thus 2-bromomethylquinoline was prepared[9a] and allowed to react with the appropriate heterocyclic tertiary amine to give the corresponding quaternary bromide.[9b,c] These bromides were in turn converted to picrates and compared with the corresponding picrates obtained from the iodides. A summary of the mixed melting point data obtained in this comparison process is presented in Table I.

When lepidine reacts with iodine and the various heterocyclic bases the structures are formulated as V. Evidence for this assignment of structure is

(1) From the Ph.D. Thesis of S. V. Abramo (1956).

(2) (a) L. C. King, *J. Am. Chem. Soc.*, **66**, 891, 1612 (1944). (b) L. C. King, M. McWhirter, and D. Barton, *J. Am. Chem. Soc.*, **67**, 2089 (1945). (c) L. C. King, M. McWhirter, and R. L. Rowland, *J. Am. Chem. Soc.*, **70**, 289 (1948). (d) L. C. King and M. McWhirter, *J. Am. Chem. Soc.*, **68**, 716 (1946). (e) J. L. Hartwell and S. R. L. Kornberg, *J. Am. Chem. Soc.*, **68**, 868, 1131 (1946). (f) L. I. Smith and V. A. Englehardt, *J. Am. Chem. Soc.*, **71**, 2676 (1949). (g) R. H. Baker and E. N. Squire, *J. Am. Chem. Soc.*, **70**, 1487 (1948).

(3) D. I. Sapper and P. L. Southwick, *J. Org. Chem.*, **21**, 105 (1956).

(4) W. Reid and H. Bender, *Chem. Ber.*, **89**, 1893 (1956).

(5) (a) J. Schmutz, R. Hirt, and H. Lauener, *Helv. Chim. Acta*, **35**, 1168 (1952). (b) J. A. Berson and T. Cohen, *J. Am. Chem. Soc.*, **78**, 416 (1956).

(6) F. Krohnke and H. Schmeiss, *Ber.* **70**, 1728 (1937), demonstrated that compounds containing a reactive methylene group, react in basic solution with picryl chloride or chloranil to give an intense color. This process serves as a convenient test for the unsubstituted methylene group.

(7) F. Krohnke, *Ber.* **69**, 2006 (1936).

(8) C. E. Kwartler and H. G. Lindwall, *J. Am. Chem. Soc.*, **59**, 524 (1937).

(9) (a) D. Ll. Hammick, *J. Chem. Soc.* **123**, 2882 (1923). (b) B. R. Brown, D. Ll. Hammick, and B. H. Thewlis, *J. Chem. Soc.* 1145 (1951). (c) B. R. Brown and H. E. Wild, *J. Chem. Soc.* 1158 (1956).

TABLE I

MELTING POINT OF PICRATES

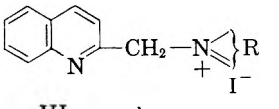
	Iodide, °C.	Bromide, °C.	Mixed M.P., °C.
1-(2-Quinolylmethyl)-pyridinium	162–163	163–164	160–163
1-(2-Quinolylmethyl)3-picolinium	147–148	146–147	145–148
2-(2-Quinolylmethyl)iso-quinolinium	197–197.5	196.5–197	196–197
3-Methyl-2-(2-quinolyl-methyl)isoquinolin-ium	147–148	144–146	147–149

based on the mode of formation, analytical data and a positive picryl chloride test in each case indicating the presence of the active methylene group. In addition, 1-(4-quinolylmethyl)pyridinium iodide (Va) was converted to 4-quinolyl-*N*(*p*-dimethylaminophenyl)nitrone (VI).

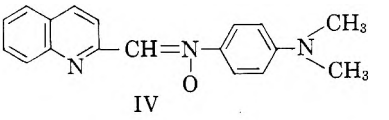
The quaternary salts produced when 2,6-dimethylquinoline reacts with iodine and the various heterocyclic bases are formulated as VII. In these cases the assignment of structure is based on the method of preparation, on physical properties and analysis, and on the presence of an active methylene group as shown by the picryl chloride test.[6] The structures VIII, are assigned to the quaternary salts produced when 1-methylisoquinoline reacts with iodine and the various heterocyclic bases. Again in these cases the assignment of structures is based on the method of preparation, on the physical properties and analytical data, and on the presence of an active methylene group.[6]

In the cases of the quaternary salts IX and X prepared from the methoiodides of quinaldine and lepidine the structures were established by basic hydrolysis. Compound IX was converted to 1-(1-methyl-2-quinolylidenylmethyl)pyridinium iodide (XI) and subsequently to the known *N*-methyl-2-quinolone.[10] Compound X was converted to *N*-methyl-4-quinolone[11] (XII).

Detailed data for the preparation, analysis, and preparation of derivatives of each of the compounds are presented in the experimental part.



III N⟩R = a, pyridine
b, 3-picoline
c, isoquinoline
d, 3-methylisoquinoline



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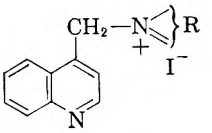
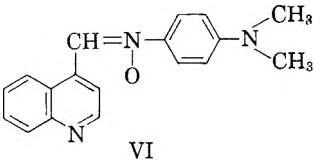
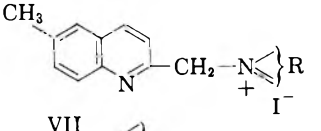


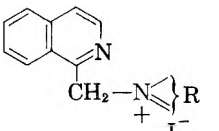
V N⟩R = a, pyridine
b, isoquinoline
c, 3-methylisoquinoline



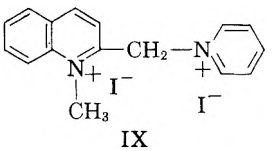
VI



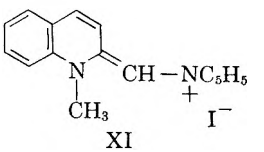
VII N⟩R = a, pyridine
b, isoquinoline
c, 3-methylisoquinoline



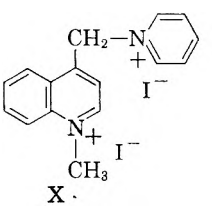
VIII N⟩R = a, pyridine
b, 3-picoline



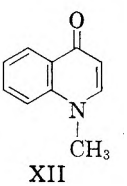
IX



XI



X



XII

Quinaldine methoiodide,[14] and lepidine methoiodide[15] were prepared by reaction of the appropriate base with methyl iodide in acetone solution.

EXPERIMENTAL[12]

Starting materials. The heterocyclic tertiaryamines pyridine, 3-picoline, isoquinoline, 3-methylisoquinoline, quinaldine, and lepidine were commercially available materials. 1-Methylisoquinoline was prepared from isoquinoline by way of a Reissert compound;[13] b.p. 126–128°/16 mm., n_D 1.6125.

(10) P. Friedländer and F. Muller, *Ber.*, **20**, 2010 (1887).
(11) H. Meyer, *Monatsh.*, **27**, 255 (1906).
(12) Analysis by H. Beck. Except where otherwise indicated, all melting point and decomposition point data was observed on a Fisher-Johns block.
(13) V. Boekelheide and J. Weinstock, *J. Am. Chem. Soc.*, **74**, 660 (1952).
(14) O. Doebner and W. Van Miller, *Ber.* **16**, 2468 (1883).
(15) S. Hoogewerfe and W. Van Dorp, *Rec. trav. chim.*, **2**, 317 (1883).

ω-Bromoquinaldine was prepared by the method of Hammick and co-workers.[9a]

Picryl chloride test for active methylene group. A few mg. of the compound being tested was suspended in 5 cc. of 2*M* sodium hydroxide solution; 3 cc. of a solution of picryl chloride in chloroform (1 g./100 cc.) was added and the mixture was shaken. A deep green or red color was taken as a positive test.[6]

Preparation of quaternary salts and derivatives. The method of preparation and work up of the quaternary iodides was essentially the same in each case. The process is described in detail for 1-(2-quinolylmethyl)pyridinium iodide (IIIa). Significant deviations in preparation work up or purification will be described when appropriate.

1-(2-Quinolylmethyl)pyridinium iodide (IIIa). To a mixture of 29 g. (0.2 mole) quinaldine and 40 g. (0.5 mole) pyridine, 50.8 g. (0.2 mole) of iodine was gradually added with stirring. The mixture was heated at 100° for 2 hr. The reaction mixture was extracted with ether to remove unreacted starting materials, with water to remove pyridinium hydroiodide, and with acetone to remove any quaternary triiodide which may have formed during the reaction. Recrystallization from 80% ethanol gave 70 g. (100%) of light yellow needles melting with decomposition at 228–233°. This compound gave a positive picryl chloride test.

Anal. Calcd. for $C_{15}H_{13}N_2I$: C, 51.74; H, 3.76. Found: C, 51.09; H, 3.63.

The compound was recrystallized from 80% ethanol containing a small amount of pyridine;[16] yield 90%, m.p. 238–239°.

Anal. Found: C, 52.04; H, 3.65.

This preparation was attempted in various quantities from 0.05 mole to 0.5 mole. The yields were consistently high.

Bromide. This compound separated as white needles from an acetone solution of pyridine and ω-bromoquinaldine; m.p. 237–239°.[9b]

Perchlorate. From the bromide or the iodide by treatment with 20% perchloric acid. Recrystallized from ethanol; m.p. 189.5–190°, from either source.

Anal. Calcd. for $C_{15}H_{13}O_4N_2Cl$: C, 56.17; H, 4.08. Found: C, 56.42; H, 4.04.

Picrate. From the bromide or from the iodide by addition of saturated picric acid in ethanol to an ethanolic solution of the salt. M.p. 162–163°, from the iodide. M.p. 163–164°, from the bromide (Table I).

1-(2-Quinolylmethyl)-3-picolinium iodide (IIIb). Prepared from quinaldine, 3-picoline, and iodine. Yield (73%) of reddish crystalline material, m.p. 189–195°. Repeated recrystallization from ethanol solution gave 58% of peach colored crystals; m.p. 201–202° with decomposition.

Anal. Calcd. for $C_{16}H_{15}N_2I$: C, 53.05; H, 4.17. Found: C, 53.38; H, 4.17.

Bromide. By reaction of ω-bromoquinaldine with 3-picoline in acetone solution; m.p. 217–219°.

Picrate. From the iodide or from the bromide by addition of saturated picric acid in ethanol. M.p. 147–148° from the iodide. M.p. 146–147°, from the bromide (Table I).

2-(2-Quinolylmethyl)isoquinolinium iodide (IIIc). Prepared from quinaldine, isoquinoline, and iodine. Extraction separately with ether, acetone, water and again with acetone gave a reddish crude material which on crystallization several times from 50% ethanol gave 39% of light yellow crystals; m.p. 201–202°, with decomposition.

Anal. calcd. for $C_{19}H_{15}N_2I$: C, 57.30; H, 3.80. Found: C, 57.03; H, 3.87.

Bromide.[9c] From isoquinoline and ω-bromoquinaldine in acetone. The crystals obtained were converted directly to the picrate.

Picrate. From the bromide or from the iodide by addition of saturated picric acid in ethanol. M.p. 197–197.5° from the iodide. M.p. 196.5–197° from the bromide (Table 1).

3-Methyl-2-(2-quinolylmethyl)isoquinolinium iodide (IIId). Prepared from quinaldine, 3-methylisoquinoline, and iodine. After heating for 12 hr. and extracting separately with ether, water, and acetone; the dark crude product was recrystallized from 80% ethanol. Yield, 81%, of tan crystals melting at 197–201°.

Anal. Calcd. for $C_{20}H_{17}N_2I$: C, 58.26; H, 4.16. Found: C, 55.31, 55.80; H, 3.79, 3.68.

Recrystallization from ethanol containing a small amount of pyridine gave material melting at 204°.[16]

Anal. Found: C, 58.28; H, 3.94.

Bromide. From 3-methylisoquinoline and ω-bromoquinaldine. The product was converted directly to the picrate.

Picrate. From the bromide or iodide by addition of saturated picric acid in ethanol. M.p. 147–148° from the iodide. M.p. 144–146° from the bromide (Table 1).

1-(4-Quinolylmethyl)pyridinium iodide (Va). Prepared from lepidine, pyridine, and iodine. Yield 63% of crude product, m.p. 209–210° with decomposition. Recrystallization from ethanol-water gave 48% of yellow prisms, m.p. 220–223° with decomposition.

Anal. Calcd. for $C_{15}H_{13}N_2I$: C, 51.74; H, 3.76. Found: C, 51.74; H, 3.76.

2-(4-Quinolylmethyl)isoquinolinium iodide (Vb). Prepared from lepidine, isoquinoline, and iodine. Yield 59% of yellow needles; m.p. 197–200° with decomposition. Recrystallization from ethanol-water-pyridine[16] gave yellow needles, 41%; m.p. 215.5–217° with decomposition.

Anal. Calcd. for $C_{19}H_{15}N_2I$: C, 57.30; H, 3.80. Found: C, 57.32; H, 3.65.

3-Methyl-2-(4-quinolylmethyl)isoquinolinium iodide (Vc). Prepared from lepidine, 3-methylisoquinoline, and iodine. Yield 80% of substance; m.p. 197–199°. Recrystallization from 80% ethanol gave 44% of yellow staves; m.p. 201–204°.

Anal. Calcd. for $C_{20}H_{17}N_2I$: C, 58.26; H, 4.16. Found: C, 57.96; H, 4.13.

1-[2-(6-Methylquinolyl)methyl]pyridinium iodide (VIIa). Prepared from 2,6-dimethylquinoline, pyridine, and iodine. Yield 87% of red solid softening at 160°, melting at 165–167°. Recrystallization from ethanol-water gave 62.3% of a yellow solid; m.p. 169–170° with decomposition. Recrystallization from ethanol-water-pyridine for an analytical sample gave white plates melting at 172–174°.

Anal. Calcd. for $C_{16}H_{15}N_2I$: C, 53.05; H, 4.177. Found: C, 53.70; H, 4.20.

2-[2-(6-Methylquinolyl)methyl]isoquinolinium iodide (VIIb). Prepared from 2,6-dimethylquinoline, isoquinoline, and iodine. Yield 53%; m.p. 190–193°. Recrystallization five times from ethanol-water using large quantities of Norit A gave 24% of light yellow product; m.p. 205.5–207° with decomposition.

Anal. Calcd. for $C_{20}H_{17}N_2I$: C, 58.26; H, 4.16. Found: C, 58.58; H, 4.15.

3-Methyl-2-[2-(6-methylquinolyl)methyl]isoquinolinium iodide (VIIc). Prepared from 2,6-dimethylquinoline, 3-methylisoquinoline, and iodine. Yield 84% of a light brown solid; m.p. 205–208°. Recrystallization from ethanol-water gave 70% of yellow prisms melting with decomposition at 209–210°.

Anal. Calcd. for $C_{21}H_{19}N_2I$: C, 59.17: H, 4.49. Found: C, 59.39; H, 4.60.

1-(1-Isoquinolylmethyl)pyridinium iodide (VIIIa). Prepared from 1-methylisoquinoline,[13] pyridine, and iodine. Yield 97% of dark crystalline material; m.p. 170–200°. Recrystallization from ethanol-water using decolorizing charcoal gave 75% of white crystals; m.p. 215–218°, with decomposition.

Anal. Calcd. for $C_{15}H_{13}N_2I$: C, 51.74; H, 3.76. Found: C, 51.83; H, 3.57.

1-(1-Isoquinolylmethyl)-3-picolinium iodide (VIIIb). Prepared from 1-methylisoquinoline, 3-picoline, and iodine. Crude yield 72%; m.p. 192–195°. On recrystallization from

(16) This procedure was used whenever a low carbon analysis indicated the molecule retained extra hydriodic acid.

ethanol-water, 64% of white plates; m.p. 206–211°, was obtained.

Anal. Calcd. for $C_{16}H_{15}N_2I$: C, 53.06; H, 4.17. Found: C, 52.80; H, 3.99.

1-(2-Quinolylmethyl)pyridinium iodide methoiodide (IX). Prepared from 1-methylquinaldinium iodide,[14] pyridine, and iodine. Crude yield 30% of orange needles; m.p. 178–180°. Recrystallization from 90% ethanol gave yellow needles; m.p. 183–184° with decomposition.

Anal. Calcd. for $C_{16}H_{16}N_2I_2$: C, 39.21; H, 3.29. Found: C, 38.96; H, 3.27.

1-(4-Quinolylmethyl)pyridinium iodide methoiodide (X). Prepared from N-methyllepidinium iodide,[15] pyridine, and iodine. Crystallization from ethanol gave 53% of greenish yellow plates; m.p. 186–188°. Recrystallization for an analytical sample gave yellow plates darkening at 187–191°, decomposing at 191–193°.

Anal. Calcd. for $C_{16}H_{16}I_2N_2$: C, 39.21; H, 3.29. Found: C, 39.30; H, 3.14.

2-Quinolyl-N-(p-dimethylaminophenyl)nitrone (IV). To a mixture of 3.48 g. (0.01 mole) 1-(2-quinolylmethyl)pyridinium iodide (IIIa) in 5 ml. water and 1.65 g. (0.011 mole) of *N,N*-dimethyl *p*-nitroso aniline in 50 ml. ethanol cooled to 0.5°, 10 ml. of *M* sodium hydroxide was added. The mixture was stirred for 45 min. Filtration gave 1.6 g. (54%) of reddish crystals; m.p. 154–155°. Recrystallization from benzene-hexane gave red needles; m.p. 161–161.5°.

Anal. Calcd. for $C_{18}H_{17}N_3O$: C, 74.4; H, 5.88. Found: C, 74.69; H, 5.74.

2-Quinoline carboxaldehyde-2,4-dinitrophenylhydrazone. A solution of 0.4 g. (0.0014 mole) of 2-quinolyl-*N*-(*p*-dimethylaminophenyl)nitrone (IV) was shaken with 50 cc. of 3*N* HCl. Addition of 2,4-dinitrophenylhydrazine precipitated the 2-quinoline carboxaldehyde derivative as yellow plates; m.p. 245–248°. Recrystallization from ethanol-water gave yellow needles which softened at 245° and melted at 252–254°. Reported m.p. 251–253°.[8]

4-Quinolyl-N-(p-dimethylaminophenyl)nitrone (VI). The procedure was essentially the same as for the preparation of 2-quinolyl-*N*-(*p*-dimethylaminophenyl)nitrone (IV). From 3.4 g. (0.01 mole) 1-(4-quinolylmethyl)pyridinium iodide 1.95 g. (65%) reddish crystals was obtained. Crystallization from benzene-hexane gave 1.42 g. (49%) of red needles; m.p. 179–181°.

Anal. Calcd. for $C_{18}H_{17}N_3O$: C, 74.40; H, 5.88. Found: C, 74.67; H, 5.63.

1-(1-Methyl-2-quinolylidenylmethyl)pyridinium iodide (XI). To 1 g. (0.0025 mole) of 1-(2-quinolylmethyl)pyridinium iodide methoiodide (IX) dissolved in 5 ml. of water, *M* sodium hydroxide was added dropwise until no further precipitate was observed. The red precipitate was collected by filtration. Yield 0.6 g. (82%) of red powder; m.p. 184–190°.

Anal. Calcd. for $C_{16}H_{15}N_2I$: C, 53.05; H, 4.17. Found: C, 52.90; H, 4.14.

N-Methyl-2-quinolone. To 2.5 g. (0.005 mole) 1-(2-quinolylmethyl)pyridinium iodide methoiodide (IX) dissolved in 20 cc. water, 10 ml. of 2*N* potassium hydroxide was added. After the hydrolysis was complete the product was extracted with chloroform. Yield 0.55 g. (68%) of tan material melting at 72–73°. Reported for *N*-methyl-2-quinolone, 73°.[10]

N-Methyl-4-quinolone (XII). A solution of 0.5 g. (0.001 mole) 1-(4-quinolylmethyl)pyridinium iodide methoiodide (X) dissolved in 30 cc. water was treated with 4 ml. of 10*N* sodium hydroxide and the mixture heated on the steam bath for 20 min. Extraction with chloroform followed by evaporation of solvent gave 0.17 g. (100%) of white crystals; m.p. 149°.[10]

Acknowledgment. We wish to thank the American Cyanamid Co. for a research fellowship.

EVANSTON, ILL.

[CONTRIBUTION FROM THE ILLINOIS STATE GEOLOGICAL SURVEY]

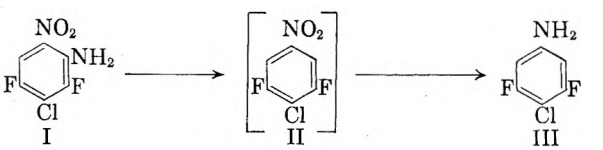
A Combined Deamination and Nitro Reduction Method for Nitroanilines[1]

G. C. FINGER AND R. H. WHITE

Received June 5, 1958

The hypophosphorous acid–cuprous oxide deamination method on nitroanilines has been modified so that the nitro compounds which are formed are reduced in turn by cuprous oxide to the corresponding amines. Over-all yields of 55–65% are reported for three halogenated nitroanilines.

It was reported previously from this laboratory that in the hypophosphorous acid–cuprous oxide deamination of 2-nitro-3,4,6-trifluoroaniline[2] to 2,3,5-trifluoronitrobenzene, a small amount of 2,3,5-trifluoroaniline was isolated as a by-product. Later other halogenated nitroanilines were observed to give similar results. This indicated that part of the desired nitro compound was reduced to the corresponding amine. At the same time it became apparent that the yield of amine varied considerably between similar experiments. The secondary reaction was investigated. As a result of this study, the deamination process has been modified so that complete reduction of the nitro compound also takes place, and the corresponding amine is isolated as the final product.



As the deamination mixture contains two reducing agents, hypophosphorous acid and cuprous oxide,[3] there is the question whether one agent or the combination of both is chiefly responsible for the

(1) Published by permission of the Chief of the Illinois State Geological Survey.

(2) G. C. Finger, F. H. Reed, and R. E. Oesterling, *J. Am Chem. Soc.*, **73**, 152 (1951).

(3) Reduction of nitro compounds by copper sponge with sodium hypophosphite has been reported by A. Maihle and M. Murat, *Bull. soc. chim. France*, **7**, 952 (1910).

reduction of a nitro group. The literature[4] is rather mute on the formation of secondary reduction products in the hypophosphorous acid or cuprous oxide catalyzed ethanol deamination procedures. Many nitroanilines are deaminated to the nitro derivatives in high yields by both methods thus inferring that the reducing agents or catalyst have no significant effect on the nitro groups. For a more satisfactory answer, the reducing agents were tested on 4-chloronitrobenzene. To stirred aqueous slurries of sodium hypophosphite, cuprous oxide, and a mixture of both, a solution of 4-chloronitrobenzene dissolved in a large excess of concentrated sulfuric acid was added. The resulting mixtures were heated to about 100° for several hours and then examined for amine formation. Cuprous oxide gave a substantial yield of 4-chloroaniline, whereas sodium hypophosphite gave very little evidence of nitro reduction. Reduction occurred in the sodium hypophosphite–cuprous oxide mixture in proportion to the cuprous oxide content. This explains the variation in amine formation in the earlier deaminations where an arbitrary amount of cuprous oxide was used with only catalysis in mind.

The cuprous oxide reduction of 4-chloronitrobenzene in concentrated sulfuric acid was examined further. With a molar ratio of 3:1 and higher of cuprous oxide to nitro compound, and a heating period of about 4 hr., a yield of 83–90% of steam distilled 4-chloroaniline was obtained. The ratio is as expected on the basis of a simple oxidation-reduction reaction. In practice, however, a ratio of 4:1 or more is recommended. Other nitrobenzenes gave similar results. Due to its convenience, cuprous oxide could be used more frequently for the reduction of nitro compounds.

It was quite evident now that in the deamination of nitroanilines, the resulting nitro compounds could be reduced to the amines in the same operation if sufficient cuprous oxide was present. Due to interest in halogenated nitroanilines, a number of these compounds were submitted to the deamination procedure as modified with excess cuprous oxide. In general, the nitroanilines were diazotized by the nitrosylsulfuric–phosphoric acid procedure.[5,6] The diazonium solutions were added slowly to a water slurry of sodium hypophosphite and cuprous oxide. Subsequent heating at 90–100° for about 4 hr. completed the deamination and nitro reduction. After neutralization with alkali, steam distillation removed the amines. The crude amine yields are based on the amount of nitroaniline used.

Yield data obtained on three nitroanilines are (1) 5-fluoro-2-nitroaniline to 4-fluoroaniline, 55%, (2) 2,6-dichloro-4-nitroaniline to 3,5-dichloroaniline 59%; and (3) 4,6-difluoro-5-chloro-2-nitroaniline to 3,5-difluoro-4-chloroaniline, 64%.

EXPERIMENTAL[7]

As the nitroanilines under investigation were weakly basic amines, they were diazotized by the nitrosylsulfuric–phosphoric acid procedure. In contrast to earlier studies,[2,8] the diazonium solutions were added to the reducing agents thus reversing the order of addition. To complete the deamination and reduction of the nitro group, the reaction was heated on a steam bath. As a routine procedure, a 4-hr. heating period is essential, although in some instances the entire process appeared to be complete in a very short time. The free amine may also be recovered by solvent extraction with the disadvantage that a large volume of solution must be handled.

The method and procedure are illustrated by the preparation of 3,5-difluoro-4-chloroaniline.

3,5-Difluoro-4-chloroaniline (III). A mixture of 119 g. (0.57 mole) of 4,6-difluoro-5-chloro-2-nitroaniline (I),[9] m.p. 96–97°, and 84 ml. of glacial acetic acid was dissolved in 640 ml. of concd. sulfuric acid. Nitrosylsulfuric acid was prepared by adding 46 g. (0.66 mole) of sodium nitrite to 424 ml. of concd. sulfuric acid at 20–25°. To the amine salt at room temperature was added the nitrosylsulfuric acid, and the mixture stirred for 2 hr. The diazotization was completed by addition at 0–10° of sirupy phosphoric acid (85%) and the mixture warmed on a steam bath to 65–70°. After cooling, the diazonium solution was added slowly to an efficiently stirred slurry of 301 g. of sodium hypophosphite,[10] 326 g. of cuprous oxide,[11] and 500 ml. of water in a large flask. Considerable foaming takes place during the addition. The temperature was allowed to rise to 50°. To complete the reaction process, the mixture was heated at 90–100°, usually on a steam bath, for 4 hr. Steam was passed into the mixture to remove unreduced 3,5-difluoro-4-chloronitrobenzene (II),[9] m.p. 41–42°; usually less than one gram was recovered. The reaction mixture was neutralized with strong sodium hydroxide solution, and the amine was removed by steam distillation. Yield of crude amine, 60 g. or 64%. Recrystallization from ethanol gave 3,5-difluoro-4-chloroaniline as white needles, m.p. 78–79°.

Anal. Calcd. for $C_6H_4ClF_2N$: C, 44.07; H, 2.51; Cl, 21.69; N, 8.56. Found: C, 44.12; H, 2.50; Cl, 21.85; N, 8.60.

The acetyl derivative was recrystallized from benzene to give white needles, m.p. 166–166.5°.

Anal. Calcd. for $C_8H_6ClF_2NO$: N, 6.80. Found: N, 6.74.

URBANA, ILL.

(4) N. Kornblum, *Org. Reactions*, **2**, 262–340 (1944).

(5) J. Schoutissen, *J. Am. Chem. Soc.* **55**, 451 (1933).

(6) C. Weygand, *Organic Preparations*, Interscience Publishers, Inc., New York, N. Y., 1945, Ch. 2, p. 110.

(7) Analyses by D. R. Dickerson, microanalyst for the Survey.

(8) G. C. Finger, F. H. Reed, and J. L. Finnerty, *J. Am. Chem. Soc.*, **73**, 153 (1951).

(9) G. C. Finger, R. E. Oesterling, and R. H. White, *Abstracts, 130th Meeting*, American Chemical Society, Sept. 1956, Atlantic City, N. J., p. 26-O.

(10) Sodium hypophosphite, NF grade, 98%.

(11) Red cuprous oxide, USN Type 1, 97%.

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

Pyridine Derivatives. II. Some Halogen Substituted 2-Pyridoxyacetic Acids[1]

M. P. CAVA AND N. K. BHATTACHARYYA

Received June 6, 1958

A number of halogenated 2-pyridoxyacetic acids have been prepared, *via* their ethyl esters, by the reaction of ethyl diazoacetate with the appropriate halogenated 2-pyridones.

A number of halo derivatives of phenoxyacetic acid have attracted considerable interest, both theoretical and practical, because of the marked hormonal activity which they exhibit in higher plants.[2] The study reported here was undertaken with the object of synthesizing some pyridine analogs of these halo acids for plant physiological testing purposes.

The reaction of 2-pyridone with ethyl diazoacetate has been reported to give a mixture of *N*- and *O*-alkylation products; the latter, ethyl 2-pyridoxyacetate, was converted by hydrolysis to 2-pyridoxyacetic acid.[3] This sequence of reactions has been extended to a number of halogenated 2-pyridones. The initially produced pyridoxyacetic esters were, in some cases, purified and analyzed. In other cases, the crude esters were hydrolyzed directly to the crystalline oxyacetic acids. In two cases (V and XI) the esters were converted also to the corresponding amides. The results of these experiments are summarized in Table I.

Of the substituted 2-pyridones employed as starting materials, only 3-methyl-5-chloro-2-pyridone and 3,5-dichloro-6-methyl-2-pyridone have not been described previously. They were obtained by direct chlorination of 3-methyl-2-pyridone and 6-methyl-2-pyridone, respectively, as described further in the experimental section.

The direct chlorination of 2-pyridone itself to 3,5-dichloro-2-pyridone deserves comment. The only recorded observation of this reaction[4] mentions the use of chloroform as solvent: no further details or yields are given. It has been found now, after investigating this chlorination under a variety of conditions, that it proceeds best at room temperature in 20% sulfuric acid, 3,5-dichloro-2-pyridone being obtained in 63% yield. It was found necessary, however, to remove the dichloro derivative by filtration several times during the course of the chlorination, since it is converted slowly by excess chlorine to water soluble decomposition products.

The most interesting of the pyridoxyacetic acids prepared are 3,5-dichloro-2-pyridoxyacetic acid (X) and 3,5,6-trichloro-2-pyridoxyacetic acid (XVI), which are direct pyridine analogs of the well-known herbicides[2] 2,4-dichlorophenoxyacetic acid and 2,4,5-trichlorophenoxyacetic acid. The plant physiology of these and other compounds described here is under investigation by Dr. R. L. Weintraub[5] and will be described elsewhere.

EXPERIMENTAL[6]

Pyridones. The following pyridines were prepared following methods in the literature: 3-chloro-2-pyridone,[7] 4-chloro-2-pyridone,[8] 5-chloro-2-pyridone,[9] 6-chloro-2-pyridone,[7] 5-bromo-2-pyridone,[10] 3,5-dibromo-2-pyridone,[10] 3,5,6-trichloro-2-pyridone.[11]

3,5-Dichloro-2-pyridone. The more readily prepared sodium 2-pyridoxide[12] gave results identical to those obtained using 2-pyridone itself: A stream of chlorine was passed through a stirred solution of sodium 2-pyridoxide dihydrate (8.0 g.) in a mixture of water (25 ml.) and sulfuric acid (5 ml.) at room temperature. After 6 min. white solid appeared and the solution soon set to a paste of crystals. These were filtered and washed with a little cold water. The combined filtrate and washings were treated with chlorine as before, and additional crystals were removed in three further crops. The combined 3,5-dichloro-2-pyridone, m.p. 170–173°, weighed 6.5 g. (63%). Recrystallization from benzene raised the melting point to 179–181° (reported[13] 178–179°).

3-Methyl-5-chloro-2-pyridone. Gaseous chlorine was passed through a solution of 3-methyl-2-pyridone[14] (12.0 g.) in chloroform (175 ml.) until the odor of chlorine persisted after introduction of the gas was stopped. The resulting paste of pyridone hydrochloride was filtered, washed with chloroform, and suspended in fresh chloroform (200 ml.). The suspension was refluxed gently, when hydrogen chloride

(1) Supported by a contract with the U. S. Army Chemical Corps., Fort Detrick, Frederick, Md.

(2) *E.g.* see: *Plant Regulators in Agriculture*, edited by H. B. Tukey, John Wiley and Sons, Inc., New York, 1954.

(3) G. B. R. deGraaff, J. Maas, and H. J. den Hertog, *Rec. trav. chim.*, **74**, 175 (1955).

(4) M. Dohrn and R. Dirksen, U. S. Patent **1,706,775**; *Chem. Abstr.*, **23**, 2189 (1929).

(5) U. S. Army Biological Warfare Laboratories, Fort Detrick, Md.

(6) Analyses carried out by Galbraith Laboratories, Knoxville, Tenn. Melting points are uncorrected.

(7) M. P. Cava and N. K. Bhattacharyya, *J. Org. Chem.*, **23**, 1287 (1958).

(8) R. Graf, *Ber.*, **64**, 21 (1931).

(9) A. E. Chichibabin and A. F. Egorov, *J. Russ. Phys.-Chem Soc.*, **60**, 683 (1928).

(10) A. E. Chichibabin and V. S. Tyazhelova, *J. Russ. Phys.-Chem. Soc.*, **50**, 483 (1920).

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(12) W. T. Caldwell, F. T. Tyson, and L. Lauer, *J. Am. Chem. Soc.*, **66**, 1479 (1944).

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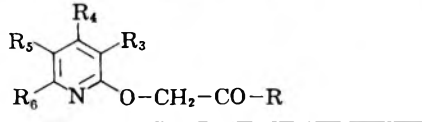
TABLE I

SUBSTITUTED 2-PYRIDOXYACETIC ACIDS AND DERIVATIVES



Cpd.[a]	R	R_3	R_4	R_5	R_6	Yield, %	B.p. °C.	B.p. Mm.	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Halogen, % Calcd.	Halogen, % Found
I	OH	Cl	H	H	H	85[c]	—	—	141–142	$C_7H_6ClNO_3$	44.80	44.83	3.20	3.11	7.46	7.36	18.93	18.85
II	OH	H	Cl	H	H	85[c]	—	—	134–135	$C_7H_6ClNO_3$	44.80	45.08	3.20	2.86	7.46	7.31	18.93	18.98
III	OH	H	H	Cl	H	86[c]	—	—	130–131	$C_7H_6ClNO_3$	44.80	44.96	3.20	3.21	7.46	7.41	18.93	18.89
IV	OH	H	H	H	Cl	87[c]	—	—	126–127	$C_7H_6ClNO_3$	44.80	45.28	3.20	3.19	7.46	7.53	18.93	18.93
V	OEt	H	H	Cl	H	76[b]	107–115	2	32–33	$C_9H_{10}ClNO_3$	50.11	50.03	4.64	4.41	6.50	6.42	16.47	16.49
VI	NH_2	H	H	Cl	H	81[c]	—	—	126–128	$C_7H_7ClN_2O_2$	45.10	45.23	3.75	3.85	15.06	14.95	19.05	19.00
VII	OEt	Cl	H	H	H	36[b]	115–116	2	—	$C_9H_{10}ClNO_3$	50.11	50.14	4.64	4.54	6.50	6.46	16.47	16.31
VIII	OEt	H	Cl	H	H	68[b]	110–112	3	38–39	$C_9H_{10}ClNO_3$	50.11	50.17	4.64	4.66	6.50	6.43	16.47	16.38
IX	OH	H	H	Br	H	71[b]	—	—	134–135	$C_7H_6BrNO_3$	36.20	36.19	2.58	2.69	6.04	5.88	34.50	34.47
X	OH	Cl	H	Cl	H	93[c]	—	—	170–171	$C_7H_5Cl_2NO_3$	37.83	37.62	2.25	2.65	6.30	6.10	31.98	31.55
XI	OEt	Cl	H	Cl	H	74[b]	115–117	2	40–41	$C_9H_9Cl_2NO_3$	43.20	43.73	3.60	3.80	5.06	5.43	28.41	27.62
XII	NH_2	Cl	H	Cl	H	83[c]	—	—	167–168	$C_7H_6Cl_2N_2O_2$	38.00	37.89	2.72	2.48	12.67	12.50	32.12	31.78
XIII	OH	Br	H	Br	H	82[c]	—	—	166–167	$C_7H_5Br_2NO_3$	27.00	27.13	1.61	1.69	4.51	4.55	51.50	51.29
XIV	OEt	Br	H	Br	H	80[b]	122–124	2	134–135	$C_9H_9Br_2NO_3$	31.90	32.19	2.66	2.73	4.14	4.13	47.20	47.02
XV	OH	CH_3	H	Cl	H	65[b]	—	—	131–132	$C_8H_8ClNO_3$	47.90	48.07	3.98	4.15	6.98	7.09	17.65	17.39
XVI	OH	Cl	H	Cl	Cl	17[b]	—	—	149–150	$C_7H_4Cl_3NO_3$	32.70	32.63	1.56	1.51	5.45	5.61	41.50	41.24
XVII	OH	Cl	H	Cl	CH_3	46[b]	—	—	144–145	$C_8H_7Cl_2NO_3$	40.60	40.76	2.97	3.20	5.94	6.03	30.50	30.23

[a] For the acids (R = OH): benzene; for the esters (R = OEt): petroleum ether; for the amides (R = NH_2): ethanol. [b] Based on the pyridone used. [c] Based on the corresponding oxyester.

was evolved gradually and most of the solid dissolved. The filtered solution was concentrated and 30–60° petroleum ether was added to yield the methylchloropyridone as a white solid, m.p. 160–162° (9.0 g.). From the mother liquor was obtained a further 2.5 g. (total yield 11.5 g., 73%). Recrystallization from benzene gave long white needles, m.p. 162–163°.

Anal. Calcd. for C_6H_6ClNO: C, 50.02; H, 4.18; N, 9.77; Cl, 24.42. Found: C, 50.23; H, 4.13; N, 9.83; Cl, 24.37.

3,5-Dichloro-6-methyl-2-pyridone. Gaseous chlorine was passed through a cooled solution of 6-methyl-2-pyridone[15] (18.0 g.) in 2*N* sodium hydroxide (90 ml.). The precipitated solid was filtered, and the mother liquor chlorinated once more to obtain a second crop. The combined solids were dissolved in benzene, the solution dried (sodium sulfate), concentrated, and cooled. The crystalline precipitate (11.5 g., 40%: m.p. 215–218°) was filtered and dried. Recrystallization from benzene raised the melting point to 219–220°.

Anal. Calcd. for $C_6H_5Cl_2NO$: C, 40.50; H, 2.81; N, 7.86; Cl, 39.30. Found: C, 40.93; H, 2.87; N, 8.08; Cl, 38.99.

2-Pyridoxyacetic acids and derivatives. The procedures employed are exemplified by the following preparations in the 3,5-dichloro series: *Ethyl 3,5-dichloro-2-pyridoxyacetate* (XI). A 150 ml. 3-necked flask fitted with a reflux condenser, mechanical stirrer, and dropping funnel, and containing 3,5-dichloro-2-pyridone (8.0 g.), was heated in an oil bath (bath temperature 160–165°). Ethyl diazoacetate (10.0 ml.) was added dropwise to the stirred pyridone over a period of 3 hr. (bath temperature 155–165°). Heating was continued for 1 additional hr. and the hot dark sirup transferred to a Claisen flask. Distillation at 2 mm. yielded the desired ester XI (b.p. 110–120°; 9.0 g., 74%). On redistillation most of the ester boiled at 115–117° (2 mm.), and solidified on cooling. Crystallized from 30–60° petroleum ether, it formed needles, m.p. 40–41°. For analysis see Table I.

Distillation of the pot residue from the diazoacetic ester reaction gave a small amount of viscous liquid (b.p. 160–200° at 2 mm.), solidifying on standing to a semisolid mass. After several crystallizations from chloroform–petroleum ether, the pure *ethyl 3,5-dichloropyridone N-acetate* formed gleaming white flakes, m.p. 105–106°.

Anal. Calcd. for $C_9H_9Cl_2NO_3$: C, 43.20; H, 3.60; N, 5.06; Cl, 28.41. Found: C, 43.36; H, 3.62; N, 5.22; Cl, 28.20.

3,5-Dichloro-2-pyridoxyacetic acid (X). To a solution of the ethyl ester XI (3.0 g.) in ethanol (20 ml.) was added 1.023*N* sodium hydroxide (25 ml.), and the mixture was refluxed for 5.5 hr. The solvent was removed under vacuum and the residue dissolved in the minimal amount of water and neutralized by the addition of the theoretical quantity (22 ml.) of 1.162*N* sulfuric acid. The precipitated oxyacetic acid (2.45 g., 93%) was filtered, washed with a little cold water, and dried. Recrystallization from benzene gave small hard prisms, m.p. 170–171°. For analysis see Table I.

3,5-Dichloro-2-pyridoxyacetamide (XII). A solution of the ethyl ester XI (3.0 g.) in absolute ethanol (65 ml.) was cooled and saturated with gaseous ammonia. After several days in a refrigerator, the amide separated as long colorless needles, m.p. 167–168°, which were filtered and washed with cold ethanol. Concentration of the mother liquor yielded a second crop; the total yield was 2.2 g. (83%). The first crop of amide was directly analytically pure. For analysis see Table I.

COLUMBUS 10, OHIO

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

Pyridine Derivatives. III. The Rearrangement of Some Simple 3-Halopyridine-*N*-oxides[1]

M. P. CAVA AND BORIS WEINSTEIN

Received June 6, 1958

3-Chloropyridine, 3-bromopyridine, and 3-fluoropyridine were oxidized to the corresponding *N*-oxides, which were converted by hot acetic anhydride to haloacetoxypyridines. Hydrolysis of the latter yielded in all three cases the 3-halo-2-pyridones rather than the 5-halo isomers.

When pyridine-*N*-oxide is heated with acetic anhydride rearrangement of the oxygen function into the α-position of the ring occurs with the production of 2-acetoxypyridine.[2] The only simple β-substituted pyridine-*N*-oxide which has been subjected to this rearrangement is the 3-methyl derivative, which gives 3-methyl-2-acetoxypyridine, hydrolyzed by aqueous acid to 3-methyl-2-pyridone.[3] The object of the work reported here was to determine whether 3-halopyridine-*N*-oxides would rearrange in a similar manner to 3-halo-2-acetoxypyridines, or whether the rearrangement would occur para to the halogen atoms to give 5-halo-2-acetoxypyridines.

3-Fluoropyridine (I), 3-chloropyridine (II), and 3-bromopyridine (III) were converted to the corresponding *N*-oxides (IV, V, and VI) by oxidation with peracetic acid. Each *N*-oxide was rearranged by boiling acetic anhydride, and the substituted 2-acetoxypyridines (VII, VIII, and IX) which were formed were hydrolyzed to the corresponding 2-pyridones. In all cases only a single 2-pyridone was obtained, and this proved to be the 3-halo-derivative (X, XI, and XII). 3-Chloro-2-pyridone has been reported previously,[4] but 3-bromo-2-pyridone and 3-fluoro-2-pyridone are new compounds. However, 5-bromo-2-pyridone[5] and 5-

(1) Supported by a contract with the U. S. Army Chemical Corps, Fort Detrick, Frederick, Md.

(2) For a review of pyridine-*N*-oxide reactions, see: A. R. Katritzsky, *Quart. Revs.*, 10, 395 (1956).

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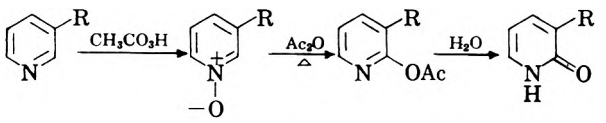
fluoro-2-pyridone[6] are known, and were shown to be different in melting point and infrared spectrum from the pyridones obtained *via* the *N*-oxide rearrangement.



I, R = F IV, R = F VII, R = F X, R = F
II, R = Cl V, R = Cl VIII, R = Cl XI, R = Cl
III, R = Br VI, R = Br IX, R = Br XII, R = Br

The effect of the 3-halo substituents on the ultraviolet spectrum of the 2-pyridone system is of some interest (Table I). 3-Fluoro-2-pyridone exhibits maxima almost identical to those of the parent 2-pyridone,[7] but 3-chloro-2-pyridone and 3-bromo-2-pyridone show appreciable bathochromic shifts.

TABLE I

ULTRAVIOLET MAXIMA OF 3-HALO-2-PYRIDONES (IN 95% ETHANOL)

3-Substituent	Mμ λ_{max} (E_{max})	Mμ λ_{max} (E_{max})
H[7]	227 (10,000)	297 (6310)
F	226 (5950)	296 (5510)
Cl	233 (5310)	306 (6060)
Br	234 (4350)	310 (6680)

EXPERIMENTAL[8]

3-Chloropyridine-N-oxide (V). A mixture of 3-chloropyridine (II, 2.50 g.), glacial acetic acid (45 ml.) and 30% aqueous hydrogen peroxide (10 ml.) was heated on a steam bath for 3 hr. An additional 5 ml. of 30% hydrogen peroxide was added and the solution was reheated for four days. The mixture was concentrated under reduced pressure to 20 ml., an equal volume of water was added, and the solution was concentrated to a sirup. Solid potassium carbonate (10.0 g.) was added and the residue was continuously extracted with chloroform overnight. The extract was concentrated under reduced pressure and the remaining liquid was distilled to give 1.00 g. (35%) of a colorless oil, b.p. 88–89° (1 mm.).

The hydrochloride of 3-chloropyridine-*N*-oxide was obtained from water as needles, m.p. 127.5–128.5°.

Anal. Calcd. for $C_5H_5Cl_2NO$: C, 36.17; H, 3.04; Cl, 42.71; N, 8.44. Found: C, 36.20; H, 2.99; Cl, 42.62; N, 8.61.

2-Acetoxy-3-chloropyridine (VIII). A solution of 3-chloropyridine-*N*-oxide (V, 0.90 g.) in acetic anhydride (15 ml.) was boiled under reflux for 4 hr. The reaction mixture was distilled directly to give 0.72 g. (61%) of a colorless liquid, b.p. 54–55° (1 mm.). The compound was not submitted to analysis since it hydrolyzed readily in air to the pyridone.

3-Chloro-2-pyridone (XI). A mixture of 2-acetoxy-3-chloropyridine (VIII, 0.68 g.) in 10% aqueous hydrochloric acid (10 ml.) was heated under reflux for 4 hr., then neutralized to the Congo Red endpoint with potassium hydroxide pellets and evaporated to dryness on a steam bath. The solid residue was broken up and was extracted several times with hot benzene. The combined extracts upon concentration and standing gave 0.40 g. (78%) of needles, m.p. 181.8–182.8°. An authentic sample[4] showed an identical infrared spectrum and gave no mixed melting point depression.

Anal. Calcd. for C_5H_4ClNO: C, 46.35; H, 3.11; Cl, 28.14; N, 10.90. Found: C, 46.70; H, 3.48; Cl, 27.75; N, 11.05.

3-Bromopyridine-N-oxide (VI). A mixture containing 3-bromopyridine (III, 10.00 g.), glacial acetic acid (50 ml.), and 30% aqueous hydrogen peroxide (10 ml.) was treated exactly as described for 3-chloropyridine. The residual liquid was distilled to give 5.07 g. (46%) of a viscous oil, b.p. 97–99° (0.5 mm.).

The hydrochloride of 3-bromopyridine-*N*-oxide was obtained from water as needles, m.p. 133.5–134.5° (dimorphism ?); reported, m.p. 181.5° and 181–182°.[9,10]

Anal. Calcd. for $C_5H_5BrClNO$: C, 28.53; H, 2.39; Br, 37.97; Cl, 16.85; N, 6.66. Found: C, 28.64; H, 2.30; Br, 37.92; Cl, 16.71; N, 6.74.

2-Acetoxy-3-bromopyridine (IX). A solution of 3-bromopyridine-*N*-oxide (VI, 2.50 g.) in acetic anhydride (15 ml.) was treated as described for 3-chloropyridine-*N*-oxide. Distillation gave 1.55 g. (50%) of a colorless liquid; b.p. 77–78° (0.5 mm.). The ready hydrolysis of the compound precluded an analysis.

3-Bromo-2-pyridone (XII). A mixture of 2-acetoxy-3-bromopyridine (IX, 1.08 g.) in 10% hydrochloric acid (10 ml.) was treated as described for 2-acetoxy-3-chloropyridine. The concentrated benzene extracts gave 0.69 g. (80%) of needles, m.p. 136.5–187.0°.

Anal. Calcd. for C_5H_4BrNO: C, 34.51; H, 2.31; Br, 45.93; N, 8.05. Found: C, 34.74; H, 1.97; Br, 46.13; N, 8.13.

3-Fluoropyridine-N-oxide (IV). A mixture containing 3-fluoropyridine (I, 7.63 g.), glacial acetic acid (50 ml.), and 30% aqueous hydrogen peroxide (10 ml.) was treated as described for 3-chloropyridine. The residual solid was sublimed under vacuum to give 2.12 g. (19%) of needles, m.p. 62.5–63.0°; on exposure to the atmosphere, the needles liquefied almost immediately.

The picrate of 3-fluoropyridine-*N*-oxide was obtained from benzene as needles, m.p. 107.0–108.0°.

Anal. Calcd. for $C_{11}H_7FN_4O_8$: C, 38.61; H, 2.06. Found: C, 38.77; H, 2.41.

2-Acetoxy-3-fluoropyridine (VII). A mixture containing 3-fluoropyridine-*N*-oxide (IV, 2.26 g.) in acetic anhydride (15 ml.) was treated as described for 3-chloropyridine-*N*-oxide. Distillation gave 2.22 g. (65%) of a colorless liquid; b.p. 82–83° (1 mm.). Ready hydrolysis of the compound prevented an analysis.

3-Fluoro-2-pyridone (X). A mixture of 2-acetoxy-3-fluoropyridine (VII, 0.51 g.) and 10% hydrochloric acid (10 ml.) was treated as described for 2-acetoxy-3-chloropyridine. The concentrated benzene extracts gave 0.27 g. (80%) of needles, m.p. 166.0–166.5°.

Anal. Calcd. for C_5H_4FNO: C, 53.10; H, 3.56; F, 16.80; N, 12.39. Found: C, 53.15; H, 3.61; F, 16.71; N, 12.37.

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[CONTRIBUTION FROM THE PIONEERING RESEARCH DIVISION OF THE QUARTERMASTER RESEARCH AND ENGINEERING CENTER]

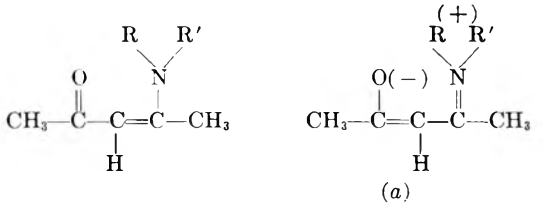
A Study of β-Amino-α,β-unsaturated Ketones[1]

JULIUS WEINSTEIN AND GEORGE M. WYMAN[2]

Received July 15, 1958

A study of the N—H stretching bands of 4-(2′-cyanoethyl)amino-3-penten-2-one (I) and 4-amino-3-penten-2-one (II) in the 3 μ region of the infrared spectrum is described. Evidence is provided for the presence of intramolecular hydrogen bonds in these compounds in both the solid and solution phases. The existence of II in polymeric aggregates, held together by intermolecular hydrogen bonding is also shown. These conclusions are confirmed by measurements in the 6 μ region, and the assignment of a band to N—H deformation is made. The spectroscopic data support the enamine (IV) structure for these compounds rather than the imine (V) structure. Photochemical isomerization studies of I and 4-*N*-(2′-cyanoethyl)methylamino-3-penten-2-one (III) provide evidence for both *cis* and *trans* isomers of these compounds. The results of a spectroscopic investigation of the positive ferric chloride test given by I and II in ethanol suggest that these compounds form complexes with ferric chloride prior to their hydrolysis to acetylacetone. Positive ferric chloride tests are reported for I and II in chloroform.

An infrared absorption study of β-amino-α,β-unsaturated ketones was carried out by Cromwell, Miller, and co-workers.[3] These investigators found the C=O band at unusually long wave lengths and attributed this to an appreciable contribution of the ionic resonance form (*a*) to the ground state. The fact that the displacement of the C=O band



(*a*)

I, R = H, R′ = $CH_2CH_2C{\equiv}N$
II, R = R′ = H
III, R = CH_3, R′ = $CH_2CH_2C{\equiv}N$

was greatest in those compounds where R or R′ = H suggested the presence of intramolecular hydrogen bonds. Their study was devoted mainly to a consideration of the absorption bands in the 6 μ region of the spectra of the amino ketones measured as solids. The work reported here was concerned, in part, with an investigation of the N—H stretching bands of I and II in the 3 μ region, in order to obtain additional information concerning the nature of the hydrogen bonding which occurs in the solid and solution states. In order to obtain additional data, measurements on I, II, and III in solution and as solids were made in the 6 μ region.

Associated with the hydrogen bonding problem is that of the geometry of the β-amino-α,β-unsaturated ketones. Chelation would tend to stabilize compounds I and II in the configuration in which the functional groups are *cis* with respect to one another. However, the existence of these compounds in the *trans* modification is possible and might be observed under the proper conditions. In the case of III, steric factors would be expected to be of importance in determining the relative stability of the two isomers. In this work, direct evidence for these *cis* and *trans* isomers was sought by photochemical studies.

When compounds I, II, and III are treated with 1% ethanolic ferric chloride, a red color is immediately formed.[3] This color might be due solely to the ferric chloride-acetylacetone complex. Acetylacetone is readily formed by the hydrolysis of the β-amino-α,β-unsaturated ketones under acidic conditions. However, the instantaneity of the color formation might signify initial complex formation between the amino-ketones and ferric chloride. It was decided, therefore, to investigate the color reaction spectroscopically.

RESULTS AND DISCUSSION

Infrared absorption spectra. The spectrum of compound I in carbon tetrachloride solution showed a band at 3.16 μ (with a shoulder at 3.11 μ). The intensity of this band did not change on dilution, indicating that the absorption band is due to the vibration of the N—H group engaged in an intramolecular hydrogen bond with the carbonyl oxygen. This assignment is further substantiated by the observation that no band attributable to free N—H was formed on dilution. The internal hydrogen bond persists in the solid state, as shown by the presence of an absorption band at 3.16 μ in the spectrum of the solid. Previous workers did not detect this band.[4]

(1) Presented before the Division of Organic Chemistry at the 131st Meeting of the American Chemical Society, Miami, Fla., April 1957.

(2) Present address: U. S. Army Research & Development Liaison Group, Rheingau Allee 2, Frankfurt a/Main, Germany.

(3) N. H. Cromwell, F. A. Miller, A. R. Johnson, R. L. Frank, and D. J. Wallace, *J. Am. Chem. Soc.*, 71, 3337 (1949).

(4) Cromwell, *et al.*, *cf.* ref. (3), attributed the failure to observe the N—H stretching frequency to a shift of this band to slightly longer wave lengths (near 3.4 μ) where it would be obscured by the C—H stretching frequencies of "Nujol."

The spectrum of II in carbon tetrachloride showed several bands in the N—H stretching region. Two of these bands (2.86 μ and 2.96 μ) were strongly affected by dilution, as shown in Fig. 1.

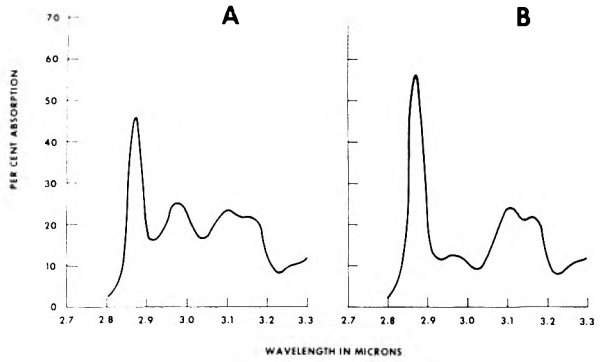


Fig. 1. Curve A represents the infrared absorption spectrum in the 3 μ region of a dilute solution of II in CCl_4, measured in a 0.5 mm. cell. Curve B is the spectrum observed after the solution was diluted to 1/4 its original concentration and measured in a 2.0 mm. cell

The band at 2.86 μ which showed an intensity increase on dilution is attributed to free N—H. The 2.96 μ band, which on dilution showed a decrease in intensity, is due to intermolecularly bonded N—H. The doublet at 3.09 and 3.15 μ showed no intensity change, and is assigned to intramolecularly bonded N—H. In the spectrum of II in the solid phase two absorption bands were found, one at 2.98 μ and the other at 3.14 μ. The 2.98 μ band corresponds to the 2.96 μ band in the solution spectrum, and is due to intermolecularly bonded N—H. The absence of an absorption band at shorter wave lengths, attributable to free N—H, indicates that association through intermolecular hydrogen bonding is complete in the solid state. The band at 3.14 μ is attributed to intramolecularly bonded N—H. Band assignments in the 3 μ region are listed in Table I.

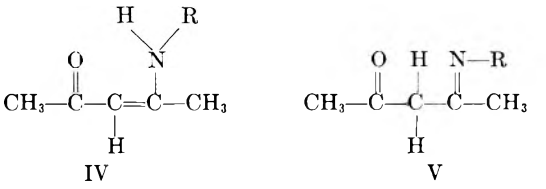
TABLE I

INFRARED BAND ASSIGNMENTS IN THE 3μ REGION

Compound	State	Free N—H (μ)	Intermolecularly Bonded N—H (μ)	Intramolecularly Bonded N—H (μ)
I	Solid	[a]	[a]	3.16 (3.11)[b]
	Solution	[a]	[a]	3.16 (3.11)
II	Solid	[a]	2.98	3.14
	Solution	2.86	2.96	3.09, 3.15

[a] No absorption band. [b] Shoulders on the main absorption band are indicated in parentheses.

In agreement with the evidence of Cromwell and co-workers,[3,5-7] the present spectroscopic data support the enamine (IV) structure for the compounds investigated, rather than the imine (V) structure.



The imine structure was recently proposed by Edwards and Petrow[8] for the condensation products of *o*-, *m*- and *p*-chloroaniline with acetylacetone. If I possessed the imine structure, then the spectrum of I would not show an N—H band.

The carbonyl absorption band of I and III in carbon tetrachloride appeared at 6.18 μ and 6.04 μ respectively. On dilution the carbonyl band did not show a wave length or intensity change in either case. This observation provides additional support for a chelate structure for I, and also agrees with the expected behavior of III, where there is no N—H available for the formation of intermolecular hydrogen bonds.

The spectra in the 6 μ region of II in carbon tetrachloride and in the solid state are shown in Fig. 2.

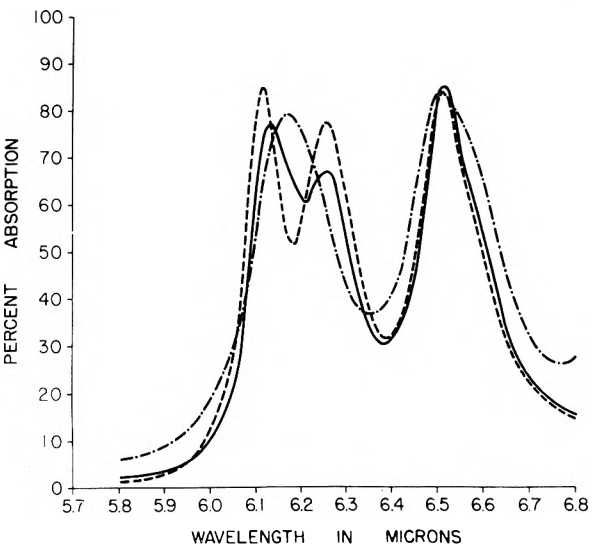


Fig. 2. The infrared absorption spectra of II in the 6 μ region: (———) CCl_4 solution measured in a 0.1 mm. cell; (– – –) solution diluted to 1/5 its initial concentration and measured in a 0.5 mm. cell; (–·–·–) solid dispersed in a KBr pellet

In the spectrum of the solid a strong, broad band was found at 6.17 μ. This absorption, however, was resolved into two strong bands in the solution spectra. In the more concentrated solution the carbonyl band appeared at 6.13 μ and the second band at 6.26 μ. On dilution the carbonyl band was found at 6.12 μ, and showed a marked intensity increase. This behavior is attributed to the dissociation of

(5) N. H. Cromwell and W. R. Watson, *J. Org. Chem.*, **14**, 411 (1949).

(6) N. H. Cromwell and R. S. Johnson, *J. Am. Chem. Soc.*, **65**, 2481 (1943).

(7) N. H. Cromwell and R. S. Johnson, *J. Am. Chem. Soc.*, **65**, 316 (1943).

(8) W. G. H. Edwards and V. Petrow, *J. Chem. Soc.*, 2853 (1954).

intermolecular hydrogen bonds. The intensity increase also shown by the 6.26 μ band on dilution suggests its assignment to an N—H deformation vibration. The 6.26 μ band is found within the wave-length range observed for primary amines.[9] In the spectrum of the solid the broad band at 6.17 μ results from the overlapping of the carbonyl band shifted to longer wave lengths and the N—H band shifted to shorter wave lengths. It was found, when solid and solution samples of comparable concentrations were measured, that the area under the 6.17 μ band in the spectrum of the solid agreed within 4% with the total area under the 6.13 μ and 6.26 μ bands in the solution spectrum. Shifts of the carbonyl stretching and N—H deformation bands in opposite directions upon changes of state result from the formation or dissociation of intermolecular hydrogen bonds, and have been reported for amides.[10] In the spectrum of the more concentrated solution a significant contribution from the 6.17 μ band was observed on the long wavelength side of the C=O absorption.

A strong band at 6.30 μ appeared in both the solution and solid spectra of I. This absorption is found within the wave-length range observed for the N—H deformation band of secondary amines.[9] Normally this band is weak, but it appears as a medium to strong band in secondary amides.[10,11] Compound I, as well as II and III, is a vinylog of an amide, and this may account for the enhanced intensity of the N—H deformation band. Failure to observe a wave-length shift of this band upon a phase change can be attributed to the fact that I is not associated through hydrogen bonding.

In the solid and solution spectra of the tertiary amine (III) there was no absorption corresponding to the bands assigned to N—H deformation in the spectra of I and II. Band assignments in the 6 μ region are listed in Table II.

TABLE II

INFRARED BANDS IN THE 6μ REGION

Compound	State	C=O Stretching (μ)	N—H Deformation (μ)	(μ)[a]
I	Solution	6.18	6.30	6.62
	Solid[b]	6.20	6.30	6.59
II	Solution	6.13[c]	6.26	6.52
	Solid[b]	6.17[d]	6.17[d]	6.50
III	Solution	6.04	[e]	6.44
	Solid[b]	6.11	[e]	6.51

[a] See ref. (3) for a discussion of the origin of this band. [b] Samples were dispersed in potassium bromide pellets. [c] In more dilute solution the band was found at 6.12 μ. [d] Results from the overlapping of the C=O and N—H bands. [e] No absorption band.

In a recent infrared study of II in the liquid phase a carbonyl band was reported at 5.88 μ.[12] This was interpreted as evidence for structure V (R = H) in a non-hydrogen bonded configuration. In the present investigation no evidence for this structural assignment was found in either the solution or solid phase. The 5.88 μ band was also missing from the solid spectrum of the analogous compound, 4-amino-3-methyl-3-penten-2-one, studied by Cromwell.[3]

Photochemical isomerization and decomposition. It has been shown for other conjugated, unsaturated compounds that irradiation of their solutions with light of a wave length corresponding approximately to the wave length of their absorption band, results in some geometrical isomerization.[13] Reversal of the reaction occurs when the solution is allowed to stand after the exciting radiation is removed.

In Fig. 3, the curve of highest absorption intensity represents the ultraviolet spectrum of an isooctane solution of I prior to irradiation. When the solution was irradiated for 6 minutes with the 313 mμ line from a medium pressure mercury arc, partial conversion to the less stable isomer occurred, as shown by the decrease in the intensity of absorption and the shift of the band to shorter wave lengths. The original spectrum was again observed when the solution was allowed to stand in darkness for 35 minutes at room temperature. Since the infrared data provide evidence for chelation, the

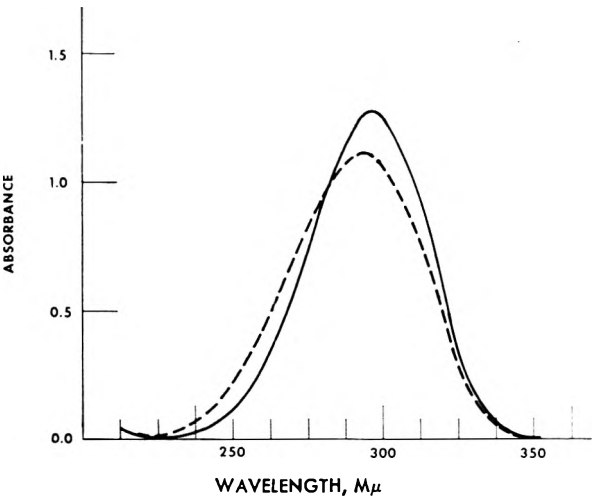


Fig. 3. The ultraviolet absorption spectra of I in isooctane before irradiation with the 313 mμ line from a mercury arc (———) and after irradiation for six minutes (– – – –). The original curve (———) is obtained when the solution is allowed to stand for 35 minutes in the dark, after irradiation

(9) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley & Sons, New York, 1954, p. 212.

(10) R. E. Richards and H. W. Thompson, *J. Chem. Soc.*, 1248 (1947).

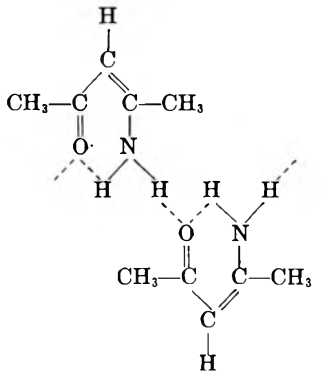
(11) *The Chemistry of Penicillin*, Princeton University Press, Princeton, N. J., 1949, p. 389.

(12) H. F. Holtzclaw, Jr., J. P. Collman, and R. M. Alire, *J. Am. Chem. Soc.*, **80**, 1100 (1958).

(13) G. M. Wyman, *Chem. Revs.*, **55**, 625 (1955).

more stable isomer is that in which the carbonyl and amino groups are *cis*.

Compound II decomposed under the conditions employed (irradiation with the 254–265 mμ mercury lines) as shown by the irreversibility of the spectral changes. No evidence was obtained for the existence of geometrical isomers. However, it can be inferred from the infrared data that the more stable structure is that in which both the carbonyl and amino groups lie on the same side of the molecule. The hydrogen bonding and geometrical arrangement in this molecule may be represented by structure VI. This structure also indicates the existence of II in polymeric aggregates.



VI

A reversible spectral change, similar to that observed with compound I, was noted when an isooctane solution of III was irradiated with the 313 mμ mercury line for 4 minutes. In the *cis* configuration (similar to VI) this compound could not be coplanar, due to overcrowding introduced by the bulky groups on the nitrogen atom. Consequently, it is probable that the more stable isomer is the one in which the functional groups are in a *trans* configuration with respect to one another.

Ferric chloride test. The visible absorption spectra of I, II, and III in 1% ethanolic ferric chloride were measured. In the spectra of I and II an initial absorption band was observed which gradually shifted to shorter wave lengths, and became more intense as the compounds hydrolyzed to give finally the 434 mμ band of the iron-acetylacetone complex. For compound I these absorption changes are shown in Fig. 4. The initial absorption band may be attributed to complex formation between the β-amino-α,β-unsaturated ketones and ferric chloride. The nature of this complex must be speculative at this time. However, complex formation may signify that I and II exist to a slight extent in the enol (VII) structure in ethanol, although the enamine (IV) structure apparently predominates in the solid phase and in the non-polar solvent, carbon tetrachloride. Removal of the enol by complex formation would rapidly shift a keto-enol equilibrium toward the formation of more enol.[14]

(14) A. Hantzsch, *Ber.*, **43**, 3049 (1910).

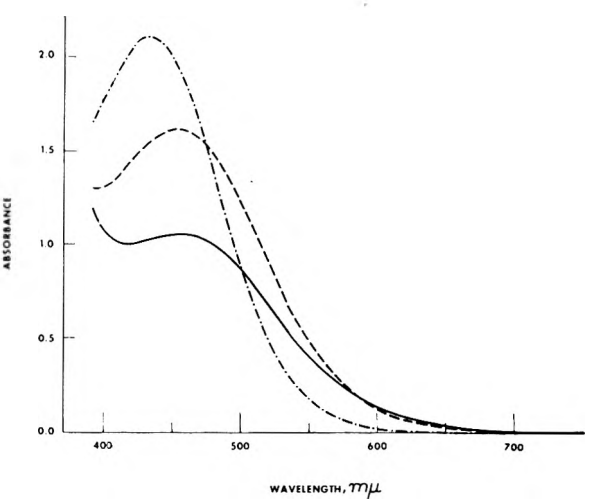
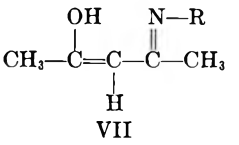


Fig. 4. The visible absorption spectra of I in ethanolic $FeCl_3$. Initial absorption (———); absorption after 15 minutes (———); absorption after 35 minutes, when the change was complete (-·-·-·)



VII

No change was observed in the initial absorption spectrum of III. The absorption band at 434 mμ due to the iron-acetylacetone complex was found immediately. For this compound the positive ferric chloride test results solely from its rapid hydrolysis to acetylacetone under the experimental conditions.

Chloroform solutions of compounds I and II immediately produced a pink color when treated with a few drops of chloroform solution of anhydrous ferric chloride. The color change may be attributed to complex formation between ferric chloride and the amino ketones. Compounds I and II may possibly exist to a small extent in the enol form in chloroform.

No immediate color change occurred when III was treated in the same way. On standing, however, the chloroform solution gradually became yellow. In this compound there is no enolizable hydrogen. The yellow color probably results from the gradual formation of a ferric chloride complex of a decomposition product of III.

EXPERIMENTAL

β-Aminopropionitrile. The procedure of Buc, Ford, and Wise[15] was employed using 1950 ml. (30 moles) of concentrated ammonium hydroxide and 396 ml. (6 moles) of acrylonitrile. The yield was 100 g. (23%), b.p. 46–48° (4 mm.). The picrate had m.p. 178° (lit.,[3] 178°).

β-Methylaminopropionitrile. The procedure of Whitmore and co-workers[16] was employed using 106 g. (2.00 moles) of

(15) S. R. Buc, J. H. Ford, and E. C. Wise, *J. Am. Chem. Soc.*, **67**, 92 (1945).

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

acrylonitrile and 372 g. (3.00 moles of amine) of 25% aqueous methylamine. The yield was 110 g. (65.5%), b.p. 37° (4 mm.).

4-(2'-Cyanoethyl)-amino-3-penten-2-one (I). The method of Cromwell and coworkers[3] was employed using 13.5 g. (0.19 mole) of β-aminopropionitrile and 20.0 g. (0.20 mole) of acetylacetone. The yield was 28 g., m.p. 89.5–90° (lit.,[3] 89.5–90°), after three recrystallizations from benzene–petroleum ether (3:1).

4-Amino-3-penten-2-one (II). The method of Combes and Combes[17] was applied using 10.0 g. (0.1 mole) of acetylacetone and anhydrous ammonia. The product crystallized on standing and was purified by distillation at reduced pressure. The yield was 8.3 g., m.p. 43° (lit.,[16] 43°).

4-N-(2'-Cyanoethyl)-methylamino-3-penten-2-one (III). The method of Cromwell and coworkers[3] was employed using 20.0 g. (0.20 mole) of acetylacetone and 17.0 g. (0.20 mole) of β-methylaminopropionitrile. The yield was 32.5 g. The product was recrystallized three times from benzene–petroleum ether, and gave m.p. 69–70° (lit.,[3] 69–70°).

Ferric chloride studies. Solutions for the spectroscopic study were prepared by the addition of excess ketone to a small volume of 1% ethanolic ferric chloride solution. The solutions were measured in a 1 cm. cell against ethanol as the reference solvent.

The ferric chloride tests in chloroform solution were carried out according to the method of Soloway and Wilen.[18]

Measurements in the visible and ultraviolet region. The Cary Spectrophotometer (Model 11) was used for measurements in these regions. Spectra were measured on solutions (against the solvent as reference).

Measurements in the infrared region. The samples were measured as solids dispersed in potassium bromide pellets (against a pure potassium bromide pellet as reference) or mulled in "Halocarbon Oil"[19] (against the pure oil as reference). The samples were also studied in solution in carbon tetrachloride, against carbon tetrachloride as reference. A Beckman IR-3 spectrophotometer was used for the measurements. Lithium fluoride and sodium chloride optics were used for studies in the 3 μ and 6 μ regions, respectively.

Photochemical isomerization. The solutions contained in a 1 cm. quartz cell were exposed to ultraviolet radiation from a General Electric AH-4 mercury arc without the glass envelope. To prevent excessive heating of the sample, a water filled cell was placed between the source and the sample cell. For irradiation with the 313 mμ mercury line, a Pyrex glass filter was used to cut off radiation lines below 300 mμ. No filter was used for irradiation with the 254–265 mμ mercury lines.

NATICK, MASS.

TABLE III

ULTRAVIOLET ABSORPTION BANDS OF THE AMINO KETONES IN VARIOUS MEDIA (mμ)

Compound	95% EtOH	Isooctane	H_2O	0.1N KOH
I	308	298	310	311
II	300	286	300	301
III	306	289	313	313

(17) A. Combes and C. Combes, *Bull. Soc. Chim.*, (3) **7**, 779 (1892).

(18) S. Soloway and S. H. Wilen, *Anal. Chem.*, **24**, 979 (1952).

(19) "Halocarbon Oil" is a blend of completely halogenated chlorofluorocarbons and was obtained from the Halocarbon Products Corp., Hackensack, N. J.

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, BUTLER UNIVERSITY]

Use of Anion Exchange Resins in the Synthesis of Benzyl Ethers of Phenols

EDWARD J. ROWE, KARL L. KAUFMAN, AND CLAUDE PIANTADOSI[1]

Received February 18, 1958

Benzyl ether formation of a number of phenols can be effected by treating the phenolate of a strongly basic anion exchange resin with an ethanol solution of benzyl chloride. The conventional column and batch techniques are used. Eleven benzyl ethers have been prepared and their identification shown.

Benzyl ethers of phenols are usually synthesized by coupling an alkali phenolate and benzyl halide in an appropriate solvent with the aid of heat. This report presents a method for carrying out the synthesis at room temperature by the use of the phenolates of strongly basic anion exchange resins. The resins used are based on polystyrene and contain quaternary ammonium groups.

The method consists of absorbing the phenol on the resin.[2] The phenol-absorbed resin is then treated with an ethanol solution of benzyl chloride by the conventional column or batch techniques employed in ion exchange resin technology. Generally a pure product may be obtained on a single crystallization of the residue from evaporation of the eluate or filtrate.

The method is particularly applicable to the synthesis of benzyl ethers of monohydric phenols. The dihydric phenols, hydroquinone and resorcinol, yield, in the case of hydroquinone, a mixture of both mono and dibenzyl ethers; in the case of resorcinol, the dibenzyl ether only.

The phenol benzyl ethers prepared by both column and batch techniques are summarized in Table I. The yields are based upon the amount of the phenol converted to the benzyl ether.

(1) Present address: School of Pharmacy, University of North Carolina, Chapel Hill.

(2) The reaction also occurs if the phenol is dissolved in the ethanol with the benzyl chloride. Subsequent separation of the benzyl ether is simplified and the yield improved if absorption of the phenol on the resin is carried out first.

TABLE I

BENZYL ETHERS PREPARED FROM BENZYL CHLORIDE AND PHENOLS WITH ANION EXCHANGE RESINS

Benzyl Ether	Resin	Yield, % Column techn.	Yield, % Batch techn.	M.P., °C.	M.P., °C. (lit.)	Analyses[a]	Calcd.	Found
Phenol	A[b]	57	62	39–39.5[c]	39[6] 40[7]			
	D[d]	66	—[e]					
Chlorothymol	A	74	83	54.5–55	55[10]	C	74.30	74.21
						H	6.97	7.01
Thymol	A	90	81	Oil[f]				
Guaiacol	A	66	63	57.5–58.5[g]	57.5–58.5[16]			
	D	63	—[e]					
Eugenol	A	72	79	27–27.5	30–31[17]	C	80.24	80.83
						H	7.13	7.64
p-Bromophenol	A	55	38	63–64	64[6]	Br	30.38	30.4
p-Nitrophenol	A	20	23	106–106.5	106[18]	C	68.11	68.40
						H	4.84	4.83
Alpha Naphthol	A	52	52	77–77.5	77–77.5[19]	C	87.15	87.23
						H	6.02	6.49
Beta Naphthol	A	43	53	99.5–100	99[20] 100[21]	C	87.15	87.92
						H	6.02	6.37
Hydroquinone	A	Mono 9	14	121–121.5[h]	121–122[14]			
		Di 10	27	128.5–129	128–129[12] 130[13]	C	82.73	82.82
						H	6.25	6.66
Resorcinol	A	Mono —[i]	—[i]					
		Di —[j]	16	73–74	73–74[14]	C	82.73	83.06
						H	6.25	6.45

[a] Carried out by Drs. Weiler and Strauss, Oxford, England, and by the Microanalytical Laboratory, Organic Chemistry Division, Eli Lilly & Co., Indianapolis. [b] Refers to Amberlite IRA-400. [c] B.p. 285–286° uncorr.; lit.[8] b.p. 286–287° uncorr. [d] Refers to Dowex 1-X4. [e] Not carried out. [f] B.p. 169–170° (7 mm.), n^{25}_{D} 1.5553; lit.[15] b.p. 169–170° (7 mm.), n^{20}_{D} 1.5556. [g] n^{20}_{D} 1.5737; lit.[16] n^{25}_{D} 1.5780. [h] Mixture melting point with authentic sample showed no depression. [i] Attempts to isolate monobenzyl ether were unsuccessful. [j] Attempts to isolate dibenzyl ether were unsuccessful.

EXPERIMENTAL

Resin preparation. Amberlite IRA-400[3] and Dowex 1-X4[4] as supplied commercially (20–50 mesh) were converted to their hydroxyl form by the usual column technique with 5% aqueous sodium hydroxide (4 to 5 times the volume of resin). The resins were rinsed with distilled water until the washings were neutral, and then with absolute methanol. The residual methanol was removed by passing a current of carbon dioxide–free air through the column of resin.

Absorption of the phenol on the resin. The quantity of resin employed for each benzyl ether synthesis was based upon the absorption capacity of the air-dried resin as determined by the method of Kunin and Myers.[5] About 15 to 20% excess resin was used to absorb the phenol. A general procedure was followed: The phenol (0.05 mole) was dissolved in 250 to 300 ml. distilled water or, if necessary, in dilute sodium hydroxide solution and passed through the resin in a column 20 mm. in diameter. The resin column was first rinsed with distilled water until the washings were neutral, then with two 75-ml. portions of ethanol.

Benzyl ether formation of monohydric phenols. The preparation of phenyl benzyl ether illustrates the synthesis of the benzyl ethers by the *column technique.*

A column 20 mm. in diameter packed with 35 g. of Dowex 1-X4 upon which 4.7 g. (0.05 mole) of Phenol U.S.P. had been absorbed was eluted with 400 ml. of ethanol containing 16.4 g. (0.13 mole) of benzyl chloride. The rate of flow was 1 ml. per minute. The column was then rinsed with 150 ml. of ethanol. Evaporation to dryness of the combined eluate and rinse yielded 6.10 g. (66%) of phenyl benzyl ether, m.p. 38–38.5°. The product on a single crystallization from ethanol melted at 39–39.5°; lit.[6,7] m.p. 39°, 40°. The b.p. was 285–286° uncorr.; lit.[8] b.p. 286–287° uncorr.

The preparation of chlorothymol benzyl ether illustrates the synthesis of the benzyl ethers by the *batch technique.*

Twenty-five grams of Amberlite IRA-400 upon which 9.23 g. (0.05 mole) of chlorothymol had been absorbed was placed in a 500-ml. ground glass-stoppered erlenmyer flask. Three hundred milliliters of ethanol and 9.5 g. (0.075 mole) of benzyl chloride were then added. The mixture was mechanically agitated for 72 hr. At the end of this period the resin was filtered off and washed on the filter with 150 ml. ethanol.[9] Evaporation to dryness of the combined filtrate and washings yielded 11.74 g. of white crystals melting at 52.5–53.5°. The product crystallized once from ethanol yielded 10.9 g. (83%) of chlorothymol benzyl ether melting at 54.5–55°; lit.[10] m.p. 55°.

Anal. Calcd. for $C_{17}H_{19}ClO$: C, 74.30; H, 6.97. Found: C, 74.21; H, 7.01.

Benzyl ether formation of dihydric phenols. The preparation of the benzyl ethers of hydroquinone and resorcinol paralleled the column and batch operations described for the synthesis of phenyl benzyl ether and chlorothymol benzyl ether; except that the quantities of benzyl chloride were increased[11] and the quantity of resin (for the batch opera-

(3) Analytical grade manufactured by Rohm & Haas Co., Philadelphia, Pa.

(4) Supplied through the courtesy of Dow Chemical Co., Midland, Mich.

(5) R. Kunin and R. J. Myers, *Ion Exchange Resins,* John Wiley and Sons, Inc., New York, 1950, p. 150.

(6) S. G. Powell and R. Adams, *J. Am. Chem. Soc.,* **42,** 656 (1920).

(7) C. A. Bischoff and A. von Hedenström, *Ber.,* **35,** 3434 (1902).

(8) F. Sintenis, *Ann.,* **161,** 337 (1872).

(9) Ether was found to be more satisfactory for washing the resin on the filter in subsequent experiments with other phenols.

(10) B. Jones, *J. Chem. Soc.,* 364 (1941).

(11) For the column technique, 16.4 g. (0.13 mole) of benzyl chloride in 400 ml. of ethanol was used; for the batch technique, 9.4 g. (0.075 mole) in 300 ml. of ethanol.

tion only) approximately doubled. The eluates and filtrates from the column and batch operations, respectively, required further processing to separate the mixtures of the mono and dibenzyl ethers formed.

Hydroquinone dibenzyl ether. The separation of the dibenzyl ether of hydroquinone was accomplished by treating the residues from evaporation of the eluate and filtrate with 0.1*N* sodium hydroxide solution and extracting the resulting alkaline-aqueous mixtures with several portions of ether. Evaporation of these ether extractives, first washed free of alkali, yielded hydroquinone dibenzyl ether which when crystallized once from ethanol melted at 128.5–129°; lit.[12,13] m.p. 128–129°, 130°. Yield: column technique, 1.6 g. (10%); batch technique, 4 g. (27%).

Anal. Calcd. for $C_{20}H_{18}O_2$: C, 82.73; H, 6.25. Found: C, 82.82; H, 6.66.

Hydroquinone monobenzyl ether. The alkaline-aqueous portions from which the hydroquinone dibenzyl ether was removed were acidified with diluted hydrochloric acid and extracted with ether. These ether extractives washed free of acid and evaporated to dryness left crystalline residues. Crystallization of the residues from diluted ethanol yielded hydroquinone monobenzyl ether, m.p. 121–121.5°; lit.[14] m.p. 121–122°. A mixture melting point with an authentic sample of hydroquinone monobenzyl ether showed no depression. Yield: column technique, 0.96 g. (9%); batch technique, 1.46 g. (14%).

Resorcinol dibenzyl ether. Although both column and batch techniques were applied to the preparation of this ether, only the latter technique yielded the compound. The monobenzyl ether of resorcinol could not be obtained by either the column or the batch techniques.

The isolation of the resorcinol dibenzyl ether was accomplished in the same manner as described for the isolation of the dibenzyl ether of hydroquinone. The yield was 2.35 g. (16%), m.p. 73–74°; lit.[14] m.p. 73–74°.

Anal. Calcd. for $C_{20}H_{18}O_2$: C, 82.73; H, 6.25. Found: C, 83.06; H, 6.45.

Experiments are being continued to acertain whether any ethers of phenols other than benzyl can be prepared by the method herein described; and similarly, whether any benzyl or alkyl groups can replace non-carboxylic hydrogens on other types of compounds.

INDIANAPOLIS, IND.

(12) A. Colson, *Bull. soc. chim.*, **3**, 347 (1889).
(13) H. Schiff and G. Pellizzari, *Ann.*, **221**, 369 (1883).
(14) J. Druey, *Bull. soc. chim.*, **5**, 1740 (1935).
(15) F. Caujolle, C. Franck, and L. Girard, *Compt. rend.* **218**, 572 (1944).
(16) I. M. Heilbron, *Dictionary of Organic Compounds*, Oxford University Press, New York, 1946, Vol. II, p. 136.
(17) T. F. West, *J. Chem. Soc.*, 490 (1945).
(18) G. Kumpf, *Ann.*, **224**, 123 (1884).
(19) V. H. Dermer and O. C. Dermer, *J. Org. Chem.*, **3**, 291 (1938).
(20) W. Staedel, *Ber.*, **14**, 899 (1881).
(21) HLA, BAW, *Quart. J. Indian Chem. Soc.*, **3**, 101 (1926); *Chem. Abstr.*, **20**, 3695 (1926).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, AIN SHAMS UNIVERSITY]

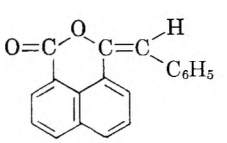
Comparative Study between Phthalides and Naphthalides. II[1]

O. M. ALY, W. I. AWAD, AND A. M. ISLAM

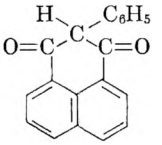
Received March 27, 1958

In addition to the β-diketone (II), 3-benzalnaphthalide (I) was isolated from the product of interaction of naphthalic anhydride and phenylacetic acid. Infrared curves for the naphthalide (I) and the phthalide (VI) together with the β-diketones (II), (III) and (IV) are discussed.

Recently, Aly, Awad, and Islam,[1] investigated the condensation of naphthalic anhydride with phenylacetic acid in the presence of sodium acetate, and obtained a product (m.p. 214°) to which they assigned the benzalnaphthalide structure (I).



I



II

Cesaris[2] obtained from the same condensation a product which possessed no ketonic properties and to which he gave β-diketone structure (II). He claimed that in contrast to ortho-anhydrides such as phthalic anhydride, which gives only the phthalide, naphthalic anhydride gives directly the β-diketone (II).

In the light of the above controversial results, we decided to reinvestigate the whole problem in more detail.

We have now isolated from the reaction mixture of the above Perkin condensation, two products. The main product is orange in color, m.p. 214°, and is fairly soluble in cold dilute sodium hydroxide and dilute sodium carbonate solutions. Infrared measurements of this compound (Fig. 1) show a clear carbonyl stretching frequency (1570 cm.$^{-1}$) in the normal carbonyl group region (the carbonyl stretching frequency for β-diketones is 1640–1540 cm.$^{-1}$).[3] Similar carbonyl stretching frequencies are present in the infrared curves of the two β-diketones, III[4] (Fig. 2) and IV[1] (Fig. 3), being 1620

(1) Compare Comparative Study between Phthalides and Naphthalides, O. M. Aly, W. I. Awad, and A. M. Islam, *J. Org. Chem.*, **22**, 517 (1957).
(2) M. Cesaris, *Gazz. chim. ital.*, **42**, II, 453.
(3) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, Metheun, London, 1957, p. 114.
(4) G. Errera, *Gazz. chim. ital.*, **41**, I, 190.

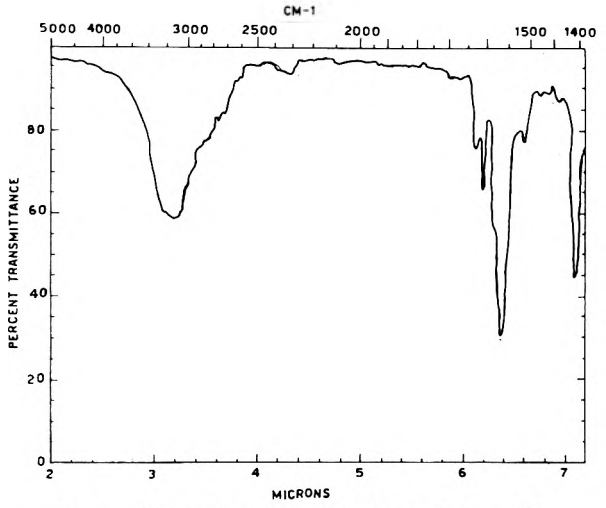


Fig. 1. 8-Phenyl-*peri*-naphthindan-7,9-dione (II)

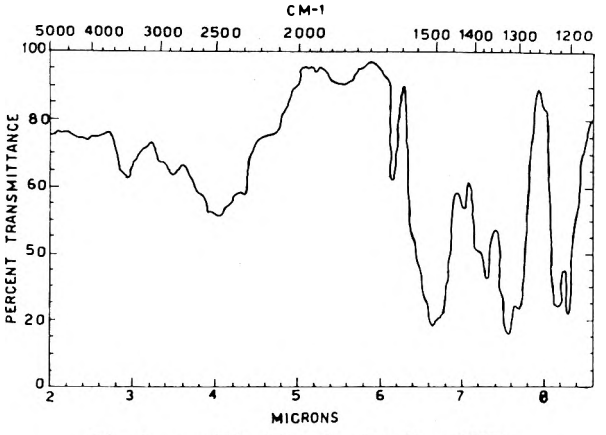
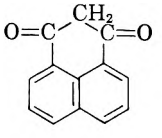
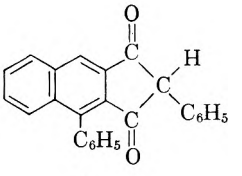


Fig. 2. *peri*-Naphthindan-7,9-dione (III)



III

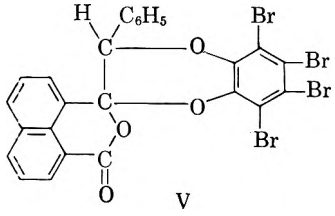


IV

cm.$^{-1}$ and 1600 cm.$^{-1}$, respectively. The β-diketone structure (II) is therefore given for this compound which is in agreement with Cesaris's consideration.

Whereas the infrared curve of the diketone (IV) shows a free —OH stretching frequency at 3400 cm.$^{-1}$, it is remarkable that neither of the peridiketones (II and III) showed frequencies in the solid state or in solution which indicates a minimum contribution for the enol configuration.

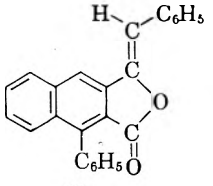
The second product isolated from the reaction mixture of the above condensation is obtained in lower yield through extraction with petroleum ether, in which it is comparatively soluble. This compound is yellow in color, m.p. 146°, and is insoluble in both dilute sodium hydroxide and sodium carbonate solutions. The constitution of this compound as the naphthalide (I) is supported by the following facts: (*a*) on treatment with an alcoholic sodium methoxide solution, it is converted quantitatively to the β-diketone (II) (Nathanson[5] and Eibner[6]), (*b*) it reacts in sunlight with tetrabromo-*o*-quinone to give the photo-addition product (V),[1,7] (*c*) the infrared measurements show a



V

carbonyl stretching frequency at 1710 cm.$^{-1}$ (Fig. 4) (δ-lactones have stretching frequency in the range 1750–1735 cm.$^{-1}$).[8] Unsaturated δ-lactones are expected to have a slightly higher stretching frequency than the saturated ones as is the case with saturated γ-lactones.

The infrared curve of the phthalide (VI)[1] shows also a carbonyl stretching frequency in the unsaturated γ-lactone region (1760 cm.$^{-1}$) (Fig. 5).



VI

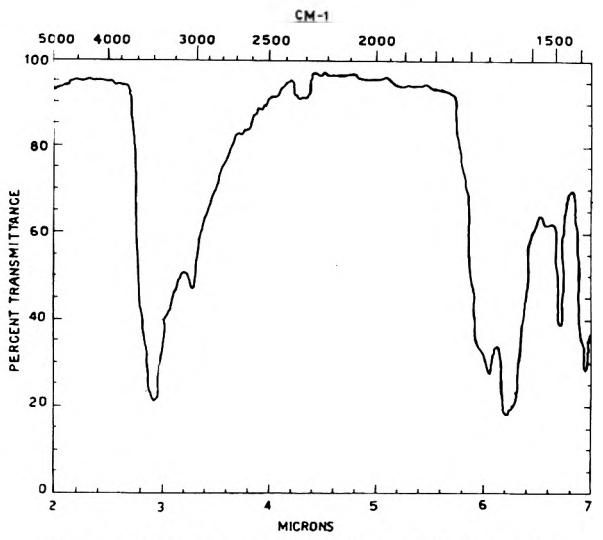


Fig. 3. 2,4-Diphenyl-5,6-benzindan-1,3-dione (IV)

(5) Nathanson, *Ber.*, **26**, 2576 (1893).
(6) Eibner, *Ber.*, **39**, 2203 (1906).
(7) A. Schönberg, and A. Mustafa, *Chem. Revs.*, **40**, 190 (1948).
(8) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, Metheun, London, 1956, p. 153.

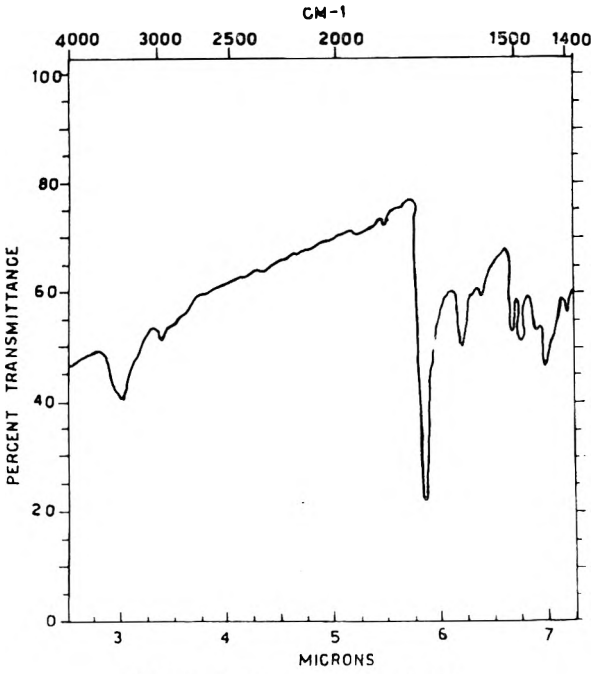
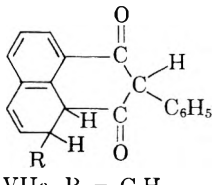


Fig. 4. 3-Benzalnaphthalide (I)

The non-isolation of the naphthalide (I) as reported in our previous publication[1] was due to the fact that I is easily adsorbed during the purification of the reaction product, then leaving the β-diketone (II) as the sole product.

As II is the major product, it is feasible to suggest that the naphthalide (I) is first formed which then rearranges, in the presence of sodium acetate and at the high temperature of the reaction, to the β-diketone (II).

In the presence of excess phenylmagnesium bromide or excess methylmagnesium iodide, the β-diketone (II) reacts as a monoketone. It adds only one molecule of Grignard reagent. Koelsch and Rosenwald[9] reported the isolation of VIIa from the interaction of II and phenyllithium, the mode of interaction being a 1:4 addition. They were unable, however, to obtain this compound, VIIa, by the direct interaction of II and phenylmagnesium bromide. Our product from II and phenylmagnesium bromide proved to be identical with VIIa by a mixture melting point.



VIIa, R = C_6H_5
VIIb, R = CH_3

In accordance with the above considerations, the product from II and methylmagnesium iodide should have structure VIIb. VIIa was previously described[1] as a hemiketal, owing to the fact that the diketone II was erroneously given the benzalnaphthalide structure.

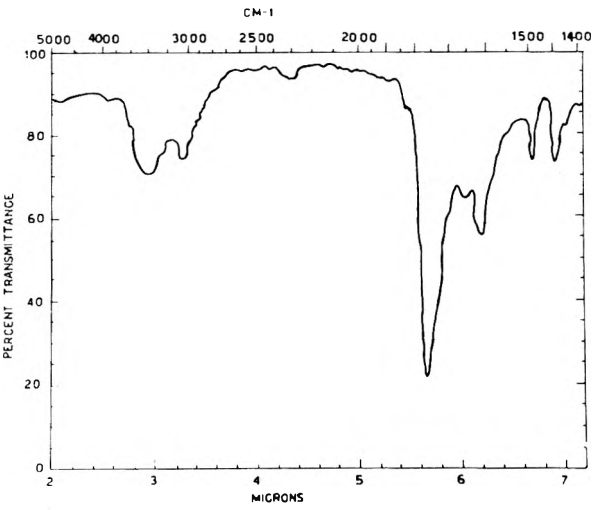
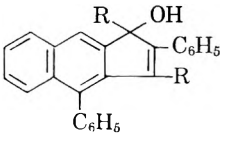
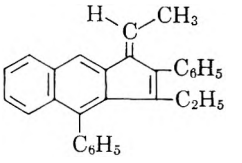


Fig. 5. Benzal-7-phenyl-5,6-benzophthalide (VI)

On the other hand, the five-membered compound IV reacted with Grignard reagents as a diketone. With excess methylmagnesium iodide or excess phenylmagnesium bromide, IV gives colorless or almost colorless products which possess carbon and hydrogen figures corresponding to VIIIa and VIIIb, respectively, which results from the addition of two molecules of the Grignard reagent followed by the loss of one molecule of water.



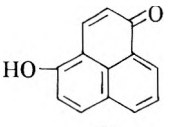
VIIIa ; R = C_6H_5
VIIIb ; R = CH_3



IX

With excess ethylmagnesium iodide, however, IV gives rise to an oxygen-free compound IX.

On the constitution of perinaphthindan-7,9-dione. The non-appearance of ketonic properties for the diketone II, as reported by Cesaris[2] and as confirmed by the authors, was unusual, since compounds of structure similar to X[10] and XI[11] are reported to give carbonyl derivatives.

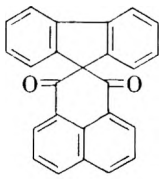


X

(9) C. F. Koelsch and R. H. Rosenwald, *J. Am. Chem. Soc.*, 59, 2166 (1937).

(10) J. London and R. Razdan, *J. Chem. Soc.*, 4299 (1954).

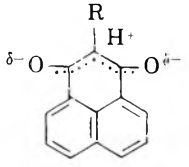
(11) E. J. Greenhow, E. N. White, and D. McNeil, *J. Chem. Soc.*, 3099 (1953).



XI

By comparing the infrared curves (in the solid state and in solution) for the three diketones II, III, and IV, the following facts are observed. While they all show a clear absorption in the normal carbonyl stretching frequency range, compounds II and III show no free OH stretching frequency as found for the diketone IV.

Among the different unperturbated structures for II or III, it is not unreasonable to consider structure XII as a possible representative. Such



XII

R = H or C_6H_5

a structure would then explain the empirical facts such as the non-appearance of normal ketonic properties, the strong acidic character of the hydrogen atom at position (8) (II being soluble in dilute sodium carbonate solution) and the non-appearance of a free OH stretching frequency in the infrared curve.

EXPERIMENTAL[12]

Reaction of naphthalic anhydride with phenylacetic acid. A mixture of naphthalic anhydride (5 g.), phenylacetic acid (3.5 g.), and fused sodium or potassium acetate (0.2 g.) was heated to 230–240°, 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 g.). The crude product was boiled with 150 ml. of petroleum ether (70–80°) and filtered. The filtrate acquired a brownish yellow coloration and on concentration, brownish yellow needles separated out, m.p. 135–140°. This product was washed with a warm solution of sodium carbonate (100 ml. of 10% solution), to remove 8-phenyl-*peri*-naphthindan-7,9-dione. Recrystallization from petroleum ether (70–80°), yielded 3-benzalnaphthalide (I), 2.4 g. (34%), as yellow long needles, m.p. 146–148°.

This product could also be obtained in pure form, by chromatographing the petroleum ether extract on alumina. On elution by anhydrous benzene and concentration of the eluted benzene solution, 3-benzalnaphthalide (I) separated as yellow needles. The phenyl-*peri*-naphthindan-7,9-dione could not be eluted under these conditions.

Anal. Calcd. for $C_{19}H_{12}O_2$: C, 83.8; H, 4.4. Found: C, 83.4; H, 4.4.

This compound was insoluble in a dilute solution of sodium hydroxide or sodium carbonate. It gave a brownish red coloration with concentrated sulfuric acid.

Recrystallization of the product which was insoluble in petroleum ether from boiling alcohol (charcoal) gave 3 g. (48%) of 8-phenyl-*peri*-naphthindan-7,9-dione as orange needles, m.p. 214–216° (previously[1] analyzed).

Rearrangement of 3-benzalnaphthalide (I). 3-Benzalnaphthalide (I) (0.3 g.) was boiled for 15 min. with a 2% methyl alcoholic solution of sodium methoxide (50 ml.). The reaction mixture was diluted with water, filtered, cooled, and acidified with ice cold dilute hydrochloric acid. Crystallization of the precipitated product from alcohol gave 0.25 g. (75%) of 8-phenyl-*peri*-naphthindan-7,9-dione (II).

Photo-addition of 3-benzalnaphthalide (I) *with tetrabromo-o-quinone.* A mixture of 3-benzalnaphthalide (I) (0.3 g.) and tetrabromo-*o*-quinone (0.4 g.) in dry thiophene-free benzene (30 ml.) was placed in Schlenck tube[13] under a carbon dioxide atmosphere and exposed to sunlight. After 48 hr. the red color disappeared and the solution acquired a pale yellow coloration. On concentration of the benzene solution, a colorless product was obtained. Recrystallization from benzene gave 0.2 g. (29%) of the adduct (V) as colorless needles, m.p. 273–275°.

Anal. Calcd. for $C_{25}H_{12}O_4Br_4$: Br, 45.9. Found: Br, 44.5.

Action of methylmagnesium iodide on (II). A solution of 8-phenyl-*peri*-naphthindan-7,9-dione (II) (1 g.) in dry benzene (100 ml.) was added to an ethereal solution of methylmagnesium iodide (from methyl iodide, 2.8 g., and magnesium, 0.5 g.) and the reaction mixture was heated under reflux for 2 hr., then left overnight. The reaction mixture was decomposed with an aqueous solution of ammonium chloride. On concentration of the washed and dried benzene extracts followed by addition of petroleum ether (40–60°), a yellowish product was obtained. Recrystallization from a benzene–petroleum ether mixture (1:1) gave 0.2 g. (20%) of 1-methyl-8-phenyl-1,9-dihydro-*peri*-naphthindan-7,9-dione (VIIb) as yellow needles, m.p. 138–140°.

Anal. Calcd. for $C_{20}H_{16}O_2$: C, 83.3; H, 5.6. Found: C, 83.8; H, 5.1.

The product was soluble in a methyl alcoholic solution of sodium methoxide with an orange-red coloration and in sodium hydroxide solution with a yellowish orange coloration. In both cases the product was recovered unchanged on acidification.

Action of phenylmagnesium bromide on II. A solution of 8-phenyl-*peri*-naphthindan 7,9-dione (II) (1 g.) in dry benzene (100 ml.) was added to an ethereal solution of phenylmagnesium bromide (from bromobenzene, 1.8 g., and magnesium, 0.3 g.) and the reaction mixture was heated under reflux for 4 hr. then left overnight. Decomposition with aqueous ammonium chloride solution, and concentration of the washed and dried benzene extracts followed by addition of petroleum ether (40–60°), gave a pale yellow product. Recrystallization from a benzene–petroleum ether mixture (1:1) gave 0.2 g. (17%) of 1,8-diphenyl-1,9-dihydro-*peri*-naphthindan 7,9-dione (VIIa) as pale yellow plates, m.p. 177–178°. The melting point of this product was undepressed on admixture with the product obtained by Koelsch and Rosenwald[2] by the action of phenyllithium on II.

Anal. Calcd. for $C_{25}H_{18}O_2$: C, 85.7; H, 5.2. Found: C, 85.5; H, 5.3.

The substance gave a pale yellow coloration with concentrated sulfuric acid.

Action of methylmagnesium iodide on IV. A solution of 2,4-diphenyl-5,6-benzindan-1,3-dione (IV) (1 g.) in dry benzene (100 ml.) was added to an ethereal solution of methylmagnesium iodide (from methyl iodide, 3 g., and magnesium, 0.5 g.) and the reaction mixture was heated under reflux for 3 hr. The reaction mixture was then decomposed with aqueous ammonium chloride solution and on concentration of the washed and dried benzene extracts followed by addition of petroleum ether (40–60°), gave a yellowish product.

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

(13) Houben, *Die Methoden der Organischen Chemie*, 2nd. ed., Vol. 4, Georg Thieme, Leipzig, 1924, p. 960.

Recrystallization from benzene–petroleum ether mixture (1:1) gave 0.3 g. (30%) of VIIIa as pale yellow needles, m.p. 197–200°.

Anal. Calcd. for $C_{27}H_{22}O$: C, 89.4; H, 6.1. Found: C, 88.9; H, 6.6.

Action of ethylmagnesium iodide on IV. A solution of 2,4-diphenyl-5,6-benzindan-1,3-dione (IV) (1 g.) in dry benzene (100 ml.) was added to an ethereal solution of ethylmagnesium iodide (from ethyl iodide, 3.5 g., and magnesium, 0.5 g.) and the reaction mixture was heated under reflux for 2 hr., then left overnight. Decomposition with aqueous ammonium chloride solution, and concentration of the washed and dried benzene extracts, gave a pale yellow product. Recrystallization from benzene gave 0.25 g. (24%) of IX as almost colorless needles, m.p. 182–184°.

Anal. Calcd. for $C_{29}H_{24}$: C, 93.5; H, 6.5. Found: C, 92.8; H, 6.4.

The product gave a rose red coloration with concentrated sulfuric acid.

Action of phenylmagnesium bromide on IV. A solution of 2,4-diphenyl-5,6-benzindan-1,3-dione (IV) (1 g.) in dry benzene (100 ml.) was added to an ethereal solution of phenylmagnesium bromide (from bromobenzene, 2 g., and magnesium, 0.5 g.) and the reaction mixture was heated under reflux for 3 hr. then left overnight. Decomposition with aqueous ammonium chloride solution, and concentration of the washed and dried benzene extracts followed by addition of petroleum ether (40–60°), gave a colorless product. Recrystallization from benzene–petroleum ether mixture (1:1) gave 0.4 g. (30%) of VIIIb as colorless prisms, m.p. 198–199°.

Anal. Calcd. for $C_{37}H_{26}O$: C, 91.3; H, 5.4. Found: C, 91.1; H, 5.4.

The product gave a bluish coloration with concentrated sulfuric acid.

Acknowledgment. The authors wish to express their thanks and gratitude to Messers. Samuel P. Sadtler & Son, Inc., Research Laboratories, Philadelphia, Pa., for kindly carrying out the infrared spectrograms of II, III, IV, and VI. The samples were vacuum dried and the spectrograms were carried out using the potassium bromide Wafer technique. The infrared measurements of I, II, and III were also carried out in solution by Mr. Nagib Doss, Chemistry Department, Ohio State University, U.S.A., to whom we are greatly indebted.

ABBASSIA, CAIRO, EGYPT

[CONTRIBUTION FROM THE WHITMORE LABORATORY OF THE COLLEGE OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE UNIVERSITY]

Higher Hydrocarbons. VI.[1] Polyalkylbenzenes and Polyalkylcyclohexanes[2]

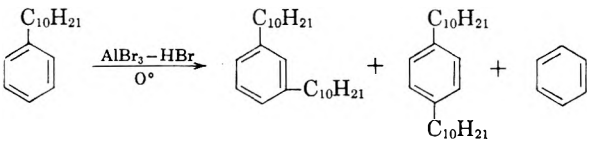
S. G. CLARK II AND J. A. DIXON

Received May 15, 1958

The syntheses of six new high molecular weight polyalkylbenzenes and polyalkylcyclohexanes are reported.

As a portion of a continuing study of high molecular weight hydrocarbons, the synthesis and physical properties of six new monocyclic hydrocarbons are reported. They are 1,3-didecylbenzene, 1,3-didecylcyclohexane, 2,5-dimethyloctadecylbenzene, 2,5-dimethyloctadecylcyclohexane, 2,4,6-trimethyloctadecylbenzene, and 2,4,6-trimethyloctadecylcyclohexane.

Three different synthetic routes were used for the preparations of the above hydrocarbons. The 1,3-didecylbenzene was prepared by the disproportionation of decylbenzene with aluminum bromide–hydrogen bromide catalyst.[3–6]



It has been found from studies of the hydrogen fluoride and aluminum halide catalyzed disproportionations of a series of lower alkylbenzenes that the dialkylbenzenes obtained are exclusively the meta isomers except in the case of isopropyl or tertiary butylbenzene.[3,4] It was believed that the increased branching of the alkyl group in these two cases decreased the differences in the stability of the isomeric hydrocarbon catalyst complexes.[5] In the present work it was observed that the disproportionation of decylbenzene catalyzed by aluminum chloride–hydrogen chloride yielded a four to one ratio of *meta*- to *para*-didecylbenzene while aluminum bromide–hydrogen bromide produced the isomers in a nine to one ratio. The ortho isomer was looked for but not found. Analysis was by infrared, density, and viscosity, after separation of the isomers by fractional distillation. The identity of the para isomer was unequivocally established by comparison with an authentic sample which had been prepared previously in this labora-

(1) For the previous paper in this series: R. W. Schiessler, A. W. Rytina, and F. C. Whitmore, *J. Am. Chem. Soc.*, **70**, 529 (1948).

(2) Taken from a portion of a dissertation submitted by S. G. Clark to the Graduate School of The Pennsylvania State University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(3) A. P. Lien and D. A. McCaulay, *J. Am. Chem. Soc.*, **75**, 2407, 2411 (1953).

(4) R. D. Kinney and L. A. Hamilton, *J. Am. Chem. Soc.*, **76**, 786 (1954).

(5) H. C. Brown and C. R. Smoot, *J. Am. Chem. Soc.*, **78**, 2176 (1956).

(6) R. M. Roberts and S. G. Brandenberger, *J. Am. Chem. Soc.*, **79**, 5485 (1957).

TABLE I

PROPERTIES OF THE HYDROCARBONS

Hydrocarbon	Viscosity at 98.9° C. (Centipoise)	Density in G./Cc. at 98.9°C.	B.P. at 1.00 Mm., °C.	Refractive Index (n'_D), 20° C.	M.P., °C.
1,3-Didecylbenzene	2.496	0.8018	201.0	1.4813	—
1,3-Didecylcyclohexane	2.863	0.7816	205.0	1.4618	—
2,5-Dimethyloctadecylbenzene	2.887	0.8078	210.5	Solid	45.0–45.5
2,5-Dimethyloctadecylcyclohexane	2.963	0.7829	204.0	1.4619	—
2,4,6-Trimethyloctadecylbenzene	3.580	0.8125	219.0	Solid	54.5–55.0
2,4,6-Trimethyloctadecylcyclohexane	3.268	0.7856	210.5	1.4629	—

tory from terephthalic acid.[7] This also confirmed the previous observations[3–5] that the disproportionation is not accompanied by isomerization of the normal alkyl group.

For the synthesis of 2,5-dimethyloctadecylbenzene the precursor, 2,5-dimethyloctadecanoylbenzene, was prepared both by the acylation of *p*-xylene with stearoyl chloride, and from 2,4-dimethylbrombenzene and octadecanoyl chloride through the Grignard and cadmium reagents. In each case the ketone was reduced directly to the hydrocarbon by the modified Wolff-Kishner reaction of Herr *et al.*[8] The Friedel-Crafts acylation is not accompanied by rearrangement of the methyl groups (or by isomerization of the normal octadecyl chain) since the ketones obtained from the two procedures were shown to be identical. The yield of purified ketone from the acylation was 62 per cent and from the Grignard reaction 34 per cent.

The 2,4,6-trimethyloctadecylbenzene was prepared from mesitylene by acylation with octadecanoyl chloride, reduction with lithium aluminum hydride, dehydration over alumina at 350° and finally hydrogenation over copper chromite catalyst. The best commercial mesitylene contained a hydrocarbon impurity boiling within a few degrees of the desired 1,3,5-trimethylbenzene. A fractionating column possessing 100 theoretical plates was required to separate this impurity which from physical property data appeared to be a methylethylbenzene. Attempts at direct reduction of the ketone to the hydrocarbon *via* the Clemmensen[9] or the Wolff-Kishner[10] methods were unsuccessful. In each case the ketone was recovered unchanged, apparently because of the steric hindrance of the ortho methyl groups.

The 1,3-didecylcyclohexane and 2,5-dimethyloctadecylcyclohexane were prepared by complete hydrogenation of the respective aromatic analogs over a nickel catalyst[11] at 150–200°. The 2,4,6-trimethyloctadecylcyclohexane was prepared by complete hydrogenation of 1-(2,4,6-trimethylphenyl)-1-octadecene.

The cyclohexane derivatives are mixtures of geometric isomers and the properties given were determined on these mixtures.

Several of the important physical properties determined for the hydrocarbons are listed in Table I. The methods of determining the properties and their precisions were discussed in the first paper of the series.[12]

EXPERIMENTAL[13]

Intermediates. Careful purification of the intermediates greatly simplifies the purification of the final hydrocarbons. Where possible, all intermediates were fractionally distilled through distillation columns having at least 35–40 theoretical plates. The boiling points of the intermediates are uncorrected unless otherwise specified. The properties listed are for the fractions having similar boiling points, refractive indices, and melting points or viscosities.[14]

(a) *Decanoic acid.* Capric acid (Armour Neo-Fat 10) was purified by fractional distilllation: b.p. 168°/28 mm., setting point found 31.3°; reported[15] 31.24°.

(b) *Octadecanoic acid.* Stearic acid (Armour Neo-Fat 18) was converted to methyl stearate which was purified by fractional distillation through a "solids high vacuum column:"[16] $Z^{37.8}$ 5.984 cs. The ester was converted to the acid by saponification with aqueous sodium hydroxide, followed by acidification with dilute hydrochloric acid: m.p. found 69.0–69.6°, reported[15] 69.60°.

(7) R. W. Schiessler, F. C. Whitmore, J. A. Dixon, J. N. Cosby, W. P. Acton, D. G. Clarke, W. K. Conn, R. C. East, N. R. Eldred, F. B. Fischl, David Flitter, E. J. Goldberg, C. H. Herr, J. F. Hosler, F. T. Kerr, H. H. Kuehner, R. L. McLaughlin, P. C. Miller, G. W. Pearce, C. S. Rowland, A. W. Rytina, W. S. Sloatman, R. M. Speck, L. H. Sutherland, and C. A. Weisel, *Ind. Eng. Chem.*, **47**, 1660 (1955).

(8) C. H. Herr, R. W. Schiessler, and F. C. Whitmore, *J. Am. Chem. Soc.*, **67**, 2061 (1945).

(9) E. L. Martin, *Org. Reactions*, **I**, 166 (1942).

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

(11) A kieselguhr-supported nickel supplied by the Universal Oil Products Co., Chicago, Ill.

(12) F. C. Whitmore, L. H. Sutherland, and J. N. Cosby, *J. Am. Chem. Soc.*, **64**, 1360 (1942).

(13) Microanalyses by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

(14) Only those fractions whose viscosities agreed within 0.3% were combined as high purity material.

(15) C. W. Ralston, *Fatty Acids and Their Derivatives*, John Wiley and Sons, New York, 1948, p. 323.

(16) The packed section of this column is 90 cm. long with an inside diameter of 25 mm. and is packed with 0.24 × 0.24 inch protruded metal packing. The efficiency is estimated to be approximately 15 theoretical plates.

(c) *Decanoyl chloride* was prepared by reaction of *n*-decanoic acid with thionyl chloride at 25°. Yield of product obtained upon distillation of the reaction mixture through a Claisen head was 94.7%; b.p. 133°/30 mm.

(d) *Octadecanoyl chloride* was prepared by the reaction of octadecanoic acid with phosphorus pentachloride. The crude acid chloride, after removal by distillation of the phosphorus oxychloride, was used for the subsequent acylations.

(e) *1,4-Dimethylbenzene.* Oronite Chemical Company *p*-xylene was purified by fractional distillation through a glass-helices packed column having 40 theoretical plates: b.p. 138°/745 mm., n_D^{25} 1.4931, Z^{20} 0.748 cs; reported:[17] b.p. 138.35/760 mm.; n_D^{25} 1.49325: Z^{20} 0.748 cs.

(f) *1,3,5-Trimethylbenzene.* Matheson, Coleman and Bell Chemical Co. mesitylene was purified by fractional distillation through a column having 100 theoretical plates: n_D^{25} 1.4967, Z^{20} 0.813 cs, b.p. 164°/24 mm.; reported:[17] n_D^{25} 1.49684.

1,3-Didecylbenzene. Decanoyl chloride (1718 g., 9.01 moles) was stirred with a suspension of anhydrous aluminum chloride (1370 g., 10.27 moles, Allied Chemical and Dye Co.) in thiophene-free benzene (1300 g., 16.7 moles) for 4 hr. at 25°. Hydrolysis over cracked ice followed by distillation of the hydrolysis product through a "solids high vacuum column"[15] gave 1653 grams (78.9%) of nonyl phenyl ketone: m.p. 34.3°, 2,4-dinitrophenylhydrazone, m.p. 108.7–109.2°.

Reduction of the ketone by the modified Wolff-Kishner reaction[7] followed by fractional distillation of the reduction product through a 40 plate column gave 1029 grams (74.1%) of decylbenzene: b.p. 158°/9 mm. n_D^{25} 1.4812, Z^{20} 4.45 cs; reported[7,17] n_D^{25} 1.48112, Z^{20} 4.44. The infrared spectrum was identical with an authentic sample kindly supplied by Professor Cecil Boord of the Ohio State University. A typical disproportionation was conducted as follows: Decylbenzene (253.2 g., 1.16 moles) and aluminum bromide (Fisher Scientific Co., 199.1 g., 0.75 mole) were cooled to 0° and anhydrous hydrogen bromide (Matheson Co., 29.9 g., 0.37 mole) was bubbled into the hydrocarbon–aluminum bromide mixture while stirring. The mixture was stirred for 40 hr. at 0° to yield a mixture of benzene, decylbenzene, 1,3-didecylbenzene and a small quantity of 1,4-didecylbenzene. Fractional distillation of the disproportionation product through a spinning band column[18] gave a 48.1% yield of high purity 1,3-didecylbenzene: (See Table I for properties).

Anal. Calcd. for $C_{26}H_{46}$: C, 87.07; H, 12.93. Found C, 87.25; H, 12.96.

1,3-Didecylcyclohexane. Hydrogenation of 1,3-didecylbenzene (208.0 g., 0.58 mole) over a nickel catalyst[11] (10% by weight) at 150° and 1900 p.s.i. gave 199.5 grams (94.3%) of 1,3-didecylcyclohexane: (See Table I for properties).

Anal. Calcd. for $C_{26}H_{52}$: C, 85.63; H, 14.37; MR, 120.5. Found C, 85.61; H, 14.46; MR, 120.1.

2,5-Dimethyloctadecylbenzene. A solution of aluminum chloride (366.8 g., 2.75 moles) in nitrobenzene (2 l.) was added slowly with stirring to a solution of stearoyl chloride (644.0 g., 2.13 moles) and *p*-xylene (227.2 g., 2.14 moles) in nitrobenzene (1 liter). The reaction mixture was stirred at 0° for 4 hr. After hydrolysis on cracked ice, the organic layer was fractionally distilled through a spinning band column, (b.p. 185°/0.25 mm).[18] After one recrystallization from 95% ethanol the yield of 2,5-dimethyloctadecanoylbenzene was 492.1 grams (62.1%); m.p. 58.0–58.5°.

Anal. Calcd. for $C_{26}H_{44}O$: C, 83.80; H, 11.90. Found C, 84.15; H, 11.64.

Reduction of 2,5-dimethyloctadecanoylbenzene by the modified Wolff-Kishner reaction[8] gave 345.2 grams (72.4%) of 2,5-dimethyloctadecylbenzene: (See Table I for properties).

Anal. Calcd. for $C_{26}H_{46}$: C, 87.07; H, 12.93. Found: C, 87.13; H, 12.94.

2,5-Dimethyloctadecylcyclohexane. Hydrogenation of 2,5-dimethyloctadecylbenzene (294.0 g., 0.82 mole) over a nickel catalyst[11] (10% by weight) at 200° and 2500 p.s.i. gave 289.2 grams (96.5%) of 2,5-dimethyloctadecylcyclohexane: (See Table I for properties).

Anal. Calcd. for $C_{26}H_{52}$: C, 85.63; H, 14.37; MR, 120.4. Found: C, 85.75; H, 14.35; MR, 120.1.

2,4,6-Trimethyloctadecylbenzene. Acylation of 1,3,5-trimethylbenzene (144.2 g., 1.2 moles) with stearoyl chloride (365.5 g., 1.2 moles), following the procedure described for the acylation of 1,4-dimethylbenzene gave 346.5 grams (74.3%) of 2,4,6-trimethyloctadecanoylbenzene: b.p. 178°/0.23 mm., m.p. 50.9–51.5°.

Anal. Calcd. for $C_{27}H_{46}O$: C, 83.87; H, 11.99. Found: C, 83.71; H, 11.99.

2,4,6-Trimethyloctadecanoylbenzene (489.2 g., 1.26 moles) was reduced to the corresponding alcohol by stirring with lithium aluminum hydride (17.8 g., 0.47 mole, Metal Hydrides. Inc.) in anhydrous diethyl ether at the reflux temperature for 20 hr. After decomposition of the excess hydride by slow addition of an ether-methanol-water (1:1:1) solution and coagulation of the aluminum hydroxide by refluxing for an hour the ether solution was decanted. The alcohol was obtained as white needles by cooling the ether solution to −10°. The yield of 1-(2,4,6-trimethylpentyl)-1-octadecanol was 478.1 grams (97.6%); m.p. 61.5–62.0°. The alcohol was dehydrated to 1-(2,4,6-trimethylphenyl)-1-octadecene in 98.0% yield by passage over activated alumina at 340–360° and *ca.* 1 mm. pressure. Hydrogenation of the olefin over copper chromite catalyst (10% by weight) at 150° and 2000 p.s.i. gave a 96.5% yield of 2,4,6-trimethyloctadecylbenzene. The hydrocarbon was purified by one crystallization from hexane: (See Table I for properties).

Anal. Calcd. for $C_{27}H_{48}$: C, 87.02; H, 12.98. Found: C, 86.81; H, 13.03.

2,4,6-Trimethyloctadecylcyclohexane. Hydrogenation of 1-(2,4,6-trimethylphenyl)-1-octadecene (397.3 g., 1.07 moles) over a nickel catalyst[11] (10% by weight) at 195° and 1650 p.s.i. gave 394.3 grams (97.3%) of 2,4,6-trimethyloctadecylcyclohexane: (See Table I for properties).

Anal. Calcd. for $C_{27}H_{54}$: C, 85.63; H, 14.37; MR, 125.0. Found: C, 85.51; H, 14.26; MR, 124.7.

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(17) F. D. Rossini, K. S. Pitzer, R. L. Arnett, R. M. Braun, and G. C. Pimental, *Selected Values of Physical and Thermodynamic Properties of Hydrocarbons and Related Compounds*, Carnegie Press, Pittsburgh, Pa., 1953.

(18) This column is manufactured by the Nester-Faust Co., Exton, Pa. The packed section is three feet long with an internal diameter of 11 mm. The band is a spiral of 300 mesh stainless steel screen.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF AMERICAN OIL COMPANY]

Alkylation of Xylenes with Ethylene and Propylene

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With strong alkylation catalysts such as $AlCl_3$, *m*-xylene is selectively monoalkylated to the symmetrical isomer. The other two xylene isomers yield mixed products, part of which are symmetrical. Addition of water to $AlCl_3$ forms a different catalyst system, and the amount of unsymmetrical isomers in the product increases with an increase in added water. BF_3-P_2O_5 is a mild alkylation catalyst which promotes the selective monoalkylation of *m*- and *p*-xylene. The products are 4-alkyl-*m*-xylene and 2-alkyl-*p*-xylene, respectively. This catalyst also promotes selective dialkylation of *m*-xylene. The product is 4,6-dialkyl-*m*-xylene. 2,5-Dialkyl-*p*-xylene can be crystallized from the mixture of dialkylation products of *p*-xylene.

The studies presented are concerned with selective alkylation techniques in which choice of catalyst and reaction conditions are adjusted to produce predominantly a single isomer or a mixture that can be easily resolved by fractionation. The alkylation reaction of olefins and xylenes has been examined using catalysts such as anhydrous $AlCl_3$, $AlCl_3$-H_2O, BF_3-H_3PO_4, and BF_3-P_2O_5. By use of the latest analytical techniques, analyses of the product mixtures provide a more accurate picture of isomer distribution than has been possible in earlier works.

Alkylation with $AlCl_3$. Strong alkylation catalysts, such as $AlCl_3$, generally promote substitution at positions meta to existing alkyl side chains in aromatic compounds accompanied by isomerization or disproportionation.[1-4] However, by using less than 0.05 mole $AlCl_3$/mole of aromatic and reaction temperatures below 100°, some aromatic hydrocarbons undergo a relatively small amount of isomerization. Experimental data showing the distribution of 1,3,5 and 1,2,4 isomers obtained in the $AlCl_3$ catalyzed alkylation of meta, para, and mixed xylenes are summarized in Table I.

TABLE I

ALKYLATION OF XYLENES WITH $AlCl_3$

Aromatic Alkylated	Reaction Temp., °C.	Olefin (Moles/Mole Aromatic)	$AlCl_3$ (Moles/Mole Aromatic)	Monoalkylate, % 1,3,5	Monoalkylate, % 1,2,4
m-Xylene	30–100	C_3 (0.7)	0.0125	99	1[a]
m-Xylene	85–90	C_2 (1.2)	0.016	47	24[a]
Xylene[b]	90–95	C_3 (0.67)	0.03	64	17
p-Xylene	90–95	C_3 (0.97)	0.0125	44	44[c]

[a] 4-Alkyl-1,3-dimethylbenzene. [b] 21% ortho, 39% meta, and 14% para isomers. [c] 1,4-Dimethyl-2-isopropylbenzene.

The reaction of *m*-xylene with propylene in the presence of $AlCl_3$ as described results in the predominant production of the 1,3,5 isomer. Reactions in which less than 0.05 mole $AlCl_3$/mole of aromatic was used resulted in 90–99% 1,3-dimethyl-5-isopropylbenzene. The high proportion of the 1,3,5 isomer in the monoalkylate is also independent of the extent of aromatic conversion. Monoalkylation predominates up to 70% xylene conversion; further alkylation results in a diisopropylxylene fraction containing more than one isomer. Ethylation of *m*-xylene under similar reaction conditions yields an ethylxylene fraction containing a lower proportion of the symmetrical 1,3,5 isomer than is obtained by propylation; the fraction contained 47% 1,3-dimethyl-5-ethylbenzene. The differences observed in the distribution of products with these olefins may be the result of "different activity of the attacking species," namely, the olefins, as proposed by Brown and Nelson.[5] A similar relationship in the alkylation of toluene with ethylene and propylene has been reported by Nelson.[6]

In the alkylation of mixed xylenes with propylene, as shown in Table I, a mixture of isomers containing 64% of the 1,3,5 compound is produced. These results can be accounted for by the isomerization of *o*- and *p*-xylenes with accompanying alkylation of the meta isomer. 1,3-Dimethyl-4-isopropylbenzene can be recovered from this mixture in 69% purity by fractionation while 1,3-dimethyl-5-isopropylbenzene of 95% purity can be obtained in a similar manner.

(1) W. C. Howell, U. S. Patent **2,443,247**, June 15, 1948.
(2) A. P. Lien and D. A. McCauley, U. S. Patent **2,564,073**, Aug. 14, 1951.
(3) A. P. Lien, D. A. McCauley, and P. J. Launer, *J. Am. Chem. Soc.*, **76**, 2354 (1954).
(4) D. V. Nightingale and B. J. Carton, *J. Am. Chem. Soc.*, **62**, 281 (1940).
(5) H. C. Brown and K. L. Nelson, *J. Am. Chem. Soc.*, **75**, 6292 (1953).
(6) K. L. Nelson, *J. Org. Chem.*, **21**, 145 (1956).

TABLE II

ALKYLATIONS OF XYLENES WITH BF_3·P_2O_5 AND BF_3·H_3PO_4

Catalyst	Reaction Temp., °C.	Olefin (Moles/Mole Aromatic)	Aromatic	Monoalkylate[a] 1,2,4	Monoalkylate[a] 1,3,5
BF_3·H_3PO_4	80–85	C_3 (0.5–1.5)	*m*-Xylene	65–75[b]	21–34
BF_3·P_2O_5	35–140	C_3 (1.4)	*m*-Xylene	75–82[b]	8–13
BF_3·P_2O_5	94–97	C_2 (1.0)[c]	*m*-Xylene	80–90[b]	—
BF_3·P_2O_5	75–80	C_3 (0.8–1.6)	*p*-Xylene	100[d]	0

[a] Yield limits for a number of alkylations. [b] 4-Alkyl-1,3-dimethylbenzene. [c] 350–400 p.s.i.g. ethylene. [d] 1,4-Dimethyl-2-isopropylbenzene.

Alkylation with BF_3·H_3PO_4 and BF_3·P_2O_5. Mild alkylation catalysts generally promote ortho-para alkylation without isomerization of the parent aromatics. Such catalysts include HF,[7–10] phosphoric acid,[11] ferric chloride,[12,13] calcium hydrogen phosphate,[14] and sulfuric acid.[15–17]

While BF_3 alone has limited use as an aromatic alkylation catalyst, complexes of BF_3 are numerous and have been extensively used as catalysts.[18] These complexes are generally mild alkylation catalysts except the HF·BF_3 system which is a strong acid catalyst[19] that often causes extensive isomerization. BF_3 in combination with P_2O_5[20,21] has been reported to be an active catalyst for the alkylation of aromatic compounds with alcohols. A similar type catalyst prepared by passing BF_3 over a pellet bed of P_2O_5 on kieselguhr (UOP polymerization catalyst) was used in these olefin alkylation studies.

Data are presented in Table II showing the distribution of isomers for the alkylation of *m*- and *p*-xylenes using BF_3·P_2O_5 (solid) and BF_3·H_3PO_4 (liquid) catalysts. In the propylation of *m*-xylene with the BF_3·P_2O_5 catalyst, little change in isomer distribution was noted in varying the reaction temperature from 35° to 140°, the olefin charge rate from 0.22 to 0.62 mole/mole of xylene/hour, or the total olefin/xylene molar ratio from 0.16 to 1.5. Only trace amounts of diisopropylxylenes were obtained at olefin/xylene molar ratios below 0.4. While propylene reacts readily with *m*-xylene over solid BF_3·P_2O_5 at atmospheric pressure, little or no reaction was observed with ethylene under these conditions. However, substantial reaction of *m*-xylene and ethylene occurs at pressures above atmospheric to produce predominantly 1,3-dimethyl-4-ethylbenzene. Data are also included in Table II which compare alkylate compositions obtained with BF_3·H_3PO_4 and BF_3·P_2O_5. It can be seen that by using a BF_3·H_3PO_4 catalyst[22] the ratio of the 1,2,4 isomer to the 1,3-dimethyl-5-isopropylbenzene is approximately 2.5 compared to 7.5 with BF_3·P_2O_5 catalyst.

Studies have also been made in which reaction conditions were adjusted to maximize the production of tetraalkylbenzenes. Such data are summarized in Table III for the alkylation of a number of aromatic compounds using BF_3·P_2O_5 as a catalyst. The tetraalkylbenzene yields with the liquid BF_3·H_3PO_4 catalyst were similar.

TABLE III

PREPARATION OF TETRAALKYLBENZENES WITH BF_3·P_2O_5 CATALYST

Reactants: Olefin (Moles/Mole Aromatic)	Reactants: Aromatic	Tetraalkylbenzene Fraction[a]
C_3 (0.5–4.0)	*m*-Xylene	83–92% 1,2,4,5 Isomer[b]
C_2 (5–6)	*m*-Xylene	Mix[c]
C_3 (3–5)	*p*-Xylene	50–60% 1,2,4,5 Isomer[d]
C_3 (0.7)	Pseudocumene	Mix[c]
C_3 (0.7)	1,3,5-Isopropylxylene	Mix[c]

[a] Yield limits for a number of alkylations. [b] 4,6-Diisopropyl 1,3-dimethylbenzene. [c] The mixtures obtained in these experiments were not separated and could not be analyzed by infrared absorption spectroscopy due to lack of pure reference samples. Two or more isomers appear to be present, and no single isomer was formed in major proportions. [d] 2,5-Diisopropyl-1,4-dimethylbenzene.

(7) F. M. Smith, U. S. Patent **2,507,765**, May 16, 1950.
(8) F. E. Condon and M. P. Matuszak, *J. Am. Chem. Soc.*, **70**, 2539 (1948).
(9) J. H. Simons and S. Archer, *J. Am. Chem. Soc.*, **62**, 1623 (1940).
(10) F. M. Smith and R. S. Hanmer, U. S. Patent **2,507,766**, May 16, 1950.
(11) V. N. Ipatieff, H. Pines, and V. I. Kowarewsky, *Ind. Eng. Chem.*, **28**, 222 (1936).
(12) D. V. Nightingale and J. R. Jones, *J. Am. Chem. Soc.*, **66**, 154 (1944).
(13) L. Schmerling, U. S. Patent **2,402,847**, June 25, 1946.
(14) R. E. Schaad, U. S. Patent **2,290,211**, July 21, 1942.
(15) S. J. Slanina, F. J. Sowa, and J. A. Nieuwland, *J. Am. Chem. Soc.*, **57**, 1547 (1935).
(16) V. N. Ipatieff. B. B. Corson, and H. Pines, *J. Am. Chem. Soc.*, **58**, 919 (1936).
(17) V. N. Ipatieff, H. Pines, and L. Schmerling, *J. Org. Chem.*, **5**, 253 (1940).
(18) H. S. Booth and D. R. Martin, *BF_3 and Its Derivatives*, John Wiley and Sons, New York, 1949.
(19) A. P. Lien and D. A. McCauley, *J. Am. Chem. Soc.*, **75**, 2411 (1953).
(20) C. E. Welsh and G. F. Hennion, *J. Am. Chem. Soc.*, **63**, 2603 (1941).
(21) N. F. Toussaint and G. F. Hennion, *J. Am. Chem. Soc.*, **62**, 1145 (1940).
(22) W. N. Axe, U. S. Patent **2,412,595**, Dec. 17, 1946.

These data show the dialkylation of *m*-xylene is selective in that 83–92% of the diisopropylated material is 4,6-diisopropyl-1,3-dimethylbenzene. The dialkylate from *p*-xylene contains two isomers and a trace of a third. One of these isomers has been separated by freezing and appears to be 2,5-diisopropyl-1,4-dimethylbenzene. Data are also presented for the alkylation of two trialkyl benzenes to tetraalkyl isomers. Mixtures were obtained in both these cases which could not be separated.

Alkylation with $AlCl_3$-H_2O. Xylene alkylation studies were made with a catalyst of $AlCl_3$ modified with small amounts of water. Data are presented in Fig. 1 for a series of experiments in which *m*-xylene was alkylated with propylene at 90–95° with 0.0125 mole of $AlCl_3$/mole of xylene. The product distribution is shown to be a function of the amount of water present. The ratio of 1,2,4- to 1,3,5-isopropylxylene changes from approximately 0.01 with anhydrous $AlCl_3$ to 0.44 for a system containing equal molar quantities of water and $AlCl_3$ (considered to be monomolecular for this calculation).

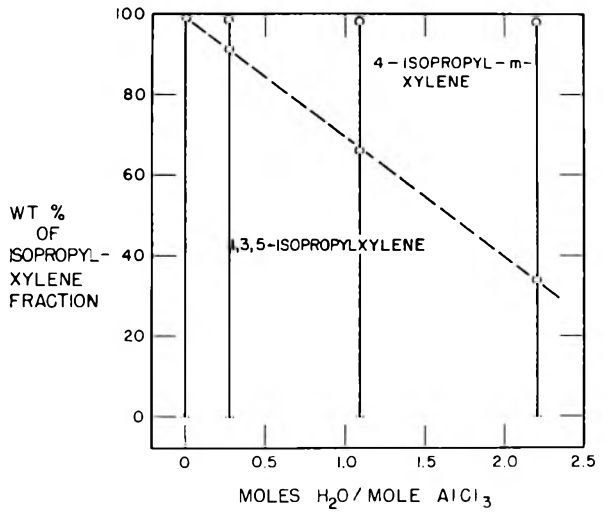

Fig. 1. Propylation of *m*-xylene with $AlCl_3$-H_2O catalysts

While the xylene conversion is observed to decrease somewhat as the amount of water is increased, a marked decline in propylation reaction is shown, in Fig. 2, to occur only with catalyst systems containing more than one mole of water/mole of $AlCl_3$. Water seems to have a somewhat greater effect on the conversion of xylene for reaction with ethylene.

These data clearly indicate the marked effect of water in altering product distribution for an $AlCl_3$ alkylation. The product variation is not equivalent to the results obtained with a lowered catalyst concentration such as might be assumed to result from destruction of part of the $AlCl_3$. The marked shift in isomer distribution resulting from the addition of water indicates a different catalyst system

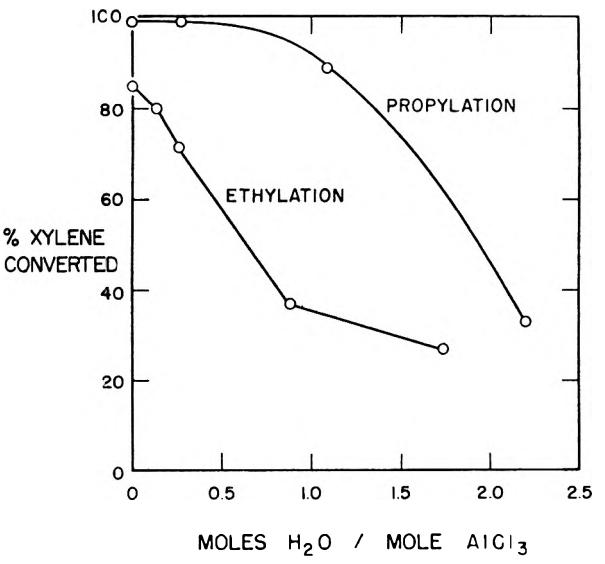

Fig. 2 *m*-Xylene conversion with $AlCl_3$-H_2O catalyst

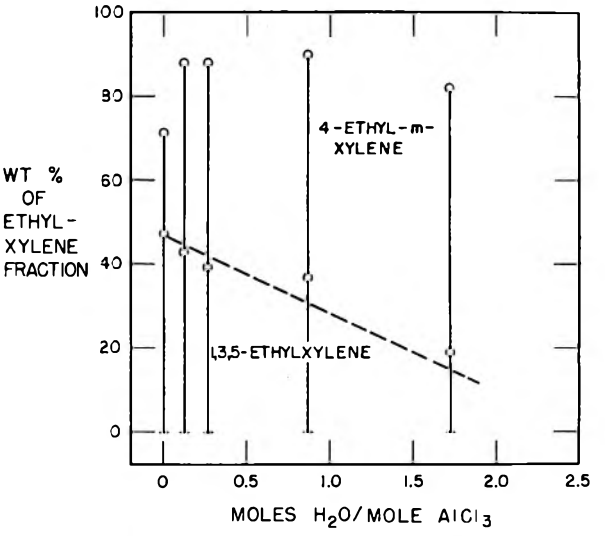

Fig. 3. Ethylation of *m*-xylene $AlCl_3$ catalyst, modified with H_2O

is formed by the reaction of water with $AlCl_3$ in xylene. The results also substantiate further the conclusion of Brown and Nelson[5] that there is no sharp division between meta-directed substitutions and reactions that produce high proportions of ortho- and para-substituted products. As noted by Brown, *et al.*,[23] the effect of water on $AlCl_3$ catalyst likely is the case of part or all of the discrepancies in previous publications regarding alkylation isomer distribution.

Similar data are supplied for the ethylation of *m*-xylene in Figs. 2 and 3. These results indicate that such catalyst systems are less selective for ethylation as compared with propylation and that

(23) H. C. Brown, H. W. Pearsall, L. P. Eddy, E. J. Wallace, M. Grayson, and K. L. Nelson, *Ind. Eng. Chem.*, **45**, 1462 (1953).

product distribution is also altered less by varying the amount of water added.

Purification and properties of alkylxylenes. Physical properties of the alkylated xylenes prepared in this work are listed in Table IV. The physical properties which have been reported in the literature[24,25] are also included.

TABLE IV

PHYSICAL PROPERTIES OF ALKYLXYLENES

	B.P., °C.	F.P., °C.[a]	d_{25}	n_D^{25}
1,3,5-Ethylxylene				
Experimental	—	—	—	—
Literature[24]	183.8	−84	0.8608	1.4958
4-Ethyl-1,3-dimethylbenzene				
Experimental	186–187	−62.5	—	1.5012
Literature[24]	188.4	−63	0.8723	1.5016
1,3,5-Isopropylxylene				
Experimental	194.6	−70	0.8593	1.4926
Literature[24]	194.5	—	0.858	1.493
4-Isopropyl-1,3-dimethylbenzene				
Experimental	199.0	−82	0.8707	1.4982
Literature[24]	199.1	—	0.869	1.498
1,4-Dimethyl-2-Isopropylylbenzene				
Experimental	196.2	—	0.8721	1.4990
Literature[24]	196.2	—	0.8699	1.4988
4,6-Diisopropyl-1,3-dimethylbenzene				
Experimental	236.4	16.8	0.8668	1.4957
2,5-Diisopropyl-1,4-dimethylbenzene				
Experimental	243.8	37.2	0.8612[b]	1.4945[b]
Literature[25]	—	37.2	—	1.4917[c]

[a] Freezing data for alkyl xylene are only approximate since all tend to form glasses. F.P. for dialkyl xylenes was determined from freezing curves. The accuracy of these is about 16.8 ± 0.3° and 37.2 ± 0.1°. [b] These measurements made at 45.1°. [c] At 50°.

Pure isopropylxylenes were obtained by fractionation through a 4′ × 1″ Hypercal column at 80/1 reflux ratio. Pure 1,3,5-ethylxylene was obtained from the National Bureau of Standards. 4-Ethyl-*m*-xylene was synthesized by hydrogenation (Clemmenson method) of 2,4-dimethylacetophenone. The ketone was prepared by reaction of *m*-xylene and acetyl chloride (Friedel-Crafts reaction) with aluminum chloride catalyst. Fractionation of the hydrogenation product gave pure hydrocarbon.

Two pure diisopropylxylenes have been obtained. 4,6-Diisopropyl-*m*-xylene was purified by fractionation of the reaction product. A freezing curve showed the material to be pure, m.p. 16.8° ± 0.3°. Pure 2,5-diisopropyl-*p*-xylene could not be separated from a close boiling isomer by fractionation. However, the compound crystallized from the contaminating isomer and recrystallized nicely from *n*-pentane. A freezing curve of the recrystallized material showed it to be quite pure, m.p. 37.2° ± 0.1°. The physical properties of this material agree with those published by Kooyman and Strang[25] for 2,5-diisopropyl-*p*-xylene.

The two diisopropylxylenes prepared in this work are believed to have the 1,2,4,5 structure because: (1) The relatively high melting points are characteristic of symmetrical tetraalkyl benzenes; (2) the infrared absorption spectrum is similar to spectra of known 1,2,4,5-tetraalkyl benzenes; and (3) each is prepared, with nonisomerizing catalysts and reaction conditions, from the corresponding isopropyxylene. In addition, vapor phase oxidation of pure 4,6-diisopropyl-*m*-xylene has yielded pyromellitic acid. Kooyman and Strang[25] reported the ultraviolet spectrum of a 2,5-diisopropyl-*p*-xylene, which has the same physical properties as our material, to indicate the structure as given.

EXPERIMENTAL

Alkylations using BF_3·P_2O_5 on kieselguhr (solid) were carried out in a vertical glass tube reactor, 30″ × 2″, equipped with an electrical heater. Cylindrical pellets, 1/4″ × 1/4″, were added to the reactor to make a catalyst bed 13″ × 2″. The P_2O_5-kieselguhr pellets were saturated with xylene and a known weight of the aromatic was charged. The catalyst and xylene were then saturated with BF_3 over a 30-min. period by introducing BF_3 at a rate of 80 cc./min. (room temperature and atmospheric pressure). Gaseous olefin was introduced into the reactor after heating to the desired temperature. The gases were dispersed at the bottom of the reactor by means of a fritted glass disk. In order to maintain catalyst activity, BF_3 was introduced continuously with the olefin charge during alkylation. The reaction product was washed free of catalyst, dried, and distilled.

The BF_3·H_3PO_4, which is a liquid, was prepared by saturating 86% phosphoric acid with BF_3 resulting in a catalyst having a mole ratio of $H_3PO_4/H_2O/BF_3$ of 6.9/6.0/13.0. The alkylations with this catalyst were carried out in the same glass reactor mentioned above. While aromatic hydrocarbons are not miscible with such a catalyst, adequate mixing was obtained by introducing the olefin charge through a fritted glass disk at the bottom of the reactor tube.

Detailed information regarding reaction conditions and product distribution for BF_3·P_2O_5 and BF_3·H_3PO_4 catalyzed reactions are summarized in Table V.

$AlCl_3$ catalyzed alkylations were carried out in conventional flasks equipped with suitable stirrers. Catalyst was removed from the reaction products by washing with dilute HCl, followed by drying and distilling.

Detailed experimental data and product distribution for $AlCl_3$ and $AlCl_3$·H_2O alkylations are summarized in Table VI.

The aromatic hydrocarbons were analyzed by infrared absorption spectroscopy, using Perkin-Elmer No. 12-B and No. 21 recording spectrometers. High purity alkylxylene isomers were separated by fractionation through a 4′ × 1″ Hypercal column operating at 80/1 reflux ratio. The di-

(24) F. D. Rossini, K. S. Pitzer, R. L. Arnett, R. M. Braun, and G. C. Pimentel, *Selected Values of Physical and Thermodynamic Properties of Hydrocarbons and Related Compounds*, Carnegie Press, Pittsburgh, 1953.

(25) E. C. Kooyman and A. Strang, *Rec. trav. chim.*, **72**, 329 (1953).

TABLE V

ALKYLATION DATA FOR BF_3 COMPLEXES

Reactants		Reaction Conditions			Products, Mole % of Aromatic Charge				Monoalkylate Analysis, Wt. %	
Hydrocarbon charge	Catalyst[a]	Temp., °C.	Duration, hours	Olefin/arom. mole ratio	Arom. converted	Monoalkylate	Dialkylate	Bottoms[b]	1,2,4 Isomer	1,3,5 Isomer
p-Xylene-C_3	BF_3·P_2O_5(s)	75–80	5.0	1.6	88	45	32.4	11.0	100	0
o-Xylene-C_3	BF_3·P_2O_5(s)	75–80	3.0	1.1	55	25.7	10.3	7.0	Ca 50	—
m-Xylene-C_3	P_2O_5	75–80	4.0	0.9	—	0	0	3.5	—	—
m-Xylene-C_3	BF_3·P_2O_5(s)	35–40	2.5	0.9	77	42	12.0	8.0	79	10
m-Xylene-C_3	BF_3·P_2O_5(s)	75–80	3.0	0.9	63	42	4.0	12.0	78	13
m-Xylene-C_3	BF_3·P_2O_5(s)	95–100	2.0	0.9	79	45	9.0	8.0	76	13
m-Xylene-C_3	BF_3·P_2O_5(s)	125–130	2.5	0.9	75	47	6.0	7.0	75	14
m-Xylene-C_3	BF_3·P_2O_5(s)	75–80	1.0	0.2	32	14	0	5.0	78	10
m-Xylene-C_3	BF_3·P_2O_5(s)	75–80	3.0	0.5	44	24	3.0	3.7	80	12
m-Xylene-C_3	BF_3·P_2O_5(s)	75–80	4.0	0.7	64	37	10.0	4.0	80	13
m-Xylene-C_3	BF_3·H_3PO_4(l)	80–85	1.8	0.5	45	24	4.0	5.0	65	34
m-Xylene-C_3	BF_3·H_3PO_4(l)	80–85	5.0	1.5	91	48	28.0	9.0	75	21
Pseudocumene-C_3	BF_3·P_2O_5(s)	75–80	2.0	0.7	62	34	0	10.0	—	—
1,3,5-Isopropylxylene[c]-C_3	BF_3·P_2O_5(s)	75–80	2.0	0.7	48	43	—	15.0	5[d]	95[d]
m-Xylene-C_3	BF_3·Al_2O_3[e]	75–80	2.5	1.5	77	25	36.0	12.0	75	20
m-Xylene-C_2[f]	BF_3·P_2O_5(s)	150–156	6.3	0.5	Ca 25	14	2.0	5.0	Ca 85	—
m-Xylene-C_2[f]	BF_3·P_2O_5(s)	94–97	5.3	1.0	Ca 60	23	4.0	15.0	Ca 85	—

[a] The (s) designates the supported BF_3·P_2O_5 on kieselguhr. The (l) designates the liquid BF_3·H_3PO_4 made as per Axe, U. S. Patent 2,412,595. [b] This value given as wt. % of aromatic charged. [c] 90% pure, also contained 6% 4-isopropyl-*m*-xylene. [d] This analysis is for the recovered isopropylxylene. [e] BF_3 added to alumina (Alcoa F-1 grade, 8–14 mesh). The solid contained 20% BF_3, by weight. [f] 350–450 p.s.i.g.

TABLE VI

ALKYLATION WITH $AlCl_3$

Reactants		Reaction Conditions			Products, Mole % of Aromatic Charge				Monoalkylate Analysis, Wt. %	
Hydrocarbon charge	$AlCl_3$ mole/mole arom. (H_2O, mole/mole arom.)	Temp., °C.	Duration, hours	Olefin arom. mole ratio	Arom. converted	Monoalkylate	Dialkylate	Bottoms[a]	1,2,4 Isomer	1,3,5 Isomer
Xylene[b]-C_3	0.0076	90–95	2.0	0.63	55	43.0	0	7.5	20	62
Xylene[b]-C_3	0.030	90–95	2.0	0.68	63	42.3	0	8.7	17	64
p-Xylene-C_3	0.0128	90–95	2.8	1.0	86	54.0	12.5	4.0	44[c]	41
m-Xylene-C_3	0.0128	30–35	5.5	1.5	99	46.5	41.0	3.5	11	88
m-Xylene-C_3	0.0128	90–95	5.0	1.5	99	53.1	34.2	5.5	1	99
m-Xylene-C_3	0.0128	125–130	4.7	1.5	100	63.7	26.2	12.0	9	81
m-Xylene-C_3	0.0128	90–95	2.7	1.5	100	41.0	38.3	4.5	4	96
m-Xylene-C_3	0.0128	90–95	5.0	1.0	79	68.0	0	5.5	9	84
m-Xylene-C_3	0.0063	90–95	2.3	0.7	24	15.8	0	4.0	10	90
m-Xylene-C_3	0.013 (0.0035)	90–95	5.7	1.5	99	49.3	28.6	11.5	6	92
m-Xylene-C_3	0.013 (0.014)	90–95	4.7	1.3	88	50.1	22.6	8.0	32	66
m-Xylene-C_3	0.013 (0.028)	90–95	5.0	1.4	33	16.4	Tr	3.0	64	34
m-Xylene-C_2	0.016	85–90	4.0	1.3	85	41.8	13.8	13.0	24[d]	47[e]
m-Xylene-C_2	0.016 (0.002)	85–90	4.0	1.2	80	42.7	15.8	15.0	45[d]	43[e]
m-Xylene-C_2	0.016 (0.004)	85–90	4.0	1.2	71	36.1	13.6	18.0	49[d]	39[e]
m-Xylene-C_2	0.015 (0.014)	85–90	4.0	1.2	37	12.2	1.0	5.8	53[d]	37[e]
m-Xylene-C_2	0.016 (0.028)	85–90	4.0	1.2	27	2.5	0	6.2	63[d]	19[e]

[a] High boiling residue measured as wt. % of aromatic charged. [b] 21% *o*-, 39% *m*-, and 14% *p*-xylene. [c] This fraction is 2-isopropyl-*p*-xylene. [d] 4-Ethyl-*m*-xylene. [e] 1,3,5-Ethylxylene.

isopropylxylenes were purified by fractionation and recrystallization. After isolation and identification, the high purity products were used as calibrating standards for conventional infrared quantitative analyses.

All hydrocarbons used were obtained from chemical supply companies and were at least 95% pure. The P_2O_5 in kieselguhr catalyst was conventional UOP No. 2 polymerization catalyst and was supplied by Universal Oil Products Company. In those reactions in which anhydrous $AlCl_3$ was used, precautions were taken to avoid contamination by atmospheric moisture. Water was carefully measured and added to systems in which $AlCl_3$·H_2O was employed as the catalyst.

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

Metalation of Cumene[1]

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Amyl- and phenyl-potassium, prepared from potassium metal and amyl chloride or anisole, respectively, metalated cumene almost exclusively in the alpha position rather than on the nucleus. These results are contrasted with those obtained previously in this and other laboratories. The cation and associated salts have a greater influence upon the position attacked than does incipient acidity of the hydrocarbon.

Three different laboratories have obtained different results in the metalation of cumene, as has been noted in a recent review.[2] A reason for these differences should be understood because one of the laboratories[3] has maintained that the inductive and field effects of the substituent group determine the position attacked. This viewpoint has been reaffirmed in the review.[2] The differences cannot be credited to errors in the identification of the products of carbonation because the three laboratories agree about the properties of the respective acids. One feature, however, stands out clearly; each laboratory has in general prepared its metalating agent by a different method. This laboratory has used amylsodium,[4,5] prepared from amyl chloride and sodium; it metalated cumene almost exclusively on the nucleus. Bryce-Smith,[3] with one exception, used an alkylpotassium reagent which was made from potassium metal and an alkyllithium compound; it metalated 81 to 87% on the nucleus and the rest at the alpha carbon atom. Gilman and co-workers made only two experiments, one with a reagent derived from sodium and diethylmercury[6] and the other from potassium and the mercury compound[7]; both caused a large amount of lateral metalation with possibly some nuclear displacement also, although the separation of the acids corresponding to the latter did not occur easily.

If three different reagents caused three different results, another method of preparing a reagent might cause a still different result. This thought has, indeed, been realized with a preparation of amylpotassium made according to Equation 1 which parallels the preparation[4,5] of amylsodium from amyl chloride and sodium. This potassium reagent

$$C_5H_{11}Cl + 2K(\text{or Na}) \longrightarrow C_5H_{11}K + KCl(\text{or NaCl}) \quad (1)$$

metalated cumene predominantly at the alpha position (2% on the nucleus) whereas Bryce-Smith's[3] amylpotassium had attacked the alpha position only 17% and amylsodium prepared as indicated in equation 1 had metalated laterally only 1%. The nearly exclusive nuclear metalation by amylsodium had already been demonstrated both here[4,5] and in the London[3] laboratory. Hence when the same materials were used for preparing the reagent, the results, as far as lateral versus nuclear attack was concerned, agreed despite the fact that the London laboratory did not use high speed stirring; and when unlike materials were used, as in the above cases, the results disagreed. Very clearly the reagent, rather than the hydrocarbon, determined the position attacked.

The idea of incipient acidity as the determinant of orientation is inconsistent also with the position attacked by phenylpotassium. That reagent, which was prepared in two ways according to Equations 2 and 3, attacked the alpha position predominantly

$$C_5H_{11}Cl + 2K + C_6H_6 \longrightarrow C_5H_{12} + KCl + C_6H_5K \quad (2)$$

$$C_6H_5OCH_3 + 2K \longrightarrow C_6H_5K + KOCH_3 \quad (3)$$

(85% and possibly higher). According to the values for incipient acidity, as determined by Bryce-Smith,[3] nuclear attack should have occurred approximately four to one and metalation should have been slight because the attacking phenyl anion would have to remove a proton from the deactivated nucleus in cumene.

The present results emphasize the importance of the cation. When the cation was potassium, and no other cation but potassium was present in the associated salt, the preferred position of attack was at the alpha carbon atom. When sodium cations only were present the preferred position was on the nucleus. This preference of potassium for the alpha position accords also with the results from metalation by potassium metal[8] and sodium oxide. The sodium cation in the oxide salt did not alter the position taken by potassium, and the potassium cation remained at the alpha position during months of aging.[9] Incipient acidity had no control in these

(1) This work was performed as part of a research project sponsored by the National Science Foundation.

(2) A. R. Benkeser, D. J. Foster, D. M. Sauve, and J. F. Nobis, *Chem. Revs.*, **57**, 867 (1957).

(3) D. Bryce-Smith, *J. Chem. Soc.*, 1079 (1954).

(4) A. A. Morton, J. T. Massengale, and M. L. Brown, *J. Am. Chem. Soc.*, **67**, 1620 (1945).

(5) A. A. Morton and E. L. Little, *J. Am. Chem. Soc.*, **71**, 487 (1949).

(6) H. Gilman and R. V. Young, *J. Am. Chem. Soc.*, **62**, 1519 (1940).

(7) H. Gilman and L. Tolman, *J. Am. Chem. Soc.*, **68**, 522 (1946).

(8) C. E. Claff, Jr., and A. A. Morton, *J. Org. Chem.*, **20**, 981 (1955).

(9) A. A. Morton and J. E. Eisenmann, *J. Org. Chem.*, **23**, 1469 (1958).

cases. The frequent failure of incipient acidity as a guiding rule in these reactions has been noted earlier.[10]

To chemists who wish to interpret and predict all things by a simple anionic concept, which has been derived from the reactions of dissolved and dissociated reagents, this situation possibly seems distressing; but to those who think in terms of reactions of complexes and associated salts and particularly of reactions at the surfaces of solids, these results are quite in order. Organic compounds are adsorbed or chemisorbed on the solids as the first step of reaction and their accessibility to the reagent determines the reaction. A change in the cation or the association of other solids with the reagent changes the number and position of the places where adsorption can occur. Consequently the degree and sometimes the type of reaction change. Already these ideas have been certified in five separate fields—polymerization,[11] alkylation,[12] metalation,[13] ether cleavage,[14] and pyrolysis.[15] The effect was very striking in the polymerization of butadiene[11] where the association of sodium isopropoxide and sodium chloride with allylsodium changed the process from the 1,2-chain growth, universally credited to anionic reagents, to a 1,4-growth which became as high as was found in free radical polymerization.

The wide variety of results obtained because the reagents were prepared differently must not obscure the fact that broadly the conclusions and opinions are the same when the separate factors are measured. For instance the two laboratories which have studied the effect of some variables agree that the anion has no appreciable influence on orientation; this laboratory because amyl- and phenyl-potassium behaved alike in metalating cumene at the alpha position and the London laboratory[3] because ethyl-, propyl-, and amyl-potassium gave the same meta/para ratio in metalation at the nucleus. Also both laboratories agree that the cation does have an influence; the former because amyl-sodium and -potassium metalated primarily at the nucleus and side chain, respectively, and the latter[3] because amyl-sodium and -potassium gave different meta/para ratios in metalation at the nucleus. However, Bryce-Smith[3] did not think that the difference was great enough to alter his opinion about the mechanism being anionic with the position of attack controlled by the incipient acidity of the hydrogen atoms. Unfortunately his comparison of cation influence was with two reagents prepared by different methods. When the comparison was with two reagents made by the same method, as has been observed with the amyl-sodium and -potassium reported in this paper, the difference is too large to ignore.

The real disagreement between the two laboratories is concerned with the influence of associated salts upon metalation. This feature is new and is not recognized generally. Indeed, the recent reviewers[2] of this field have given considerable weight to the adverse opinion of Bryce-Smith[5] and have suggested that still more evidence is required.[16] Actually the difference is one of fact versus opinion. Over many years this laboratory has shown that associated salts can exert an influence[11–15] in a variety of reactions and specifically has shown that a lithium alkoxide can affect the orientation in the dimetalation of benzene.[17] Bryce-Smith[3] stated that any effect by an alkoxide was "unlikely" but made no tests. In a previous paper[18] he had acknowledged that his potassium reagent probably contained a lithium compound (39%) and had suggested a composition of the type $(RLi)_x(RK)_y$. Apparently an inactive salt, such as an alkoxide or alkyllithium compound, which could not itself metalate a hydrocarbon, was supposed to be incapable of affecting the action of the metalating agent. Hence no control test was made of metalation in the absence of such a compound. The experiments reported in this paper show that in the absence of a lithium compound, metalation by a potassium reagent is chiefly lateral rather than nuclear.

Special attention is directed to the method of analysis of the products of metalation. Infrared measurements[19] of phenyl-sodium and -potassium, of benzyl-sodium and -potassium, of *p*-tolylpotassium, and of cumenylsodium and phenylisopropylpotassium show distinctive absorption for the aryl ions at 1210 cm.$^{-1}$ and for the benzyl type ions at 1165 cm.$^{-1}$ The two absorptions are sharply characteristic. The method has proven unusually valuable in following chemical changes, for instance in the metalation of cumene by phenylpotassium. It is superior to the usual carbonation process because any secondary changes during carbonation cannot become involved. For example some car-

(10) A. A. Morton and C. E. Claff, Jr., *J. Org. Chem.*, **21**, 736 (1956).

(11) A. A. Morton, I. Nelidow, and E. Schoenberg, *Proc. 3rd Rubber Tech. Conf.*, (1948) 108; A. A. Morton, *Advances in Catalysis*, IX 743 (1957), Academic Press Inc., New York.

(12) A. A. Morton and A. E. Brachman, *J. Am. Chem. Soc.*, **73**, 4363 (1951).

(13) A. A. Morton, C. E. Claff, Jr., and F. W. Collins, *J. Org. Chem.*, **20**, 428 (1955).

(14) A. A. Morton and A. E. Brachman, *J. Am. Chem. Soc.*, **76**, 2973 (1954).

(15) A. A. Morton and E. F. Cluff, *J. Am. Chem. Soc.*, **74**, 4056 (1952).

(16) On page 873, line 24, of the recent review[2] the yield should be 17% instead of 48%. The original report[5] gave 48% as the total yield of acids obtained by carbonation, but pointed out that 64.5% of the total acid was caproic acid, representing unchanged amylsodium which had not participated in metalation. This result therefore does not constitute an exception to the alkoxide effect.

(17) A. A. Morton and C. E. Claff, Jr., *J. Am. Chem. Soc.*, **76**, 4935 (1954).

(18) D. Bryce-Smith and E. E. Turner, *J. Chem. Soc.*, 861 (1953).

(19) E. J. Lanpher, *J. Org. Chem.*, **21**, 830 (1956); *J. Am. Chem. Soc.*, **79**, 5578 (1957).

boxyl might be introduced into the nucleus during carbonation of phenylisopropylpotassium because of a rapid change of one radical (or ion) into the other during carbonation as shown in Equation 4.

$$C_6H_5C(CH_3)_2\cdot \longrightarrow \cdot C_6H_4CH(CH_3)_2 \qquad (4)$$

For this reason the tests[5] by oxidation of the crude acid product by chromic acid or permanganate can be open to some question although that method was used twice in the present work and gave roughly confirmatory results.

EXPERIMENTS

Direct determination of the metalation product by infrared absorption. Nujol mulls[19] were prepared from 5-ml. samples of each suspension as obtained from a reaction mixture. Excess solvent was removed by evaporation under vacuum. The grease-like residue of Nujol and organometallic compound was smeared between salt plates under dry box conditions. The film was adjusted to proper thickness. Excellent spectra were obtained in these cases. The bands were sharp with strong absorption at numerous positions as would be expected for aromatic compounds. All preparations used in establishing the facts that the aryl ion absorbed at 1210 cm.$^{-1}$ and the benzyl-type ion absorbed at 1165 cm.$^{-1}$ were carried out by methods which have been shown by carbonation to give primarily or exclusively the type of acid corresponding to the carbon anion in question.

Amylpotassium and cumene. Amyl chloride (30 ml. or 0.25 mole) was added dropwise during 1 hr. at −10° to a suspension of 19.5 g. (0.5 atom) of potassium sand in heptane which contained 60 g. (0.5 mole) of cumene. The conditions were in general similar to those regularly used in the preparation of amylsodium.[20] The product showed no band at 1205 cm.$^{-1}$ characteristic for an aryl ion but absorbed strongly at 1165 cm^{-1} as is typical for phenylisopropylpotassium. In order to determine traces of nuclear metalation the crude solid, low melting, water-soluble phenylisobutyric acid (2.5 g.) from a 100-ml. aliquot of the reaction mixture was oxidized by chromic acid.[3] By this procedure an aromatic acid (any *m*- or *p*-cuminic acid) would be oxidized to an isophthalic or terephthalic acid which would be insoluble in water. The yield of insoluble acid thereby obtained was 53 mg. corresponding to only 2% of the total product.

(20) A. A. Morton, F. D. Marsh, R. D. Coombs, A. L. Lyons, S. E. Penner, A. E. Ramsden, V. B. Baker, E. L. Little, Jr., and R. L. Letsinger, *J. Am. Chem. Soc.*, **72**, 3785 (1950).

Phenylpotassium from amyl chloride and benzene. In a typical preparation potassium (39 g., 1 mole) was added to 400 ml. of heptane and 150 ml. of benzene, both liquids having been dried over sodium hydride. The temperature was raised to 95° and the mixture stirred at 5000 r.p.m. in the high speed stirring apparatus commonly used in preparations of organoalkali metal reagents in this laboratory. The mixture was cooled to −10°. Amyl chloride (61 ml., 0.5 mole) was added dropwise to the potassium sand during 1 hr. The infrared absorption at 1205 cm.$^{-1}$ was strong. The carbonated product was solely benzoic acid (m.p. 121–122°) and the yield was 34 g., or 55% based upon the amyl chloride.

Phenylpotassium from anisole. Potassium sand (19.5 g., 0.5 atom) was prepared in 500 ml. of heptane at 95° in the high speed stirring apparatus. The addition of 0.5 ml. of anisole at this time often facilitated dispersion of the metal and gave a finer sand. The mixture was allowed to cool to room temperature. Anisole (27 g. or 0.25 mole) was added dropwise over a period of 1 hr. while the mixture was stirred at 5000 r.p.m. The temperature was maintained at 25–30°. The infrared absorption from a sample of this preparation showed strong absorption at 1210 cm.$^{-1}$ typical for the phenyl ion. Carbonation by forcing the light colored suspension onto solid carbon dioxide yielded benzoic acid (m.p. 122–123°) in a yield of 60%.

Phenylpotassium and cumene. To 100-ml. suspension of phenylpotassium prepared from amyl chloride, benzene, and potassium was added 150 ml. (1 mole) of cumene which previously had been dried over sodium hydride. During five days at room temperature the infrared absorption at 1210 cm.$^{-1}$ gradually disappeared while strong absorption developed at 1165 cm.$^{-1}$ The yield of crude acid was 6.7 g. (75%). The crystals from hot water melted at 77–78°, close to that recorded[21] (80–81°) for phenylisobutyric acid and identical with a sample from a previous preparation[10] in this laboratory.

A preparation of phenylpotassium made from potassium metal and anisole showed a similar change in infrared absorption when cumene was added.

The crude carbonated product from this metalation was oxidized by permanganate according to the method of Bryce-Smith.[5] The yield of 0.55 g. (m.p. 77–78°) from 0.65 g. of crude acid corresponded to 85% phenylisobutyric acid according to the procedure prescribed.[6]

Acknowledgments. The authors are indebted to Marianne Taylor for infrared analyses and to James Howard for assistance in many of the preparations.

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(21) K. Ziegler and H. Thielmann, *Ber.*, **56**, 1740 (1923).

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

An Addition-Metalation Reaction of Benzene with Phenylpotassium[1]

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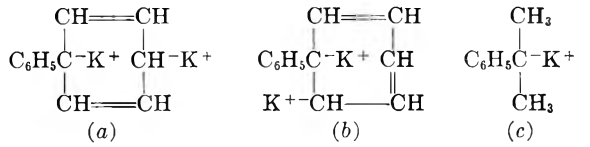
Phenylpotassium, but not phenylsodium, appears to add to benzene. The addition was accompanied by metalation so that the final product was dihydrobiphenyldipotassium. The product was similar to that which was obtained by the addition of potassium to biphenyl under the same experimental conditions. A continuation of the addition-metalation process, accompanied probably by elimination of potassium hydride, produced a cross-linked insoluble infusible polymer. In the light of the present work it is reasonable to assume that Abeljanz in 1872 had obtained phenylpotassium as an intermediate in the reaction of potassium with benzene.

For many years alkali metal amides[2] and organoalkali metal compounds[3] have been known to add to pyridine but not to benzene. This paper reports that phenylpotassium probably adds to benzene. Metalation follows immediately to give dihydrobiphenyldipotassium. Equation 1 shows

$$C_6H_5K + C_6H_6 \longrightarrow C_6H_6{-}C_6H_6{-}K \xrightarrow{C_6H_5K} C_6H_5{-}C_6H_5K_2 \quad (1)$$

these steps. The final organodipotassium product absorbed strongly at 1165 cm.$^{-1}$, which is characteristic for the benzyl type ion[4] and is identical with that shown by phenylisopropylpotassium.[4] Therefore one anion center must be at the alpha carbon as shown in (*a*) or (*b*) just as it is in phenylisopropylpotassium shown in (*c*). The second anion center is possibly at the para position as in (*a*)



(*a*) (*b*) (*c*)

rather than at the ortho position as in (*b*) because attachment of two potassium ions to distant carbon atoms seems more favored than to adjacent carbons. Other evidence to be described later supports that opinion. There may be also a general delocalization of electrons over both rings as in $[C_6H_5C_6H_5]^{--}K_2^+$ with which this paper is not concerned.

The reaction is probably a true addition of phenylpotassium to benzene rather than a union of two phenylpotassium compounds as in Equation 2

$$2C_6H_5K \longrightarrow C_6H_5{-}C_6H_5K_2 \quad (2)$$

because benzene was necessary. In petroleum which was freed from benzene, the infrared absorption at 1205 cm.$^{-1}$, characteristic for the phenyl ion,[4] changed very little during a month of aging. In the presence of benzene, however, absorption at that wave length disappeared during weeks at room temperature or hours at 70° while absorption appeared and increased at 1165 cm.$^{-1}$ characteristic for the anion center at the alpha carbon atom.

The biphenyl-type character of the product was demonstrated by pyrolysis under vacuum at 150° whereby biphenyl was recovered in about 30% yield. The same treatment applied to the starting material, phenylpotassium, yielded benzene as the volatile product. Furthermore potassium metal reacted with biphenyl in heptane under the conditions employed in the reaction of phenylpotassium with benzene. The infrared absorption of this addition product was essentially identical with that of the addition-metalation product from phenylpotassium and benzene, notably at 1165 cm.$^{-1}$ Also it yielded biphenyl when pyrolyzed at 150° under reduced pressure.

For a while the presence of a little biphenyl in the non-acid portion from the product of the addition-metalation reaction of phenylpotassium with benzene and the knowledge that potassium metal could add to biphenyl under those same conditions suggested that the course of the addition-metalation reaction might, instead, have been through decomposition of phenylpotassium to biphenyl and potassium followed by recombination, as in Equation 3. The need for benzene in the process and the

$$2C_6H_5K \longrightarrow \left[\begin{array}{l} \rightarrow 2C_6H_5\cdot \longrightarrow C_6H_5C_6H_5 \\ \rightarrow 2K \end{array}\right] \rightarrow C_6H_5{-}C_6H_5K_2 \quad (3)$$

failure to get biphenyl from the pyrolysis of phenylpotassium made this possibility seem less reasonable than the process according to Equation 1.

Identification of the product by carbonation was only partially satisfactory because separation of a pure diacid and determination of the structure were not easy. The comparatively high melting dihydrobiphenyldicarboxylic acid had the same neutralization equivalent as benzoic acid but the molecular weight of the dimethyl ester was a little over twice that of methyl benzoate. The diacid was somewhat sensitive to air oxidation as might have been expected. Previously some difficulty with a

(1) This work was performed as part of a research project sponsored by the National Science Foundation.

(2) A. E. Chichibabin and O. A. Zeide, *J. Russ. Phys. Chem. Soc.*, **46**, 1216 (1914).

(3) K. Zeigler and H. Zeiser, *Ann.*, **485**, 174 (1921).

(4) A. A. Morton and E. J. Lanpher, *J. Org. Chem.*, **23**, 1636 (1958).

structure of this type had been experienced by Schlenk and Bergmann[5] and by Hückel and Bretschneider[6] who worked with the material obtained by hydrolysis of the addition product of alkali metal with biphenyl. Three facts about the diacid, however, accord with the view that the second anion center in the addition-metalation product is para to the first as represented in (*a*); first because vacuum distillation of the diacid over copper yielded a small amount of crystalline *p*-phenylbenzoic acid, second because an attempt to prepare a crystalline anhydride (such as an ortho dicarboxylic acid should yield) by heating in acetic anhydride and distilling yielded only a thick polymer-like mass and third because the ultraviolet absorption of the dicarboxylic acid showed no double bond conjugated with another double bond or with a carboxyl group.

Phenylpotassium, but not phenylsodium, reacted with benzene. The difference between the two salts is not surprising. Already the potassium ion has shown a preference for a lateral position. For instance potassium metal and sodium oxide metalated alkylaryl hydrocarbons at the alpha carbon atom,[7] potassium hydroxide metalated fluorene[8] in spite of the greater acidity of water over fluorene, amylpotassium metalated cumene predominantly in the lateral position[4] whereas amylsodium attacked the nucleus, and phenylpotassium surprisingly metalated cumene at the alpha carbon in disregard of the accepted difference in acidity between the hydrogen atoms of the side chain and the nucleus. Therefore the addition-metalation process (Equation 1) would have been favored by a change of a potassium ion from the nucleus in phenylpotassium to the alpha carbon as in structure (a) or to the distant para carbon atom which is connected to the alpha position through a pair of vinyl groups.

Presumably the process of addition-metalation should continue until high molecular weight products are obtained. For instance the initial product (*a*) from Equation 1 would lose potassium hydride (Equation 4) to give biphenylpotassium. This

$$C_6H_5C_6H_5K_2 \longrightarrow KH + C_6H_5C_6H_5K \qquad (4)$$

compound, however, has a potassium ion attached to the nucleus just as does phenylpotassium. Therefore it should add to another aromatic ring. A continuation of this unusual addition type of polymerization should lead to high molecular weight products. Something of this type seemed to occur because the residue after pyrolysis at 150° under vacuum was an infusible insoluble cross-linked mass. The infrared absorption showed the presence of some aromatic rings. In other words the residue was not a burnt carbonaceous mass but seemed to be the result of a mixture of orderly processes which increased the molecular size.

This work throws considerable light on an early claim by Abeljanz[9](1872,1876) that he had prepared phenylpotassium. He had observed that Berthelot[10] had been able to prepare naphthalenedipotassium, $C_{10}H_8K_2$, by fusing potassium metal with naphthalene, and he sought to carry out a similar reaction with benzene. In a closed tube, reaction set in at 150–190° but the mixture was kept for 7 hr. at 230–250°. Decomposition of the bluish black apparently crystalline mixture with ethyl bromide or water yielded biphenyl and *p*-terphenyl. He attributed these products to phenylpotassium and phenylene dipotassium. thirty-six years later (1913) Schlenk and Meyer[11] maintained that Abeljanz had only coated metal with carbon. They advocated striking the reference from the literature. The current results suggest that both laboratories had made phenylpotassium, but as an intermediate rather than an end product. If potassium metal added to benzene as per Equation 5 the

$$2K + C_6H_6 \longrightarrow KC_6H_6K \longrightarrow KH + C_6H_5K \qquad (5)$$

dihydrophenyldipotassium product should be unstable at that temperature and lose potassium hydride to form phenylpotassium. From that point the steps would be as described in this paper. Diphenyl, *p*-terphenyl, and "carbon" should be formed. Both laboratories had obtained all of the products[12] which the present work, carried out at lower temperatures, would suggest.

Mention should be made also of the preparation of phenylpotassium by shaking potassium-sodium alloy and diphenyl ether in benzene as carried out by Müller and Benge.[13] Equation 6 shows that the

$$2K + C_6H_5OC_6H_5 \longrightarrow C_6H_5K + KOC_6H_5 \qquad (6)$$

process is essentially the same as the preparation from anisole in this laboratory[4] and might, indeed, be preferable because of the formation of potassium phenoxide instead of methoxide. Müller and Benge, however, happened to carry out the reaction in benzene which should react with phenylpotassium. Hence they found only a 33% yield of benzoic acid after carbonation whereas their analysis of phenol showed 95% cleavage. Much of the phenylpotassium must have reacted with benzene during the ten days shaking of the mixture, and the separation of some high melting (185–200°)

(5) W. Schlenk and E. Bergmann, *Ann.*, **463**, 90 (1928).
(6) W. Hückel and H. Bretschneider, *Ann.*, **540**, 157 (1930).
(7) C. E. Claff, Jr., and A. A. Morton, *J. Org. Chem.*, **20**, 981 (1955).
(8) A. A. Morton, C. E. Claff, Jr., and H. P. Kagan, *J. Am. Chem. Soc.*, **76**, 4556 (1954).
(9) H. Abeljanz, *Ber.*, **5**, 1027 (1872); **9**, 10 (1876).
(10) M. Berthelot, *Ann.*, **143**, 97 (1867).
(11) W. Schlenk and H. Meyer, *Ber.*, **46**, 4060 (1913).
(12) H. Podall and W. E. Foster, *J. Org. Chem.*, **23**, 401 (1958), noted the formation of some biphenyl during the alkylation of benzene over potassium graphite at 200°. It might have formed from a reaction of potassium with benzene as observed by Abeljanz and by Schlenk and Mayer.
(13) E. Müller and Benge, *Ber.*, **69**, 2171 (1936).

acid supports that idea. Lüttringhaus and Schubert[14] used a similar preparation of phenylpotassium *in situ* for their study of the metalation of diphenyl ether. In that case, however, the metal ion moved promptly from phenyl to diphenyl ether.

The reactions of phenylpotassium with a few other compounds were tested. The reagent metalated anisole in the ortho position and carbonation produced *o*-anisic acid. When this *o*-potassionisole was heated to 70°, cleavage to potassium phenoxide took place just as had occurred with the corresponding sodium reagent.[15] The large amount of tar formed simultaneously suggested that this arylpotassium compound, *o*-$KC_6H_4OCH_3$, may have undergone some addition with itself similar to Equation 2 or otherwise reacted to yield high molecular weight material. Addition of phenylpotassium to butadiene gave a polymer with a ratio of *trans*-1,4- to 1,2-structure equal to 0.71. The same product was obtained regardless of whether the phenylpotassium was in the presence of potassium chloride or methoxide, that is, whether the reagent had been prepared from amyl chloride and benzene or from anisole.[4] Also the addition-metalation product from phenylpotassium and benzene produced the same ratio of 1,4- and 1,2-structures in polybutadiene. This ratio is higher than the value (0.35) found in this laboratory for polymerization by the usual type of sodium reagent but is much lower than found for polybutadiene made with the Alfin reagent.[16] No addition took place with *t*-butylbenzene; the infrared absorption remained strong at 1210 cm.$^{-1}$ while standing a week. The metalation of cumene by phenylpotassium has been reported in a separate paper.[4]

EXPERIMENTS

Infrared absorption by the potassium compounds. The method of measurement of the infrared absorption of the organoalkali reagents and the value of these measurements have been described in another paper.[4]

Preparation of phenylpotassium. The method of preparing this reagent from amyl chloride, benzene, and potassium was described in the previous paper.[4] Benzoic acid was obtained by carbonation as described previously. A suspension of the potassium reagent was centrifuged and the solvent was replaced by dry heptane. This operation was repeated twice. Thereafter the absorption at 1205 cm.$^{-1}$ remained approximately the same for a month (the duration of the test). The benzene-heptane solvent was similarly replaced by *t*-butylbenzene which had been dried over sodium hydride. The absorption at 1205 cm.$^{-1}$ showed no change during a week. Under similar conditions, but in benzene, a noticeable change in intensity of that band took place and a new band began to appear at 1165 cm.$^{-1}$

Reaction of phenylpotassium with benzene. Examination of a preparation of phenylpotassium which happened to have stood for six months at room temperature showed that absorption at 1205 cm.$^{-1}$ had disappeared and a new band at 1165 cm.$^{-1}$ had appeared. Accordingly a portion of the preparation was carbonated by addition to solid carbon dioxide. The carboxylic acid melted at 270–280° but had a neutralization equivalent of 127, similar to benzoic acid. The crude mixture was digested several times in hot water but did not dissolve easily as would benzoic acid. The dissolved and undissolved portions showed atom ratios of carbon to hydrogen equal to 1.09 and 1.12, respectively. The calculated value for either benzoic acid or 1,4-dihydrobiphenyldicarboxylic acid is 1.17. Distillation of the undissolved portion in a 20 × 2 cm. short-path still gave a yellow appearing product on the finger tip condenser and a white powdery material on the wall. The melting point, percentage oxygen (by difference) and the atom ratio of carbon to hydrogen were 270–280°, 24.7, and 1.12 for the former and >325°, 25.1 and 1.07 for the latter. The percentage oxygen in benzoic acid is 26.2. The slightly lower value for oxygen in these products can be attributed to a small loss of potassium hydride from the mixture of organopotassium compounds present from the reaction.

A portion of the undissolved acid was esterified by methanol and acid and the ether solution of the ester was separated from traces of acid by extraction with sodium carbonate solution. The residue left by evaporation of the ether had a molecular weight of 301 in camphor. [$C_{12}H_{10}$-$(CO_2CH_3)_2$ requires 272.] Also the ester distilled at 150°/1 mm. Both facts agree with the view that the product was largely the mono adduct from phenylpotassium and benzene followed by metalation as per Equation 1.

Distillation of 1 g. of the dissolved acid with 5 g. of copper powder at 150°/1 mm. gave a white crystalline material which melted at 220–225° after being recrystallized from heptane. The acid chloride melted at 112–114° and the amide melted at 226–228°. The corresponding values recorded[17] for *p*-phenylbenzoic acid and its chloride are 228° and 114–115°. The infrared absorption of the acid was identical with that from a previous preparation in this laboratory.

From another preparation which had been made by stirring phenylpotassium with benzene at 70° for 12 hr., the yellow-white mixture of carboxylic acids was steam distilled in order to remove benzoic acid (4.3 g.) which was present because of some phenylpotassium which had not yet reacted with benzene. The residue of high molecular weight acid became yellow-brown because of aerial oxidation. This sensitivity to air generally hampered efforts to get pure compounds from the mixture.

Repeated crystallization from ethanol-water and from heptane eventually yielded minute crystals which melted with decomposition at 325° (another lot at 335–350°) and had a neutralization equivalent of 150. The analysis of carbon and hydrogen, however, corresponded to no simple product. Bromine yielded no simple product which showed a specific composition.

The mixture of carboxylic acids was heated in acetic anhydride for several hours but no crystalline product was obtained from the solution or from the mixture which was obtained therefrom by precipitation with a hydrocarbon. An attempt to sublime an anhydride from this product at 150°/1 mm. in a short path still yielded no crystalline material.

The ultraviolet absorption in ethanol showed that the diacid had a maximum absorption at 368 mμ and a molar extinction coefficient of 670. No conjugated system seemed to be present.

The non-acid portion from one of the preparations was

(14) A. Lüttringhaus and K. Schubert, *Naturwissenschaften*, 42, 17 (1955).

(15) A. A. Morton and A. E. Brachman, *J. Am. Chem. Soc.*, 76, 2973 (1954).

(16) A. A. Morton, I. Nelidow, and E. Schoenberg, Proc. 3rd Rubber Tech. Conf. (1954), 108; A. A. Morton, *Advances in Catalysis IX*, 743 (1957), Academic Press Inc., New York.

(17) I. Heilbrom, *Dict. of Organic Chemistry*, Oxford Univ. Press, New York, N. Y., 1950, Vol. II, p. 608.

distilled to remove the solvent. A small amount of biphenyl (0.1 g.) was recovered. It melted at 69–71° and showed no depression when mixed with an authentic sample.

Thermal decomposition of the potassium compounds. A suspension (50 ml.), containing 28.2 milliequiv. of phenylpotassium in heptane-benzene, was centrifuged and washed with pentane in order to remove all trace of benzene or biphenyl. Then the pentane was removed by vacuum distillation and the phenylpotassium was subjected to heat at 150°/1 mm. for 9 hr. The solid collected in the cold trap melted to a liquid with the odor of benzene. The yield was 1.06 g. (50%); n_D^{25} 1.4960. The residue from this decomposition was decomposed with methanol. The product was infusible and insoluble in common organic solvents. An analysis showed 87.03% carbon and 4.85% hydrogen with some ash. The atomic ratio of 1.5 carbon for each hydrogen atom suggests that a condensed aromatic system was present. The infrared absorption made on a sodium bromide pellet was pronounced at 1600 cm.$^{-1}$ and at 695 to 810 cm.$^{-1}$, characteristic for substituted benzene rings.

A similar decomposition was carried out on the reaction product of phenylpotassium with benzene. An aged suspension (50 ml.) containing 41.7 milliequiv. of phenylpotassium or its equivalent was centrifuged and washed with pentane. From this material 2 g. (30% yield) of a white powder was collected at 150°/1 mm. It was identified as biphenyl by its melting point (70°) and mixed melting point with an authentic sample. The residue was not soluble in benzene and common solvents and appeared similar to that obtained from phenylpotassium itself.

Potassium metal with biphenyl. Biphenyl (78 g., 0.5 mole) was stirred with 39 g. (1 atom) of potassium sand in 500 ml. of heptane at 70° for 6 hr. The infrared absorption bands of this suspension were identical with those from a fully aged preparation of phenylpotassium with benzene. After carbonation 61 g. (50%) of carboxylic acids was recovered which melted at 240–250°. The infrared absorption of these acids was the same as for the acids derived from the reaction of phenylpotassium with benzene. The melting point was lower than for some of the fractions obtained from the phenylpotassium-benzene preparation but that fact is understandable because of the numerous variations from isomers and secondary changes. Attempts to separate crystalline carboxylic acids from this material proved as difficult as with the material prepared from phenylpotassium-benzene.

Phenylsodium with benzene. A preparation of phenylsodium made from amyl chloride (61 ml., 0.5 mole) and sodium (23 g., 1 atom) in benzene which had stood for 24 months showed a strong absorption at 1205 cm.$^{-1}$ and only very weak absorption in the region of 1165 cm.$^{-1}$

Phenylpotassium and anisole. A suspension of 50 ml. (28 milliequiv.) of phenylpotassium (from amyl chloride, benzene, and potassium) in heptane was allowed to react with 27 g. (0.25 mole) of anisole at room temperature for one week. Carbonation and separation of the carboxylic acid gave 2.7 g. (60%) of a beautifully crystalline (from heptane) material which melted at 102–103°, did not depress the melting point of an authentic sample of *o*-anisic acid, and showed infrared absorption identical with that sample.

A sample of *o*-potassioanisole prepared as described above was heated at 75° for 20 hr. Carbonation yielded 26 g. of phenol which was identified by the melting point of the tribromo derivative (89–92°). The large residue of tarry product which accompanied the phenol suggested that this arylpotassium compound might have undergone some change comparable to that written for phenylpotassium in Equations 2 or 3.

Butadiene and potassium reagents. Phillips research grade of butadiene (30 ml.) was polymerized in 200 ml. of pentane by 10 ml. of (a) a suspension of phenylpotassium made from either amyl chloride, benzene, and potassium or from anisole and potassium or (b) a suspension of phenylpotassium in benzene which had aged and therefore had changed to the biphenyl type product. In each case polymerization was allowed to take place for 1 hr. Then the mixture was decomposed with methanol and the solvent and excess butadiene removed by evaporation at reduced pressure. The infrared absorptions in carbon disulfide solution showed ratios of trans 1,4- to 1,2-structures (absorption at 10.34 and 10.98 microns, respectively) of 0.71.

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A Study of the Preparation of Ketones from Mixed Aldoketene Dimers

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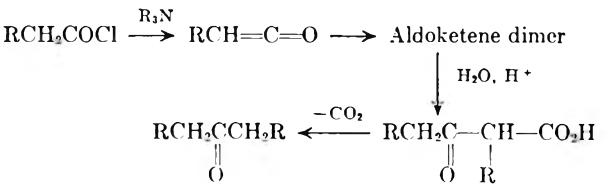
Several pairs of acid chlorides have been dehydrohalogenated by means of triethylamine, under differing conditions, to mixtures of ketene dimers. The latter have been hydrolyzed in poor yields to mixtures of symmetrical and unsymmetrical ketones. In addition, considerable amounts of acids have been obtained in most cases, which suggests that variations exist in the rates of formation and dimerization of the aldoketenes.

Sauer[2] has shown that the procedure which involves the dehydrochlorination of acid chlorides by tertiary amines to ketene dimers, followed by hydrolysis of the latter, affords symmetrical ketones in high yields. The dehydrohalogenation of a mixture of two acid chlorides would be expected to



lead to four ketene dimers. Sauer[2] has demonstrated in the case of acetyl and lauroyl chlorides the formation of the two simple dimers, and one of the

(1) Abstracted in part from the Ph. D. thesis of H. M. Molotsky, 1953.

(2) J. C. Sauer, *J. Am. Chem. Soc.*, 69, 2444 (1947).

mixed dimers, by reaction with aniline to give the corresponding acetoacetanilides. He obtained similar results with a mixture of propionyl and caproyl chlorides.

Roberts and co-workers[3] have studied the mixed aldoketene dimer of methyl and hexylketenes by the isotopic tracer technique, and have shown that it does not possess a 1,3-cyclobutanedione structure. They suggested that aldoketene dimers are best formulated probably as vinylaceto-β-lactone or β-crotonolactone derivatives.

In spite of the fact that the hydrolysis of a mixture of ketene dimers from two acid chlorides obviously will produce several ketones, it was thought that, by the proper choice conditions, one might be able to exploit the method to obtain unsymmetrical ketones in satisfactory yields. The present report describes an investigation in which several pairs of acid chlorides were dehydrochlorinated under varying conditions to mixtures of aldoketene dimers. The latter were subjected to acid hydrolysis to give mixtures of symmetrical and unsymmetrical ketones, as well as considerable amounts of other materials.

A number of preliminary experiments was carried out with acetyl chloride as the invariant reactant. The dehydrohalogenations were effected by means of triethylamine in ether solution in the usual manner.[2] After removing the triethylamine hydrochloride by filtration, the ethereal solutions were heated to reflux with dilute sulfuric acid for several hours. Although the methods employed were relatively crude, the unsymmetrical ketones were isolated in yields of 8–26% as shown in Table I. In addition to the ketonic products, dehydroacetic acid was obtained in fairly respectable yields, as well as the fatty acids corresponding to the alkyl acid chlorides employed.

TABLE I

PRELIMINARY DEHYDROHALOGENATION REACTIONS OF MIXTURES OF ACETYL AND OTHER ACID CHLORIDES

Acid Chloride	Symmetrical Ketone	% Yield[a]	Unsymmetrical Ketone	% Yield
n-Butyryl	4-Heptanone	18	2-Pentanone	13
Isovaleryl	2,6-Dimethyl-4-heptanone	12	4-Methyl-2-pentanone	8
Caprylyl			2-Nonanone	16
Undecylenyl			11-Dodecene-2-one	8
Capryl	10-Nonadecanone	13	2-Hendecanone	26

[a] Yields based upon longer chain acid chloride.

These results suggested that a more detailed investigation of the conditions for the dehydrohalogenation reaction of a mixture of two acid chlorides might lead to improved yields of the desired unsymmetrical ketones. The combination of acetyl and capryl chlorides was chosen for study, and this system was caused to react under the different experimental conditions summarized in Table II.

TABLE II

HYDROLYSIS PRODUCTS OF MIXED KETENE DIMERS FROM ACETYL AND CAPRYL CHLORIDES

Conditions	Ketones, % Yield[a]		Acidic Products, % Yield	
	2-Hendecanone	10-Nonadecanone	Capric acid	Dehydroacetic Acid
Standard procedure[b]	33	18	16	9
Ratio of acid chlorides[c] 1.4:1	13	9	17	
Ratio of acid chlorides 3:1	15	12	18	
Ratio of acid chlorides 9:1	28	17	25	17
Amine added to mixture of acid chlorides	17	18	17	
Temp. −60° for 11 hr.; 5° for 6 hr.; 25° for 24 hr.	19	20	19	15
Capryl chloride added to amine, then acetyl chloride introduced within 1 hr.	13	37	30	11
Ether replaced by toluene for solvent	18	38	29	28
Petroleum ether (b.p. 86–100°) used as solvent	10	15	19	
Carbon tetrachloride used as solvent	26	22	51	2
Acetone used as solvent	16	16	37	6
Modified standard procedure	19	12		

[a] Yields of ketones based upon longer chain acid chloride with corrections made for materials converted to corresponding acids. [b] Described in Experimental part and used in all runs with changes indicated. [c] Ratio of shorter to longer chain acid chloride.

The same basic method was followed in each of these experiments, with the exceptions indicated. The standard procedure consisted of adding an ether solution of the mixture of acid chlorides slowly to an ether solution of triethylamine which was cooled to −10 to −15°. The reaction mixture was stirred at this temperature for 9 hours, and for an additional 12 hours at room temperature. It was stirred then with 3% sulfuric acid solution to remove the triethylamine hydrochloride. The ether solution of reaction products was concentrated, and the residue was hydrolyzed with 4% sulfuric acid at 60–65° for 5 hours. The organic layer was washed with 15% sodium bicarbonate solution, dried, and fractionated. The aqueous layer was neutralized with sodium bicarbonate, extracted with ether, reacidified and again extracted with ether. Dehydroacetic acid was obtained upon concentrating the latter solution.

(3) J. D. Roberts, Rose Armstrong, R. F. Trimble, Jr., and Marion Burg, *J. Am. Chem. Soc.*, **71**, 843 (1949).

In the first four experiments listed in Table II, the ratio of acetyl chloride to capryl chloride was varied from 1.4:1 to 9:1. The results indicated that the ratio of 6:1 was the most desirable of those tried. Accordingly, this proportion was held constant during the remainder of the experiments.

The next run was designed to test the possible effects of adding the triethylamine to an ether solution of the acid chlorides. In agreement with Sauer,[2] no noticeable differences in amounts of products were observed. This may be accounted for on the basis that the tertiary amine-acid chloride complexes undergo a relatively slow rate of decomposition.

The latter factor probably was responsible also for the results obtained in the attempt to carry out the dehydrohalogenation of the mixture of acid chlorides at temperatures of 60–70° below those normally employed. It appeared that the dehydrohalogenation reaction did not occur to any appreciable extent until the reaction mixture was allowed to warm to approximately 0°.

It was thought that a variation in time of addition of the acid chlorides might have an influence on the formation of the ketene dimers. Accordingly, capryl chloride was added to an ether solution of triethylamine, and one hour was allowed to elapse before the acetyl chloride was introduced. The data from this experiment suggest that the formation of the mixed ketene dimers might have been suppressed to some extent, due perhaps to the formation of a certain amount of octylketene dimer before any ketene was present in the reaction system. It is conceivable also that the octylketene was formed fairly rapidly, but that ketene undergoes self-condensation at a rate faster than that at which it reacts with substituted ketenes.

Rice and Greenberg[4] have shown that, in general, the rate of dimerization of ketene at 0° is slower in solvents of low dielectric constant. Also, Hueter[5] has claimed that decylketene and tetradecylketene are formed from the acid chlorides of lauric and palmitic acids respectively, when they are dehydrohalogenated in carbon disulfide and benzene. Accordingly, four experiments were carried out in which the solvents were changed in the hope that it would be possible to influence favorably the rate of condensation of ketene with octylketene.

The solvents chosen for study were toluene, petroleum ether (b. p. 86–100°), carbon tetrachloride, and acetone. As shown in Table II, the yields of ketonic compounds were greatest, although perhaps not significantly so, in the case of toluene, while little or no improvements were realized with the other solvents. The results with petroleum ether were inconclusive since the overall yield of products isolated was low due to the formation of a large quantity of polymeric material.

After all but the last two experiments had been completed, it was found that the sodium bicarbonate wash had not removed all of the capric acid from the neutral fractions. This discrepancy was rectified by determining the amount of capric acid in each sample of ketone by titration with standard alkali. The neutral fractions then were washed with 15% sodium hydroxide and redistilled. In all further experiments, the mixtures from the hydrolysis reaction were extracted with sodium bicarbonate and sodium hydroxide solutions. As indicated in Table II, this is referred to as a modified standard procedure.

The dehydrohalogenations which were carried out in toluene, carbon tetrachloride, and acetone differed noticeably from the others in the larger amounts of acidic materials which were obtained. Since triethylamine hydrochloride was isolated almost quantitatively from a number of the reaction mixtures, it is conceivable that the capric acid which was recovered arose from the hydrolysis of octylketene. If this is true, then it appears that the rate of dimerization of aldoketenes is related to the nature of the solvent in which they are prepared.

Further studies were conducted then on the dehydrochlorination of the mixtures of acid chlorides shown in Table III. The following conditions were common to all of the reaction systems: ether was employed as the solvent, the ratio of the smaller to the larger acid chloride was 6:1, the ether solutions of the acid chlorides were added to an ether solution of triethylamine and the reaction mixtures were hydrolyzed by means of a 5% sulfuric acid solution at 50–65°.

TABLE III

HYDROLYSIS PRODUCTS OF MIXTURES OF KETENE DIMERS

Acid Chlorides[a]	Ketones	% Yield[b]	Acidic Products	% Yield
Acetyl and caproyl	2-Heptanone	14	Caproic acid	23
	6-Hendecanone	23	Dehydroacetic acid	10
Acetyl and stearyl	2-Nonadecanone	14	Stearic acid	23
	18-Pentatriacontanone		Dehydroacetic acid	10
Propionyl and caproyl	3-Octanone	13	Caproic acid	32
	6-Hendecanone	26	Propionic acid	8
Propionyl and capryl	3-Dodecanone	17	Capric acid	20
	10-Nonadecanone	24	Propionic acid	12

[a] Modified standard procedure used in all experiments. [b] Yields of ketones based upon the longer chain acid chloride, with correction made for materials, converted to corresponding acids.

The results of these experiments were fairly uniform in regard to the yields of products obtained. The percentages of recovered fatty acids

(4) F. O. Rice and J. Greenberg, *J. Am. Chem. Soc.*, **56**, 2132 (1934).

(5) R. Hueter, U. S. Patent **2,383,863** (1945); *Chem. Abstr.*, **40**, 351 (1946).

or related materials were almost as great as those of the carbonyl components. In all cases, residues were encountered which, on a weight basis, were equal to or greater than the ketonic fractions.

The data obtained from the present investigation indicate that the reaction sequence which involves the dehydrochlorination of mixtures of two acid chlorides, followed by hydrolysis of the resulting mixture of aldoketene dimers, offers little or no value as a synthetic procedure for obtaining unsymmetrical ketones. The reaction mixtures appear to be quite complex, and on the basis of the products isolated it seems that not only are the aldoketenes formed at varying rates, but that they also undergo dimerization at differing rates. The proportions of the symmetrical to unsymmetrical ketones which were obtained indicate that the formation of the mixed aldoketene dimers was not influenced greatly by the use of a considerable excess of one of the acid chlorides, or by varying a number of other factors.

The relatively large amounts of fatty acids found in most of the reaction products apparently arose from the hydrolysis of simple aldoketenes and not from unreacted acid chlorides. This result appeared to be most pronounced when carbon tetrachloride was used as a solvent. If the latter observations are correct, they indicate that the dimerization of aldoketenes is dependent to a considerable extent upon structure and reaction medium.

The results of this qualitative investigation suggest further that an extensive study of the rates of formation and dimerization of aldoketenes would be required before effective control might be exerted over the products which result from the dehydrohalogenation of a mixture of two acid chlorides.

EXPERIMENTAL

Materials. Acetyl, propionyl, *n*-butyryl, and isovaleryl chlorides were purchased from commercial sources. The other acyl chlorides were prepared from the corresponding acids and thionyl chloride. The triethylamine was purified by drying over potassium hydroxide pellets for 48 hr., refluxing with sodium until a fresh portion retained its luster, and then distilling into a receiver which contained sodium.

General aspects of the dehydrohalogenation procedures. The preliminary studies were carried out in most cases on a 1–3 mole scale. The majority of the dehydrohalogenation reactions described in Tables II and III were run on about 3.5 moles of acid chlorides. The ratio of solvent to reactants, which was not considered to be critical, was in the range of 350–400 ml. per mole of triethylamine. In all reactions, the latter was used in an excess of about 6–10%. All of the products of the reactions listed in the tables are known compounds. They were identified by comparison of their physical properties and derivatives, in many cases, with those reported in the literature.

The following procedure is representative, except for the scale of operation, of the last three experiments in Table II and all in Table III. It differs from the procedure employed for the first nine dehydrohalogenations described in Table II only in that the final hydrolysis products were washed with 15% sodium hydroxide solution as well as with 10% sodium bicarbonate solution.

Dehydrochlorination of a mixture of acetyl and caproyl chlorides and hydrolysis of the reaction product. A solution of 759 g. (7.5 moles) of triethylamine in 1000 ml. of anhydrous ether was cooled to −10° to −5° while a solution of 475 g. (6 moles) of acetyl chloride and 134 g. (1 mole) of caproyl chloride in 500 ml. of dry ether was added slowly with stirring over a period of 4 hr. The reaction mixture was allowed to remain in the ice bath for 10 hr., and then at room temperature for 24 hr. A sample of the reaction mixture gave a negative test for acid chlorides. The reaction mixture was extracted with 2000 ml. of 5% sulfuric acid solution to remove the amine salt. In some cases the latter was separated by filtration and the yields of dry triethylamine hydrochloride were approximately quantitative. The wet ether layer was separated and added to 500 ml. of 5% sulfuric acid. The ether was removed by distillation and the residue was heated at 50–65° with stirring for 4 hr. The oily layer was separated and washed with 10% sodium bicarbonate solution. The aqueous fraction was neutralized with a saturated sodium bicarbonate solution and extracted with ether. The oily fraction was mixed with the ether layer and the combined solution was extracted with a 15% sodium hydroxide solution, washed with water, and dried over anhydrous magnesium sulfate. The ether was removed in a steam bath and the residue was distilled under reduced pressure.

Two main fractions were obtained and identified as 2-heptanone and 6-hendecanone. The former, 12.5 g., boiled at 148–151°, n_D^{20} 1.4098, lit.,[6] b.p. 151°, n_D^{15} 1.41086. A semicarbazone was prepared; m.p., 122–123°; lit.,[7] m.p. 123°. The 6-hendecanone, 15.1 g., boiled at 88–90°/5 mm., n_D^{20} 1.4291; lit.,[8] b.p. 228°, n_D^{20} 1.42875.

The sodium bicarbonate soluble fraction was acidified to Congo Red with 15% hydrochloric acid solution and extracted with ether. The latter was removed by distillation and from the residue there was obtained 25.5 g. of dehydroacetic acid; m.p. 110–111°.

The sodium hydroxide soluble fraction was acidified to Congo Red with 15% hydrochloric acid solution and extracted with ether. From this solution there was obtained 25.5 g. of caproic acid; b.p., 107–110°/20 mm., n_D^{20} 1.4169, neut. equiv. 116; lit.,[9] b.p. 111.8°/20 mm., n_D^{20} 1.4163, neut. equiv. 116.

COLUMBIA, MO.

(6) P. Ceuterick, *Bull. soc. chim. Belg.*, **45**, 545 (1936).
(7) M. L. Sherrill, *J. Am. Chem. Soc.*, **52**, 1982 (1930).
(8) I. Simon, *Bull. soc. chim. Belg.*, **38**, 57 (1929).
(9) M. Hommelen, *Bull. soc. chim. Belg.*, **42**, 243 (1933).

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

The Dimer of 1,3-Diphenyl-1,3-butadiene[1,2]

WERNER HERZ AND EDWIN LEWIS

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A dimer of 1,3-diphenyl-1,3-butadiene has been isolated from the dehydration of 1,3-diphenyl-2-buten-1-ol and 1,3-diphenyl-1-buten-3-ol 1,3-Diphenyl-1,3-butadiene has been isolated as its maleic anhydride adduct. The structure of the dimer has been shown to be 1,3,4-triphenyl-4-styrylcyclohexene by oxidation and dehydrogenation. A styryl group migration in the tetrachloro-*o*-benzoquinone dehydrogenation of the dimer has been demonstrated.

In the course of another investigation it was found that both 1,3-diphenyl-2-buten-1-ol and 1,3-diphenyl-1-buten-3-ol on dehydration under a variety of conditions gave a hydrocarbon, m.p. 136–137°. From a study of its properties it was obvious that this compound was not 1,3-diphenyl-1,3-butadiene,[3] although it analyzed correctly for $C_{16}H_{14}$. A molecular weight determination indicated that this compound was a dimer of 1,3-diphenyl-1,3-butadiene, but it was apparently not identical with a dimer which Whitby and Gallay[4] reported as being formed by the reaction of benzalacetophenone with methylmagnesium iodide. These authors reported isolation of a dimer of 1,3-dimer of 1,3-diphenyl-1,3-butadiene, m.p. 167°, in 70% yield.

Repetition of Whitby and Gallay's procedure gave as the major product an oil which, in accord with the results of Kharasch and Sayles,[5] consisted mainly of 1,3-diphenyl-1-butanone. Crystalline products obtained in smaller yields were either 1,3,5-triphenyl-4-benzoyl-1,3-hexadiene, m.p. 175.5°, or the 1,3-diphenyl-1,3-butadiene dimer, m.p. 136–137°, and a compound of the formula $C_{31}H_{28}O_2$, 161.5–163°. This last substance is probably 1,3-dibenzoyl-2,4-diphenylpentane on the basis of its spectrum, elemental analysis, and stability toward acids and oxidizing agents. Such a compound could have been formed by a Michael condensation between benzalacetophenone and 1,3-diphenyl-1-butanone. It is to be noted that Kharasch and Sayles[5] report that the product composition of the reaction between benzalacetophenone and the methyl Grignard reagent is sensitive to the concentration of reagent and particularly to the presence of radical sources.

Addition of maleic anhydride to the gummy residues produced 5–10% yields of 3,5-diphenyl-1,2,3,6-tetrahydrophthalic anhydride, m.p. 158–159°, a Diels-Alder adduct of 1,3-diphenyl-1,3-butadiene. This adduct is reported by Cope, Wick, and Fawcett[6] to melt at 142–149°. These authors ascribed the melting point range to the presence of a mixture of stereoisomers. That ours was indeed the same adduct was shown by dehydrogenation to the 3,5-diphenylphthalic acid reported by Cope, Wick, and Fawcett. Decarboxylation of this acid produced *meta*-terphenyl.

The maleic anhydride adduct could be obtained in comparable yields from either 1,3-diphenyl-2-buten-1-ol or 1,3-diphenyl-1-buten-3-ol. This product was formed both with and without a solvent, and by addition of the maleic anhydride both before and after dehydration of the two alcohols.

Dehydration of the two diphenylbutenols in the absence of maleic anhydride gave products of varying homogeneity. A typical dimeric product (usually formed in about 80% yield) melted at 123–140°. The dimer which melted at 136–137° was the principal constituent and was the only one which could be isolated in pure form. The remainder was probably isomeric material. The infrared spectra of various fractions were very similar except for variations in the 900 cm.$^{-1}$ and 970 cm.$^{-1}$ regions. Dehydration of either alcohol with iodine produced mainly a compound which melted at 146–147°. This product analyzed correctly for $C_{32}H_{28}$, but differed from the lower melting dimer in the absence of a *trans*-ethylenic band at 970 cm.$^{-1}$ in its infrared spectrum. The higher melting dimer was not further investigated.

The dimer, m.p. 136–137°, showed two hindered non-conjugated double bonds on the basis of microhydrogenation, its ultraviolet spectrum, and various qualitative olefin tests. The ultraviolet spectrum in 95% ethanol showed absorption maxima at 253 mμ (log ε 4.56) and 294 mμ (log ε 3.19) with a minimum at 228 mμ (log ε 4.12), indicative of a slightly modified styrene chromophore. The molec-

(1) Abstracted from the thesis of Edwin Lewis, submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June 1958.

(2) While this manuscript was in preparation, the isolation and characterization of this dimer was reported by M. H. Goodrow and T. L. Jacobs at the 133rd Meeting of the American Chemical Society, San Francisco, Calif., April 17, 1958. These authors have come to the same conclusions concerning the structure of the dimer as those presented here. Their results are described in the accompanying paper, *J. Org. Chem.*, **23**, 1653 (1958).

(3) A. V. Dombrovskii, *Doklady Akad. Nauk, S.S.S.R.*, **111**, 827 (1956).

(4) G. S. Whitby and W. Gallay, *Can. J. Research.* **6**, 280 (1932).

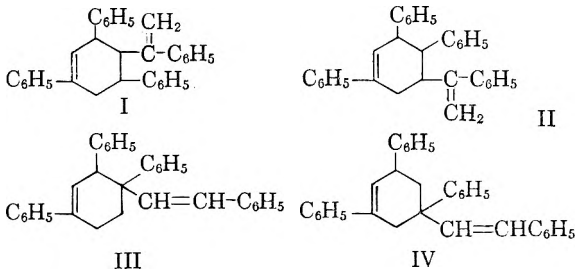
(5) M. S. Kharasch and D. C. Sayles, *J. Am. Chem. Soc.*, **64**, 2972 (1942).

(6) A. C. Cope, E. L. Wick, and F. S. Fawcett, *J. Am. Chem. Soc.*, **76**, 6156 (1954).

ular weight was 426 as determined ebullioscopically in methyl ethyl ketone. Curiously, the molecular weight as determined by the Rast method was 215 (average of six determinations). Fiesselmann and Ribka[7] have reported an analogous result for the dimer of 2-phenylacrylophenone. It is curious that the tetrahydro derivative (VIII) also showed this same discrepancy. No C-methyl was found on Kuhn-Roth oxidation either of the dimer or its tetrahydroderivative.

Dehydrogenation with sulfur at 230° gave 1,3,5-triphenylbenzene. From oxidation with either ozone or potassium permanganate, the only steam-volatile product was benzaldehyde. The non-volatile part of these oxidation products consisted of a small, but persistent, amount (5%) of 1,2-dibenzoylethane and an irresolvable mixture of unidentified carbonyl compounds.

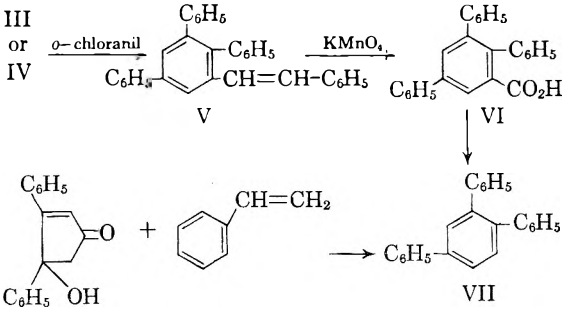
Of the four possible Diels-Alder dimers of 1,3-diphenyl-1,3-butadiene, structures I and II are eliminated by the preceding observations. The choice between structures III and IV was inconclusive. III was preferred for theoretical reasons, as



discussed below, but this structure required a phenyl migration during the sulfur dehydrogenation. IV required no migration on dehydrogenation, but would require rearrangement to give 1,2-dibenzoylethane on oxidation. Accordingly, dehydrogenations of the dimer at temperatures low enough to preclude rearrangement were explored.

Dehydrogenation of the 1,3-diphenyl-1,3-butadiene dimer with selenium dioxide at 75°, or much better, tetrachloro-*o*-benzoquinone at 80° gave a compound of formula $C_{32}H_{24}$ (V), m.p. 178–179°, which from its infrared and ultraviolet spectrum and lack of reaction with maleic anhydride was a triphenylstilbene. This compound was reduced to $C_{32}H_{26}$, m.p. 106–107°, and oxidized to an acid, $C_{25}H_{18}O_2$ (VI), m.p. 219–220° (dec.). This acid had a neutral equivalent of 355, but was not 2,4,6-triphenylbenzoic acid, m.p. 247.5–247.0° (dec.), which was prepared from 2,4,6-triphenylbromobenzene.[8] Decarboxylation of the $C_{25}H_{18}O_2$ acid gave a hydrocarbon $C_{24}H_{18}$, (VII), m.p. 99.5–100.0°. It was assumed that this hydrocarbon was 1,2,4-triphenylbenzene, and attempts were made to synthesize it by the condensation of *trans*, *trans*-1,4-diphenyl-1,3-butadiene with either styrene, phenylacetylene, or cinnamic acid. All of these failed to give any adduct in agreement with the report that *trans*, *trans*-1,4-diphenyl-1,3-butadiene is unreactive toward all but the most reactive dienophiles.[9]

1,2,4-Triphenylbenzene was finally prepared by the method of Rose and Statham.[10] This compound was identical with VII. V is therefore 2,3,5-triphenylstilbene produced by the aromatization of the cyclohexene ring, and VI is 2,3,5-triphenyl benzoic acid. This result requires either the migration of a styryl group in structure III or migration of a phenyl group in structure IV. Attempts to prepare VI by the oxidation of what is claimed to be 2,3,5-triphenyltoluene[11] failed. It was found impossible to obtain an oxidation product of this compound.



Catalytic reduction of the 1,3-diphenyl-1,3-butadiene dimer gave a tetrahydro derivative (VIII), m.p. 119–120°, whose ultraviolet spectrum was typical of compounds with isolated benzene rings. In order to make a choice between structures III and IV, it was decided to investigate the dehydrogenation of this substance. There is good evidence for the belief that dehydrogenations using quinones are initiated by hydride abstraction[13] and that blocks to aromatization presented by *gem*-dialkyl groups are overcome by migration processes similar to Wagner-Meerwein shifts. Now although the styryl group of the dimer might compete successfully with a phenyl group in migration from carbon to carbon,[14] it was

(7) H. Fiesselmann and J. Ribka, *Ber.*, **89**, 40 (1956).

(8) E. P. Kohler and L. W. Blanchard, Jr., *J. Am. Chem. Soc.*, **57**, 367 (1935).

(9) K. Alder in *Newer Methods of Preparative Organic Chemistry*, Interscience Publishers, Inc., New York, 1948.

(10) J. D. Rose and F. S. Statham, *J. Chem. Soc.*, 69 (1950).

(11) C. F. H. Allen and J. Van Allan, *J. Org. Chem.*, **10**, 333 (1945). The resistance of their compound, m.p. 131.5–132°, to oxidation is puzzling, and suggests that it is 2,3,6-triphenyltoluene in spite of the evidence cited. Moreover, Ivanov and co-workers[12] have reported that 2,3,5-triphenyltoluene melts at 94–95°.

(12) D. Ivanov, D. Ivanov, and B. Stoianova-Ivanovna, *Compt. Rend.*, **227**, 535 (1948).

(13) R. P. Linstead, E. A. Braude, L. M. Jackman, and A. N. Beames, *Chem. & Ind. (London)*, 1174 (1954); see also J. D. Loudon, *Ann. Repts.*, 194 (1954).

(14) While there is no theoretical reason why a styryl group should not migrate, possibly through an intermediate analogous to the phenonium ion, no such instance could be found in the literature.

expected that the phenyl group of the tetrahydro dimer VIII would definitely migrate in preference to a saturated aliphatic chain,[15] such as the phenylethyl group. Also, since Dost[16] has shown that 2-phenylpropane is dehydrogenated twice as fast as ethylbenzene with tetrachloro-*p*-benzoquinone, it was reasonable to expect dehydrogenation of the cyclohexane ring with subsequent rearrangement before much dehydrogenation of the phenylethyl group[17] would occur. Steric effects on the course of rearrangement should be negligible, since in IX, the intermediate just prior to rearrangement, the cyclohexadiene ring is very nearly planar and both methylene hydrogens are almost sterically equivalent.

These considerations suggested that if III were the structure of the dimer, dehydrogenation of its tetrahydro derivative should give rise to a substance different from 2,3,5-triphenylstilbene (V) or its dihydro derivative, and that this dehydrogenation product would probably be 2,4,6-triphenylstilbene or 1-(2-phenylethyl)-2,4,6-triphenylbenzene. Although no homogeneous hydrocarbon product, other than starting material, could be isolated from the reaction of VIII with tetrachloro-*o*-benzoquinone in refluxing benzene, xylene, or diethylene glycol dimethyl ether, a 22% of a hydrocarbon, $C_{32}H_{22}$ or $C_{32}H_{24}$ (XI), was obtained when the dehydrogenation was carried out in naphthalene at 140–150°. However, this substance was not oxidized by permanganate and could not be reduced catalytically. This behavior and the infrared spectrum (absence of aliphatic carbon-hydrogen stretching and *trans*-ethylenic bands) argues against the expected structures. This was confirmed by comparison with authentic samples of 2,4,6-triphenylstilbene and 1-(2-phenylethyl)2,4,6-triphenylbenzene (*vide infra*). On the other hand, XI was not identical with 2,2′-binaphthyl. To eliminate the possibility that it was formed from naphthalene in some other fashion, a blank experiment was run in which no trace of XI could be detected.

It was therefore suspected that XI was a substance which resulted from the cyclization of 1-(2-phenylethyl)-2,4,6-triphenylbenzene XIII under dehydrogenating conditions. In order to synthesize this compound the following sequence of reactions was carried out. Phenylacetyl chloride was added to 2,4,6-triphenylphenylmagnesium bromide[8] to give 1-phenylacetyl-2,4,6-triphenylbenzene XII, m.p. 125–126°. Attempts to synthesize this product by a condensation of triphenylbenzene and phenylacetyl chloride failed. Although the reaction of triphenylbenzene and benzoyl chloride with aluminum chloride is reported to give triphenylbenzophenone in almost quantitative yield,[8,18] phenylacetyl chloride gave a low yield of a $C_{32}H_{24}O$ ketone which was quite different from XII, particularly in its carbonyl reactivity. This ketone must be a product of the acylation of one of the end rings, and as such violates the observation made by Allen and Burness[19] that *meta* terphenyl structures are invariably substituted on the central ring.

As noted by Kohler and Blanchard[8] for triphenylphenyl ketones, the carbonyl of XII was quite hindered. No derivative could be obtained with 2,4-dinitrophenylhydrazine, and the lithium aluminum hydride reduction in boiling tetrahydrofuran gave only a 45% yield of 1-(2,4,6-triphenylphenyl)-2-phenylethanol, m.p. 139–140°. This alcohol was dehydrated smoothly with iodine in toluene to give 2,4,6-triphenylstilbene, m.p. 161.5–162°. Catalytic reduction gave a poor yield of 1-(2-phenylethyl)-2,4,6-triphenylbenzene (XIII), m.p. 130.0–130.5°. XIII was also synthesized from XII by a Clemmensen reduction in about the same over-all yield. Dehydrogenation of XIII with tetrachloro-*o*-benzoquinone gave in addition to 61% of recovered starting material, an 8% yield of XI.

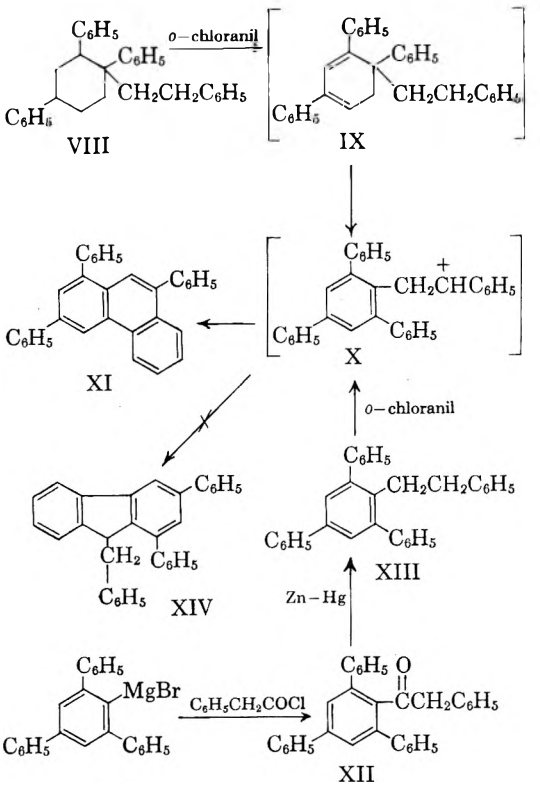
This synthesis of the hydrocarbon XI shows that 1-(2-phenylethyl)-2,4.6-triphenylbenzene (XIII) is indeed the initial dehydrogenation product of VIII. Subsequent carbonium ion formation followed by cyclization and another dehydrogenation to complete the aromatization would give either 1,3,9-triphenylphenanthrene or 1,3-diphenyl-9-benzylfluorene.[20] The latter structure was eliminated by synthesis. 1,3-Diphenylfluorenone was reduced to 1,3-diphenylfluorene, m.p. 118–119°, which was condensed with benzyl alcohol to give 1,3-diphenyl-9-benzylfluorene (XIV). The latter differed from XI not only in melting point, but in infrared and ultraviolet spectrum. The formation of 1,3,9-triphenylphenanthrene from VIII and XIII may be rationalized in terms of steric hindrance at the methylene carbon closest to the 2,4,6-triphenylmethyl radical which prevents hydride ion abstraction there and leads exclusively to the formation of ion X.

These results force the acceptance of 1,3,4-triphenyl-4-styrylcyclohexene (III) as the structure of the dimer of 1,3-diphenyl-1,3-butadiene. Therefore, in the Diels-Alder reaction the two molecules of 1,3-diphenyl-1,3-butadiene orient themselves in a manner which would be expected from that shown by the dimerization of 1- and 2-phenylbutadiene.[21,22] This orientation also follows the rule that in the Diels-Alder reaction that terminal car-

(15) For an analogous case, see ref. 12.
(16) N. Dost, *Rec. trav. chim.*, **71**, 857 (1952).
(17) E. Buchta and W. Kallert, *Ann.*, **573**, 220 (1951).
(18) D. Ivanov and C. Ivanov, *Ber.*, **77B**, 173 (1944).
(19) C. F. H. Allen and D. M. Burness, *J. Org. Chem.*, **14**, 175 (1949).
(20) Although these two products differ by two hydrogen atoms, a definite choice between formulae $C_{32}H_{22}$ and $C_{32}H_{24}$ could not be made on the basis of the elemental analysis. The absence of aliphatic carbon-hydrogen stretching in the infrared favored the phenanthrene structure over the fluorene.
(21) K. Alder, J. Haydn, and W. Vogt, *Ber.*, **86**, 1302 (1953).
(22) K. Alder and J. Haydn, *Ann.*, **570**, 203 (1950).

bon atom of the diene whose adjacent carbon atom can best stabilize a positive charge becomes attached to that carbon atom of the dienophile whose adjacent carbon atom can best stabilize a negative charge.[23]

Moreover it has been demonstrated that sulfur dehydrogenation of the dimer results primarily, if not exclusively, in phenyl migration and that *o*-chloranil dehydrogenation results in migration of a styryl group. The mechanism of the phenyl migration is not clear since the synthesis of 1,2,4-triphenylbenzene from 3,4-diphenyl-4-hydroxy-2-cyclopentenone and styrene is carried out under essentially the same conditions.



EXPERIMENTAL[24,25]

1,3-Diphenyl-2-buten-1-ol. To a solution of 10.0 g. (0.045 mole), of dypnone,[26] n_D^{23} 1.6309, in 100 ml. of methanol was added 1.5 g. (0.034 mole) of solid sodium borohydride as rapidly as the frothing allowed. The methanol boiled briefly and then slowly cooled. A smaller amount of sodium borohydride, stirring, or cooling during addition with subsequent reflux invariably resulted in very little reduction. After standing for 2 hr. the methanolic solution was extracted with ether. The ether layer was dried and concentrated at reduced pressure to give a clear green-tinted sirup, n_D^{23} 1.6003 (lit.[27] n_D^{25} 1.5989). The infrared spectrum showed a sharp band at 3655 cm.$^{-1}$ (ϵ = 24). Reduction by normal addition of a 200% excess of lithium aluminum hydride in refluxing ether gave an identical product. Because of extensive decomposition on distillation at 1 mm. the alcohol was used without further purification.

1,3-Diphenyl-1-buten-3-ol. This alcohol was prepared by the method of Cope, Wick, and Fawcett[6] in 25% isolable yield without distillation (the actual yield was 90% by infrared analysis), clumps of small needles from hexane, m.p. 57.5°–59.0° (lit.[6] 57.2–58.0°).

Dimer of 1,3-diphenyl-1,3-butadiene. To a solution of 74.0 g. (0.33 mole) of 1,3-diphenyl-2-buten-1-ol in 50 ml. benzene was added a single crystal of *p*-toluenesulfonic acid. Refluxing this solution for 24 hr. under a water trap produced 5.2 ml. (0.29 mole) of water. Concentration of the benzene solution at reduced pressure gave a yellow sirup. This residue was dissolved in ligroin and chromatographed through an alumina column. Elution with benzene–petroleum ether (1:3) produced a white solid which was separated by recrystallization from ligroin-benzene into 39.0 g. (58%), of a white solid, m.p. 132–134°, and 16.3 g. (24%) of a mixture of white solids m.p. 123–140°. The chloroform eluate produced 12.7 g. (18%) of a yellow oil which was mainly starting material from its infrared spectrum. Several further recrystallizations of fraction I gave large transparent prisms, m.p. 136–137°. Under these same conditions 1,3-diphenyl-1-buten-3-ol gave a 48% yield of material, m.p. 133–136°. The infrared spectrum showed strong absorption bands at 3058 (C—H), 3030 (C—H), 2933 (C—H), 1602 (benzene), 1500 (benzene), 1453 (benzene), 1037 (benzene), and 975 (*trans* double bond) cm.$^{-1}$ The ultraviolet spectrum showed a broad absorption curve with λ_{min} 228 mμ (log ϵ4.12), λ_{max} 253 mμ (log ϵ 4.56), and a sharp peak at 294 mμ (log ϵ 3.19). The molecular weight (calcd. 406) was 426, determined ebullioscopically in methyl ethyl ketone; 215 (average of six determinations), determined by the Rast method.

Anal. Calcd. for $C_{32}H_{28}$: C, 93.16; H, 6.84. Found; C, 93.02; H, 7.09.

The absorption of bromine from chloroform was slow, and the decolorization of permanganate in acetone was negligible. The addition of tetranitromethane gave a bright yellow color. The dimer was only partially soluble in cold, concentrated sulfuric acid. Kuhn-Roth oxidation showed the absence of C—methyl groups. Microhydrogenation showed the presence of two double bonds. The dimer was stable to refluxing alcoholic solutions of hydrochloric acid and sodium hydroxide and formed no adduct with maleic anhydride. Slightly over two moles of bromine were absorbed from a chloroform solution with copious evolution of hydrogen bromide. The product was a mixture of bromine-containing compounds.

Dehydration of either 1,3-diphenyl-2-buten-1-ol or 1,3-diphenyl-3-buten-1-ol with iodine in benzene gave a small amount of white solid, m.p. 146–147°. The infrared spectrum showed strong bands at 3063 (C—H), 3034 (C—H), 2911 (C—H), 1603 (benzene), 1500 (benzene), 1462 (benzene), 1038 (benzene), and 906 (unassigned) cm.$^{-1}$ The ultraviolet spectrum showed λ_{max} 245 mμ (log ϵ 4.39) and λ_{min} 227 mμ (log ϵ 4.16).

Anal. Calcd. for $C_{32}H_{28}$: C, 93.16; H, 6.84. Found: C, 93.15; H, 6.93.

Reaction of benzalacetophenone with methylmagnesium iodide. The procedure of Whitby and Gallay[4] was followed.

(23) J. S. Meek, R. T. Merrow, and S. J. Cristol, *J. Am. Chem. Soc.*, 74, 2667 (1952).

(24) Analyses were performed by Drs. Weiler and Strauss, Oxford, England. Molecular weights were determined by Clark Microanalytical Laboratory, Urbana, Ill. Ultraviolet and infrared spectra were determined by Miss M. A. Esquivel on Beckman Model DK and Perkin-Elmer model 21 spectrometers.

(25) Melting points are uncorrected. Ultraviolet spectra were determined in 95% ethanol solution. The infrared spectra were determined at known concentrations (3–5% solutions) in either chloroform or carbon tetrachloride, unless otherwise specified. The petroleum ether and ligroin referred to are commercial petroleum solvents of boiling range 30–60° and 65–110°, respectively.

(26) We wish to thank the Union Carbide Chemicals Co. for a generous supply of dypnone.

(27) H. H. Wasserman and N. E. Aubrey, *J. Am. Chem. Soc.*, **77**, 590 (1955).

One run resulted in a 12% yield of 1,3,5-triphenyl-4-benzoyl-1,3-hexadiene, m.p. 175.5–177.0°, (lit.[5] 176°).

Other runs in which the Grignard reagent was allowed a longer time to form gave 4–17% of a white solid m.p. 161.5–163°, a small amount of 1,3-diphenyl-1,3-butadiene dimer, m.p. 136–137°, and considerable amounts of 1,3-diphenyl-1-butanone. The addition of maleic anhydride to the gummy residues gave 5–10% of the 3,5-diphenyl-1,2,3,6-tetrahydrophthalic anhydride described below. The substance melting at 161.5–163° showed two strong bands at 1666 and 1679 cm.$^{-1}$ (Nujol). The ultraviolet spectrum showed λ_{max} 243 mμ (log ε 4.36) and 280 mμ (log ε 3.32). It is assumed to be 1,3-dibenzoyl-4-phenylpentane which could have been formed by a Michael condensation between benzalacetophenone and 1,3-diphenyl-1-butanone.

Anal. Calcd. for $C_{31}H_{28}O_2$: C, 86.08; H, 6.53. Found: C, 86.17; H, 6.63.

3,5-Diphenyl-1,2,3,6-tetrahydrophthalic anhydride. A solution of 4.0 g. (0.018 mole) of 1,3-diphenyl-2-buten-1-ol and 1.8 g. (0.018 mole) of freshly sublimed maleic anhydride dissolved in 100 ml. xylene was refluxed under a water trap. On concentration of the xylene solution at reduced pressure 1.9 g. (33%) of a white powder, m.p. 156–157°, separated. Recrystallization from benzene–petroleum ether gave clumps of woolly needles, m.p. 158–159° (lit.[6] 142–149°).

Anal. Calcd. for $C_{20}H_{16}O_3$: C, 78.93; H, 5.30. Found: C, 78.92; H, 5.51.

3,5-Diphenyl-1,2,3,6-tetrahydrophthalic acid. An aqueous solution of the anhydride was stirred and refluxed for 10 hr. Filtration gave 1.1 g. (80%) of a white solid, m.p. 216–224° (dec.). Recrystallization from acetic acid gave small needles, m.p. 221–224° (dec.). The neutral equivalent was 166 (calcd. 163).

Anal. Calcd. for $C_{20}H_{18}O_4$: C, 74.52; H, 5.63. Found, C, 74.47; H, 5.64.

3,5-Diphenylphthalic anhydride and 3,5-diphenylphthalic acid. A mixture of 3.4 g. (0.011 mole) of 1,3-diphenyl-1,2,3,6-tetrahydrophthalic anhydride and 2.0 g. (0.062 atom) of sulfur was heated at 190–210° for 6 hr. The cooled mixture was extracted with chloroform, the solvent evaporated, and the residue recrystallized from benzene–petroleum ether. The yield was 2.26 g. (67%) of small needles, m.p. 167–172°. An analytical sample melted at 173–174.5° (dec.), (lit.[6] 176–177°).

Anal. Calcd. for $C_{20}H_{12}O_3$: C, 79.99; H, 4.03. Found, C, 79.70; H, 4.02.

By extraction of the chloroform mother liquors with aqueous bicarbonate there was isolated 0.55 g. (15%) of 3,5-diphenylphthalic acid, m.p. 196–197°. Reprecipitation raised the melting point to 199.0–199.5°. The neutral equivalent was 161 (calcd. 159).

Anal. Calcd. for $C_{20}H_{14}O_4$: C, 75.46; H, 4.43. Found: C, 75.53; H, 4.53.

m-Terphenyl. A mixture of 430 mg. of 3,5-diphenylphthalic acid and 1 g. copper-bronze was heated gently with a low flame until no more material formed on the side of the flask. The yellowish, cotton-like material was scraped from the flask and sublimed at 90° (1 mm.). The yield of white powder, m.p. 85–86°, was 31 mg. (10%). The mixed melting point with an authentic sample of *m*-terphenyl showed no depression.

Sulfur dehydrogenation of the dimer. A mixture of 5.0 g. (0.012 mole) of dimer and 2.0 g. of sulfur was heated under nitrogen at 225–230° for 5 hr. The cooled mixture was dissolved in 100 ml. of absolute ethanol and refluxed 2 hr. over W-2 Raney nickel. Evaporation of the alcohol left a brown gum which was dissolved in a small amount of chloroform and chromatographed through an alumina column. Petroleum ether eluted a green oil from which separated 140 mg. (4%) of massive golden tinted needles, m.p. 171.5–172.5°. A mixed melting point with an authentic sample of 1,3,5-triphenylbenzene, prepared by the method of Reddeliens,[28] showed no depression. The infrared and ultraviolet spectra of these two samples were identical.

Ozonolysis of the dimer. A solution of 4.12 g. (0.01 mole) of 1,3-diphenyl-1,3-butadiene dimer dissolved in 150 ml. of ethyl acetate was ozonized at −10° until ozone appeared in the outlet gases (potassium iodide solution). The reaction mixture was quickly removed and added to a spoonful of Raney nickel. After stirring overnight, the faintly green solution was filtered and concentrated to a viscous oil. The oil was dissolved in ligroin (b.p. 60–90°) and a small amount of benzene and chromatographed through an alumina column. From the benzene–petroleum ether fraction was obtained 123 mg. (5%) of 1,2-dibenzoylethane, m.p. and mixed m.p. with an authentic sample,[29] 145–146°. The infrared spectra of these two samples were identical. From the ether fractions was obtained a brown oil which rapidly formed mixtures of carbonyl derivatives with 2,4-dinitrophenylhydrazine and semicarbazide. Only a small portion of this oil was base soluble. The infrared spectrum of the oil showed a broad absorption at 3600–3200 cm.$^{-1}$ (OH), and strong bands at 1775 and 1688 cm.$^{-1}$ (C=O).

In other experiments the reduced ozonide was steam distilled into either an acidic aqueous-alcoholic solution of 2,4-dinitrophenylhydrazine or a saturated aqueous solution of dimedone. The yields of the benzaldehyde derivatives of each were 30–40%. 1,2-Dibenzoylethane was also obtained on oxidation of the dimer with potassium permanganate and sodium bicarbonate in acetone. The yields were slightly lower.

2,3,5-Triphenylstilbene (V). *Dehydrogenation of the dimer with selenium dioxide.* To a well-stirred suspension of 1.11 g. (0.01 mole) of freshly prepared selenium dioxide in 40 ml. of dioxane was added 4.12 g. (0.01 mole) of 1,3-diphenyl-1,3-butadiene dimer. After heating at 75° for 37 hr., the mixture was filtered and the dioxane removed at reduced pressure. The residual yellow gum was dissolved in 20% benzene–petroleum ether and chromatographed through an alumina column. Elution gave yellow oils which showed a carbonyl band (1680 cm.$^{-1}$) in the infrared spectrum, but which were inert toward 2,4-dinitrophenylhydrazine. One of the petroleum ether eluates on standing deposited 64 mg. (2%) of 2,3,5-triphenylstilbene, m.p. 175–177°. Recrystallization from ethanol–ethyl acetate gave long needles, m.p. 178–179°. The infrared spectrum showed a strong band at 970 cm.$^{-1}$ (*trans* double bond). The ultraviolet spectrum showed a broad absorption from 260–320 mμ; λ_{max} *ca.* 270 mμ (log ε 4.60) and 310 mμ (log ε 4.44).

Anal. Calcd. for $C_{32}H_{24}$: C, 94.08; H, 5.92. Found: C, 94.00; H, 5.84.

2,3,5-Triphenylstilbene (V). *Dehydrogenation with tetrachloro-o-benzoquinone.* Tetrachloro-*o*-benzoquinone was prepared by the general method of Jackson and MacLaurin.[30] C.P. Nitric acid (dec. 1.42) was found most satisfactory for oxidation of the tetrachlorocatechol. The garnet powder, m.p. 126–128°, was difficult to purify and was used in the crude form.

To a solution of 2.0 g. (0.0048 mole) of the dimer in 40 ml. of benzene was added 3.0 g. (0.012 mole) of tetrachloro-*o*-benzoquinone. The resultant deep red solution was refluxed for 8 hr. Upon cooling the benzene solution was washed through an alumina column with 300 ml. of petroleum ether. Evaporation of the solvent produced 700 mg. (35%) of 2,3,5-triphenylstilbene (V), m.p. 173–175°. The remainder of this product was an irresolvable mixture of solids, m.p. 150–170°, whose ultraviolet spectrum was very similar to that of 2,3,5-triphenylstilbene.

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(28) Described in C. Vorländer, E. Fischer, and H. Wille, *Ber.*, **62**, 2836 (1929).

(29) P. S. Bailey and R. E. Lutz, *J. Am. Chem. Soc.*, **70**, 2412 (1948).

(30) C. L. Jackson and R. D. MacLaurin, *Am. Chem. J.*, **37**, 11 (1907).

1-(2-Phenylethyl)-2,3,5-triphenylbenzene. A solution of 100 mg. (0.00024 mole) of 2,3,5-triphenylstilbene in 50 ml. glacial acetic acid was reduced at three atmospheres with 25 mg. of 10% palladium-on-charcoal, yield 63 mg. (62%) of long needles, m.p. 105.5–106°. An analytical sample recrystallized from ethanol–ethyl acetate melted at 106–107°.

Anal. Calcd. for $C_{32}H_{26}$: C, 93.62; H, 6.38. Found: C, 93.50; H, 6.52.

Reduction in ethyl acetate resulted only in recovery of starting material.

2,3,5-Triphenylbenzoic acid. (VI). To a well-stirred solution of 740 mg. (0.0018 mole) of 2,3,5-triphenylstilbene and 100 mg. of sodium bicarbonate dissolved in 100 ml. acetone was added 4.0 g. potassium permanganate. After stirring at room temperature for 12 hr., methanol was added until the purple color was discharged. The solution was filtered and the manganese dioxide washed thoroughly with 10% sodium hydroxide. Acidification of the combined filtrate and washings produced 458 mg. (71%) of a white acid, m.p. 217–219°. The hexagonal prisms, m.p. 219–220° from acetonitrile, had a neutral equivalent of 355 (calcd. 350).

Anal. Calcd. for $C_{25}H_{18}O_2$: C, 85.69; H, 5.18. Found: C, 85.30; H, 4.92.

2,4,6-Triphenylbromobenzene. The method of Kohler and Blanchard[8] gave yields of 79–100% of 2,4,6-triphenylbromobenzene, m.p. 107–108° (lit. 104°;[31] 129–130°[8]). After repeated recrystallizations with no change in melting point, one crop melted at 131–133°. Thereafter recrystallizations gave the higher melting form. Both forms were used interchangeably in subsequent reactions.

2,4,6-Triphenylbenzoic acid. 2,4,6-Triphenylbenzoic acid was formed by the carbonation of 2,4,6-triphenyllithium[32] in low yield. Recrystallization from acetonitrile gave small needles, m.p. 248.5–249.5°.

1,2,4-Triphenylbenzene (VII). *Decarboxylation of 2,3,5-triphenylbenzoic acid* (VI). To a solution of 268 mg. (0.0077 mole) of 2,3,5-triphenylbenzoic acid dissolved in 5 ml. of freshly distilled quinoline was added 40 mg. of copper chromite catalyst.[33] After heating at 213–228° for 2 hr. in a vigorous stream of nitrogen, 40 ml. of benzene was added, and the mixture was extracted with successive 50-ml. portions of 5% HCl, 5% KOH, and water. The benzene layer was dried over sodium sulfate and concentrated to 5 ml. The residue was dissolved in ligroin and chromatographed through an alumina column. Benzene–petroleum ether (1:9) eluted 100 mg. (43%) of a hydrocarbon, m.p. 96–98°. Recrystallization from ethanol gave clumps of needles, m.p. 99.5–100.0°. The ultraviolet spectrum had λ_{max} 248 mμ (log ε 4.52) and 272 mμ (log ε 4.39).

Anal. Calcd. for $C_{24}H_{18}$: C, 94.08; H, 5.92. Found: C, 93.88; H, 6.06.

1,2,4-Triphenylbenzene (VII). *Preparation from 3,4-diphenyl-4-hydroxy-2-cyclopentenone.* To a mixture of 5.0 g. (0.02 mole) of 3,4-diphenyl-4-hydroxy-2-cyclopentenone[34] and 10.0 g. of freshly fused and pulverized potassium acid sulfate was added 5.0 g. (0.049 mole) of phenylacetylene.[35] This mixture was heated for 7.5 hr. at 180–185°. The potassium bisulfate was filtered and washed with benzene. The combined filtrate and washings were concentrated on a 230–240° bath. After the benzene was removed, the heating was continued for 20 min. The resultant black oil was dissolved in ligroin and chromatographed through an alumina column. Four fractions were obtained from the petroleum ether eluate. The first fraction consisted of 240 mg. (4%) of small prisms, m.p. 118–120°; the second fraction, 260 mg. (5%) of long needles, m.p. 96–99°; the third fraction, 450 mg. (8%) of long needles, m.p. 98–99°; the fourth fraction, 180 mg. (3%) of small prisms, m.p. 117–120°. The infrared spectra of all four fractions were identical. A mixture of fractions I and III gave an opaque melt at 100° which slowly resolidified and melted at 119–120°. Recrystallization of the higher melting form from petroleum ether gave small jewel-like prisms, m.p. 119.5–120°. A mixture of the lower melting form with the 1,2,4-triphenylbenzene (VII) from the dehydrogenation of 2,3,5-triphenylbenzoic acid (VI) melted at 99.5–100°.

Anal. Calcd. for $C_{24}H_{18}$: C, 94.08; H, 5.92. Found: C, 93.34; H, 6.05.

The procedure of Rose and Statham[10] produced the same mixture in 4% over-all yield. These authors report only a single melting point, 109°, for this product.

2,3,5-Triphenyltoluene (?). 2,3,5-Triphenyltoluene, m.p. 131.5–132.5°, was prepared by the method of Allen and Van Allan[11] in 43% yield. A dimer of 2-methyl-3,4-diphenylcyclopentadienone, m.p. 219.5–220.5° (with effervescence), was isolated from the mother liquors in 10% yield. This diketone had carbonyl frequencies at 1690 and 1790 cm.$^{-1}$ Allen and Van Allan[36] report carbonyl frequencies at 177 cm.$^{-1}$ as characteristic for bridged carbonyl compounds.

Anal. Calcd. for $C_{36}H_{28}O_2$: C, 87.77; H, 5.73. Found: C, 87.12; H, 5.97.

All attempts to oxidize 2,3,5-triphenyltoluene with permanganate, dichromate, nitric acid, or chromyl chloride resulted either in recovery of starting material or base-insoluble tars.

1-(2-Phenylethyl)-1,3,5-triphenylcyclohexane (VIII). A solution of 1.0 g. (0.0024 mole) of the 1,3-diphenyl-1,3-butadiene dimer dissolved in 40 ml. of ethyl acetate was hydrogenated at three atmospheres with 200 mg. of 10% palladium-on-charcoal for 1 hr. Removal of solvent at reduced pressure yielded 1.0 g. of a white solid, m.p. 116–118°. Subsequent runs gave yields of 75–85%. Recrystallization from ethanol–ethyl acetate produced large prisms, m.p. 119–120°. The molecular weight (calcd. 416) was 375, determined ebullioscopically in methyl ethyl ketone; 266 (average of six determinations) determined by Rast method. No C-methyl was found on Kuhn-Roth oxidation. The ultraviolet spectrum showed absorption maxima at 253 mμ (log ε 2.90), 259 mμ (log ε 2.98), 265 mμ (log ε 2.89), and 268 mμ (log ε 2.80).

Anal. Calcd. for $C_{32}H_{32}$: C, 92.26; H, 7.74. Found: C, 92.26; H, 7.90.

Dehydrogenation of 1-(2-phenylethyl)-1,3,5-triphenylcyclohexane (VIII). A mixture of 2.16 g. (0.0052 mole) of 1-(2-phenylethyl)-1,3,5-triphenylcyclohexane (VIII), 30 g. of naphthalene, and 12.5 g. (0.051 mole) of tetrachloro-*o*-benzoquinone was heated at 140–150° for 24 hr. in a stream of dry oxygen-free nitrogen. The brown mixture was dissolved in 100 ml. of benzene and passed through an alumina column. The hydrocarbon fraction was completely removed with 300 ml. of benzene. The benzene eluates were reduced in volume and steam distilled until the naphthalene was completely removed. The solid brown residue was taken up in ligroin and chromatographed through an alumina column. The benzene–petroleum ether (1:4) eluate yielded 426 mg. (22%) of a yellowish solid, m.p. 170–175°. Two recrystallizations from benzene-ligroin produced clumps of small needles, m.p. 183.5–184° (XI). This compound was not oxidized by permanganate in acetone solution after 19 hr. It was also inert to catalytic hydrogenation in either ethyl acetate or glacial acetic acid. The infrared spectrum showed no band at 970 cm.$^{-1}$ (*trans* double bond). The ultraviolet spectrum showed λ_{max} 262 mμ (log ε 4.64) with a shoulder

(31) C. Engler and H. E. Berthold, *Ber.*, **7**, 1123 (1874).

(32) J. W. Morton, Dissertation, Iowa State College, 1952.

(33) H. Adkins, E. E. Burgoyne, and H. J. Schneider, *J. Am. Chem. Soc.*, **72**, 2626 (1950).

(34) F. R. Japp and J. Knox, *J. Chem. Soc.*, **87**, 679 (1905).

(35) J. C. Hessler, *Org. Syntheses*, Coll. Vol. I, 438 (1932).

(36) C. F. H. Allen and J. Van Allan, *J. Org. Chem.*, **20**, 306 (1955).

at *ca.* 294 mμ (log ε 4.44). After refluxing with iodine in toluene, this compound was recovered unchanged.

Anal. Calcd. for $C_{32}H_{22}$: C, 94.54; H, 5.46. Found: C, 94.11; H, 5.43.

A sample of 2,2′-binaphthyl was prepared in low yield by the addition of ferrous chloride to 2-naphthylmagnesium iodide. The purified hydrocarbon, m.p. 181.5–182.5°, on admixture with the above dehydrogenation product melted at 158–167°. Their infrared spectra were different.

A blank dehydrogenation experiment under the same conditions produced, as the only benzene–petroleum ether eluable material, 180 mg. of a halogen-containing white solid. This substance was devoid of benzene bands in its infrared spectrum.

3,5-Diphenyl-4′-phenacetylbiphenyl. To a solution of 7.32 g. (0.055 mole) of anhydrous aluminum chloride dissolved in 30 ml. of dry carbon disulfide was added dropwise with stirring a solution of 15.3 g. (0.05 mole) of 1,3,5-triphenylbenzene and 7.80 g. (0.05 mole) of phenylacetyl chloride in 100 ml. of dry carbon disulfide. The resulting greenish black solution was stirred at room temperature for 8 hr. The reaction mixture was decomposed by the addition of 150 ml. of cold 4*N* hydrochloric acid. The carbon disulfide layer was separated, and the aqueous layer was extracted with three 150-ml. portions of benzene. The combined organic layers were extracted with three 150-ml. portions of sodium bisulfite solution and washed with water. The dried solution was concentrated at reduced pressure and the residual yellow gum was dissolved in ligroin and chromatographed through an alumina column. From the benzene–petroleum ether (1:9) eluate there was recovered 7.0 g. (46% recovery) of 1,3,5-triphenylbenzene. From the benzene–petroleum ether (1:4) eluate there was obtained 1.28 g. (6%) of a yellowish solid, m.p. 146–149°. Recrystallization from benzene-ligroin gave slightly yellow feathery crystals, m.p. 148.5–149.0°. The infrared spectrum showed a strong band at 1680 cm.$^{-1}$ A slow reaction with 2,4-dinitrophenylhydrazine reagent produced orange needles, m.p. 208.5–209.0°, from ethanol–ethyl acetate.

Anal. Calcd. for $C_{38}H_{28}N_4O_4$: C, 75.48; H, 4.67; N, 9.27. Found: C, 74.74; H, 4.83; N, 9.45.

3,5-Diphenyl-4′-(2-phenyl-1-hydroxyethyl)biphenyl. Reduction of 1.21 g. of the preceding ketone with lithium aluminum hydride in ether solution furnished an oil which was chromatographed over alumina. The benzene eluate, wt. 0.82 g., crystallized on trituration with petroleum ether. Slow evaporation of an ethanol solution furnished white crystals, m.p. 130–131.5°.

Anal. Calcd. for $C_{32}H_{26}O$: C, 90.10; H, 6.14. Found: C, 89.57; H, 6.44.

3,4-Diphenyl-4′-styrylbiphenyl. A mixture of 0.159 g. of the preceding alcohol, 30 ml. of toluene, and a crystal of iodine was refluxed for 12 hr., cooled, and treated with sodium thiosulfate solution. The toluene layer was dried and concentrated to small volume. The solid, wt. 0.114 g., was recrystallized from ligroin, m.p. 185.5–186°, mixed m.p. with XI 163–175°. The infrared spectrum had the typical *trans*-ethylenic band at 970 cm.$^{-1}$

Anal. Calcd. for $C_{32}H_{24}$: C, 94.08; H, 5.92. Found: C, 93.92; H, 5.80.

1-Phenylacetyl-2,4,6-triphenylbenzene (XII). 2,4,6-Triphenylphenylmagnesium bromide was prepared from 1.0 g. of magnesium (0.041 g.-atom) and 15.0 g. (0.039 mole) of 2,4,6-triphenylbromobenzene by the method of Kohler and Blanchard.[8] To the refluxing Grignard solution was added dropwise 6.0 g. (0.039 mole) of phenylacetyl chloride dissolved in 50 ml. of dry benzene. After the addition was complete, stirring was continued for 12 hr. at room temperature. The reaction mixture was poured onto a solution of 30 ml. of hydrochloric acid in 200 ml. of ice water and the layers separated. The organic layer was washed with two 100-ml. portions of 10% sodium hydroxide, water, and saturated calcium chloride solution. The solution was dried and concentrated. The residue was dissolved in ligroin and chromatographed through an alumina column. Petroleum ether eluted 2.7 g. (18%) of triphenylbenzene. From the benzene–petroleum ether (3:7) eluate was isolated 8.6 g. (52%) of a white solid, m.p. 121–124°. Recrystallization from benzene-ligroin produced small plates, m.p. 125–126°. The infrared spectrum showed a carbonyl band at 1702 cm.$^{-1}$ (ε 180) but the substance was inert toward 2,4-dinitrophenylhydrazine. The ultraviolet spectrum showed λ_{max} 245 mμ (log ε 4.64) with a shoulder at ca. 310 mμ (log ε 3.54).

Anal. Calcd. for $C_{32}H_{24}O$: C, 90.53; H, 5.70. Found: C, 91.26; H, 5.72.

1-(2,4,6-Triphenylphenyl)-2-phenylethanol. A solution of 4.0 g. (0.0094 mole) of 1-phenylacetyl-2,4,6-triphenylbenzene (XII) and 0.18 g. (0.0047 mole) of lithium aluminum hydride dissolved in 100 ml. of anhydrous tetrahydrofuran was stirred and refluxed under a stream of dry, oxygen-free nitrogen for 5 hr. Water was added to the reaction mixture, and the organic layer was decanted. The yellow gum obtained on concentration was dissolved in ligroin and chromatographed through an alumina column. The benzene-ligroin eluate yielded 1.7 g. (43% recovery) of starting material. Evaporation of the ether eluate produced 1.8 g. (45%) of a white solid, m.p. 137–140°. Recrystallization from ligroin gave small star-shaped crystals, m.p. 139–140°.

Anal. Calcd. for $C_{32}H_{26}O$: C, 90.10; H, 6.14. Found: C, 89.76; H, 5.96.

2,4,6-Triphenylstilbene. A single crystal of iodine was added to a solution of 1.62 g. (0.0038 mole) of 1-(2,4,6-triphenylphenyl)-2-phenylethanol dissolved in 35 ml. of toluene. After refluxing for 21 hr., the solution was poured onto aqueous sodium bisulfite until the iodine color disappeared. The toluene layer was separated, dried, and concentrated. From the residue separated 1.35 g. (87%) of a white solid, m.p. 158–161°. Recrystallization from ligroin yielded fluffy needles, m.p. 161.5–162.0°. The infrared spectrum showed a strong band at 973 cm.$^{-1}$ (*trans* double bond) and the ultraviolet spectrum showed λ_{max} 253 mμ (log ε 4.23) and λ_{max} 314 mμ (log ε 4.54).

Anal. Calcd. for $C_{32}H_{24}$: C, 94.08; H, 5.92. Found: C, 93.85; H, 5.91.

1-(2-Phenylethyl)-2,4,6-triphenylbenzene (XIII). A solution of 1.35 g. (0.0033 mole) of 2,4,6-triphenylstilbene and 0.2 g. of platinum oxide dissolved in 100 ml. of glacial acetic acid and 50 ml. of ethyl acetate was hydrogenated at four atmospheres for 3 hr. The filtered solution was concentrated to give 0.41 g. (30%) of a white solid, m.p. 123–127°. Recrystallization from petroleum ether yielded long needles, m.p. 130.0–130.5°. The same product was obtained by the reduction of 1-phenylacetyl-2,4,6-triphenylbenzene (XII) with zinc-amalgam,[36] hydrochloric acid, and toluene. The yield after refluxing for 130 hr. was 15%.

Anal. Calcd. for $C_{32}H_{26}$: C, 93.62; H, 6.38. Found: C, 93.42; H, 6.40.

Cyclization of 1-(2-phenylethyl)-2,4,6-triphenylbenzene (XIII). A mixture of 400 mg. (0.0016 mole) of tetrachloro-*o*-benzoquinone, 590 mg. (0.0015 mole) of 1-(2-phenylethyl)-2,4,6-triphenylbenzene, and 10 g. of naphthalene was heated at 145° for 24 hr. The solid mass was steam-distilled until the naphthalene was completely removed. The brown residue was dissolved in ligroin and chromatographed through an alumina column. From the ligroin eluate was recovered 360 mg. (61%) of 1-(2-phenylethyl)-2,4,6-triphenylbenzene (XIII). Evaporation of the benzene–petroleum ether (1:9) eluate produced 45 mg. (8%) of a white solid, m.p. 179.5–182°. A mixed melting point with XI showed no depression. The infrared spectra of these two samples were identical. A repetition of this reaction with slightly over two equivalents of tetrachloro-*o*-benzoquinone led to a 41% recovery of 1-(2-phenylethyl)-2,4,6-triphenylbenzene (XIII), and a 6% yield of XI. The discrepancy between these yields

(36) E. L. Martin in *Org. Reactions*, I, 163 (1942).

and the initial yield of XI may be due to slight steam volatility of 2,4,9-triphenylphenanthrene.

1,3-Diphenylfluorene. Reduction of 2.5 g. of 1,3-diphenylfluorenone[8] by the Huang-Minlon modification of the Wolff-Kishner reaction gave an oil which recrystallized on trituration with petroleum ether. Recrystallization from ligroin and petroleum ether yielded 1.7 g. of colorless needles, m.p. 118–119°. The infrared spectrum had a band at 2900 cm.$^{-1}$ (—CH_2—) and no carbonyl absorption, in contrast with 1,3-diphenylfluorenone which exhibited a C=O band at 1708 cm.$^{-1}$ (cyclopentenenone) and had no —CH_2— band.

Anal. Calcd. for $C_{25}H_{18}$: C, 94.30; H, 5.70. Found: C, 94.23; H, 5.83.

9-Benzyl-1,3-diphenylfluorene (XIV). Benzylation of 0.95 g. of 1,3-diphenylfluorene by the method of Sprinzak[38] furnished 0.9 g. of a product which was recrystallized from petroleum ether, m.p. 115–118°, mixed m.p., with 1,3-diphenylfluorene, 95–108°. The infrared spectrum differed considerably from the spectrum of 1,3-diphenylfluorene.

Anal. Calcd. for $C_{32}H_{24}$: C, 94.08; H, 5.92. Found: C, 94.33; H, 5.74.

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(38) Y. Sprinzak, *J. Am. Chem. Soc.*, **78**, 466 (1956).

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

1,3-Diphenyl-1,3-butadiene Dimers[1]

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Attempts to prepare 1,3-diphenyl-1,3-butadiene by dehydration of *trans*-2,4-diphenyl-3-buten-2-ol gave two solid dimers. Dimer I, the main product, was shown to be 4-*trans*-styryl-1,3,4-triphenylcyclohexene. Dimer II may be a stereoisomer. Dimer I was also obtained from 2,4-diphenyl-3-buten-1-ol.

In connection with work on the polymerization of phenylacetylene which might be expected to give, at least as an intermediate, a conjugated polyene with phenyl groups on alternate carbons, it was of interest to study conjugated polyenes possessing such a structure. The simplest such compound is 1,3-diphenyl-1,3-butadiene, which was unreported in the literature when our work began. It has since been prepared by the reaction of 2-phenyl-1,3-butadiene with benzenediazonium chloride.[3]

Whitby and Gallay[4] reported that the addition of benzalactophenone to methylmagnesium iodide at −10° gave a 70% yield of a compound, m.p. 167°, which had the composition and molecular weight of a dimer of 1,3-diphenylbutadiene; this compound possessed two double bonds on the basis of bromine addition. The 1,4-addition product, 1,3-diphenyl-1-butanone, was also isolated in 21% yield. Exact experimental details were not given.

In our hands the addition of benzalacetophenone to methylmagnesium iodide under nitrogen using conditions of temperature, etc., as nearly like those of Whitby and Gallay as their directions permitted gave a 60% yield of the 1,4-addition product and 27% of 4-benzoyl-1,3,5-triphenyl-1,3-hexadiene; none of the dimeric material could be isolated. These products are the same as were obtained from benzalacetophenone and methylmagnesium bromide.[5]

Reaction of benzalacetone with phenyllithium essentially as described by Cope and co-workers[6] gave *trans*-2,4-diphenyl-3-buten-2-ol. Dehydration of this carbinol under a variety of conditions gave a yellow gum from which were obtained by chromatography and recrystallization two solid dimers and 2–5% of yellow oily polymeric material. The optimum yield of a solid mixture of the dimers was 95–98%; dimer I, m.p. 137–138°, a crystalline white solid, was readily isolated in 40–50% yield, but dimer II, m.p. 125–126°, an amorphous white solid, was more difficult to purify and may not have been obtained completely pure. A mixture of the two dimers melted over the range 124–135° and the ultraviolet spectra differed only slightly in the intensity of the absorption at the principal band (λ_{max} 254 mμ, dimer I, ε 35200; dimer II, ε 36000). The infrared spectra of the dimers were identical except for the presence of two additional weak bands at 888 and 1000 cm.$^{-1}$ in the spectrum of di-

(1) This report is taken from a dissertation submitted by Marvin H. Goodrow to the graduate school of the University of California, Los Angeles, in partial fulfillment of the requirements for the Ph.D. degree, August 1956. The material was presented at the San Francisco meeting of the American Chemical Society, April 1958 (Abstracts of that meeting, p. 78-N). At that meeting Dr. Werner Herz informed us that he and E. Lewis had also investigated this problem; his results will be found in this issue, *J. Org. Chem.*, **23**, 1646 (1958).

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(3) A. V. Dombrovskii, *Doklady Akad. Nauk S.S.S.R.*, **111**, 827 (1956); *Chem. Abstr.*, **51**, 9507 (1957).

(4) G. S. Whitby and W. Gallay, *Can. J. Research*, **6**, 280 (1932).

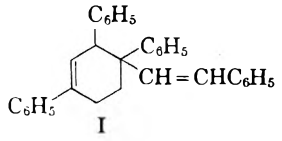
(5) M. S. Kharasch and D. C. Sayles, *J. Am. Chem. Soc.*, **64**, 2972 (1942).

(6) A. C. Cope, E. L. Wick, and F. S. Fawcett, *J. Am. Chem. Soc.*, **76**, 6156 (1954).

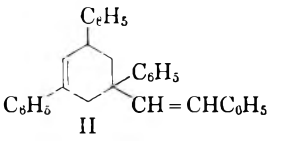
mer II. The best evidence that these dimers are different arises from chromatography experiments: Dimer II is more tightly held on alumina, and during elution an intermediate, low melting mixture comes off between the dimers. It is possible that these two dimers are stereoisomers.

Preliminary attempts were also made to synthesize 1,3-diphenyl-1,3-butadiene from 2,4-diphenyl-3-buten-1-ol.[7] The carbinol was prepared by reduction of methyl 2,4-diphenyl-3-butenoate with lithium aluminum hydride, but the product was a mixture containing approximately 18% of unchanged ester. Attempts to purify the alcohol by saponification of the ester were not successful, but some of the alcohol was apparently dehydrated in the process since a low yield of dimer I was isolated from the reaction mixture. The 3,5-dinitrobenzoate of 2,4-diphenyl-3-buten-1-ol was prepared, but attempts to pyrolyze the very small amounts of this derivative that were available yielded neither the diene nor its dimer.

trans-1,3-Diphenyl-1,3-butadiene would be expected to dimerize by a Diels-Alder reaction to give one of structures I–IV. By analogy with the be-



I



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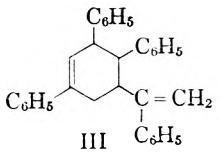
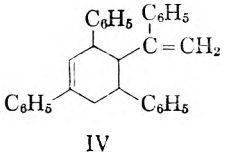


III



IV

havior of other 1,3-disubstituted butadienes,[8,9] of 1-phenyl-1,3-butadiene[10] and of 2-phenyl-1,3-butadiene,[11] I would be the most probable structure.

Dimer I, although somewhat resistant to hydrogenation, gave a tetrahydro derivative with the ultraviolet and infrared spectra expected for a tetrahydro derivative of I–IV. Partial hydrogenation with absorption of one mole of hydrogen or reduction with hydroiodic acid gave impure dihydro derivatives that could not be purified successfully. An attempt to rearrange the double bonds in dimer I by refluxing for 16 hr. in ~0.9*M* sodium ethoxide in ethanol was unsuccessful. The dimer absorbed bromine in carbon tetrachloride very slowly. A Kuhn-Roth determination showed that C—methyl groups were absent.

The infrared spectrum of dimer I is that expected for structure I and makes structures III and IV unlikely. The absence of a band in the 1420–1410 cm.$^{-1}$ region, characteristic of in-the-plane deformation of the CH_2 of $RR'C = CH_2$[12] is a significant feature. Although there is a weak band at 905 cm.$^{-1}$ not far from the position expected for the out-of-plane deformation band of the CH_2 group of $R_1R_2C = CH_2$ (892–887 cm.$^{-1}$), such a band should be strong if the group $= CH_2$ were present. A weak band at 1635 cm.$^{-1}$ and a medium band at 1595–1600 cm.$^{-1}$ might be expected for phenyl conjugated double bonds. Very strong bands at 690 and 735 cm.$^{-1}$ as well as four evenly spaced bands in the 2000–1700 cm.$^{-1}$ region suggest the presence of only mono-substituted phenyl groups.[13] A strong band at 968 cm.$^{-1}$ indicates that one of the two double bonds is *trans*. The ultraviolet spectrum of dimer I shows typical β-substituted styrene absorption with the principal maximum at 254 mμ (log ϵ 4.546) and a small but sharp side peak at 294 mμ (log ϵ 3.250). The principal band has several small inflections and one small side peak at 271 mμ (log ϵ 4.342). The position of the principal maximum and the high extinction coefficient indicate that both double bonds are present as styryl functions, and a comparison with the spectrum of *trans*-1,3-diphenyl-1-butene,[14] which displays maxima at 294 (log ϵ 3.100), 286 (log ϵ 3.240), and 253 mμ (log ϵ 4.250), suggests that the dimer contains two 1,3-diphenyl-1-butene systems. The ultraviolet absorption is evidence against structures III and IV because the α-substituted styryl chromophore absorbs in the 242–244 mμ region and has extinction coefficients lower than 10,000.[15,16]

The evidence discussed above makes structures III and IV improbable, but does not permit a choice between structures I and II. Dimer I is somewhat resistant to oxidative degradation except under conditions so vigorous that benzoic acid is the principal product. Ozonization followed by either reductive or oxidative decomposition of the ozonide gave up to 5% yields of 1,2-dibenzoylethane in addition to benzoic acid, polymeric material, and small amounts of carbonyl compounds which were never isolated as pure compounds in sufficient amounts for structural determination. Structure II cannot give 1,2-dibenzoylethane without an unlikely rearrangement; structure I is therefore believed to be correct for dimer I, although the results of dehydrogenation studies described below tend to confuse the matter.

(7) These experiments were carried out by E. Staggs, *An Attempted Synthesis of 1,3-Diphenyl-1,3-butadiene*, M.S. thesis, University of California, Los Angeles, June 1955.

(8) K. Alder and W. Vogt, *Ann.*, **564**, 120 (1949).

(9) J. S. Meek and J. W. Ragsdale, *J. Am. Chem. Soc.*, **70**, 2502 (1948).

(10) K. Alder, J. Haydn, and W. Vogt, *Chem. Ber.*, **86**, 1302 (1953).

(11) K. Alder and J. Haydn, *Ann.*, **570**, 201 (1950).

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

(13) C. W. Young, R. B. Du Vall, and N. Wright, *Anal. Chem.*, **23**, 709 (1951).

(14) M. Grumez, *Ann. chim* [11], **10**, 378 (1938).

(15) American Petroleum Institute Research Project No. 44, Ultraviolet Spectral Data, Carnegie Institute of Technology, June 30, 1952, No. 119.

(16) Y. Hirschberg, *J. Am. Chem. Soc.*, **71**, 3241 (1949).

Sulfur dehydrogenation of dimer I gave a mixture which was difficult to separate. Pure 1,3,5-triphenylbenzene and a sulfur-containing compound, $C_{18}H_{14}S$, whose structure was not determined, were isolated by chromatography. Dehydrogenation over a palladium-on-carbon catalyst at 300° gave ethylbenzene, 1,3,5-triphenylbenzene, and small amounts of 1,2,4-triphenylbenzene. It was difficult to separate the unsymmetrical derivative from the symmetrical, and the former was not isolated in a completely pure state, but melted at 96–99.5°. Pure 1,2,4-triphenylbenzene, prepared for comparison,[17] melted at 101.5–102°. A mixture melted between these values. The ultraviolet and infrared spectra indicated that the compound from the dehydrogenation was mainly *uns*-triphenylbenzene contaminated with small amounts of the *sym.* isomer. An attempt to isomerize the *uns.* to the *sym.* compound under the conditions of the dehydrogenation was unsuccessful. Dehydrogenation of dimer I with chloranil was not attempted at first because when this dehydrogenation was applied to dimer II, only very low yields of crystalline products were obtained. After learning that Herz and Lewis had obtained 2,3,5-triphenylstilbene from dimer I by dehydrogenation with tetrachloro-o-benzoquinone, we dehydrogenated dimer I with chloranil and isolated 34% of 2,3,5-triphenylstilbene, m.p. 176–179°.

Dimer II was not investigated in any detail. Its spectra are very similar to those of dimer I, and catalytic dehydrogenation gave ethylbenzene and 1,3,5-triphenylbenzene. Hydrogenation with Adams' catalyst gave mixtures of dihydro compounds as with dimer I; the more active catalyst which gave the tetrahydro derivative with dimer I was not tried with dimer II.

Dehydrogenation with chloranil gave mixtures from which very low yields of two crystalline products were isolated. The first of these, m.p. 81–82°, had approximately the composition and molecular weight of $C_{32}H_{26}$; the second, m.p. 179–179.5° also gave an unsatisfactory analysis which corresponded to $C_{32}H_{26}$. In the light of the results obtained by Herz and Lewis, this second material was probably 2,3,5-triphenylstilbene.

On the basis of the above evidence it is concluded that dimer I is 4-*trans*-β-styryl-1,3,4-triphenylcyclohexene, I. Dimer II may be a stereoisomer. The rearrangement that occurs during the dehydrogenation is interesting and has been discussed in greater detail by Herz and Lewis[1] and in the thesis of Marvin H. Goodrow.[1]

EXPERIMENTAL[18]

The reaction of benzalacetophenone with methylmagnesium iodide. To 3.9 g. (0.16 g.-atom) of magnesium turnings in a 200-ml. flask was added dropwise under nitrogen with stirring 6.9 ml. (0.17 mole) of methyl iodide in 75 ml. of anhydrous ether so that the mixture refluxed gently. After the addition, the mixture was refluxed for 30 min., cooled, and 15.3 g. (0.074 mole) of benzalacetophenone in 100 ml. of anhydrous ether was added dropwise with vigorous stirring. The reaction mixture was kept at −12° to −7° throughout the addition, then allowed to warm to room temperature and decanted into 100 ml. of a solution containing 10% sulfuric acid and 50 g. of ice. The ethereal solution was separated, washed with 5% sodium hydroxide, 5% sodium bisulfite, and water, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to give a light yellow gum. This gum was dissolved in 300 ml. of ether and the solution cooled to −80° to yield 9.0 g. (60%) of light yellow 1,3-diphenyl-1-butanone. Long white crystals, m.p. 72–73° were obtained after several recrystallizations from ethanol (reported[5] m.p. 72°). These were sublimed at 60–70° and 1 to 2 mm. before analysis.

Anal. Calcd. for $C_{16}H_{16}O$: C, 85.67; H, 7.19. Found: C, 85.48; H, 7.14.

Infrared spectrum (10% solutions in carbon tetrachloride and carbon disulfide): strong bands at 3065, 3030, 2960, 1691, 1600, 1587, 1500, 1457, 1272, 1217, 1203, 1180, 1101, 990, 749, 695, and 686 cm.$^{-1}$ Ultraviolet spectrum (in ethanol): λ_{max} 276–278 (log ϵ 3.00), 243 mμ (log ϵ 4.123).

The ethereal filtrate was concentrated to half volume and allowed to stand for several days. A powder separated and was recrystallized from ethanol to give 4.4 g. (27%) of 4-benzoyl-1,3,5-triphenyl-1,3-hexadiene, m.p. 177–178° (reported[5] 176°). As reported earlier,[5] difficulties were encountered in the analysis.

Anal. Calcd. for $C_{34}H_{26}O$: C, 89.83; H, 6.28. Found: C, 89.23, 89.16, 89.10; H, 7.52, 7.27, 7.21.

Infrared spectrum (10% solutions in carbon tetrachloride and carbon disulfide): strong bands at 1650, 1600, 1498, 1455, 1358, 1273, 1157, 1102, 1076, 1067, 1050. 1030, 1016, 760, 741, and 695 cm.$^{-1}$ Ultraviolet spectrum (in ethanol): λ_{max} 265 (log ϵ 4.068), λ_{min} 240 mμ (log ϵ 3.709).

trans-1,3-Diphenylbuten-1-ol-3. The procedure of Cope[6] was employed and the alcohol obtained in 84–89% yield, m.p. 57.0–57.8° (reported 57.2–58.0°). The ultraviolet spectrum in 95% ethanol showed λ_{max} 292 (log ϵ 3.098), 284 (log ϵ 3.295), and 252 mμ (log ϵ 4.328). Infrared spectrum (6% solution in carbon tetrachloride and 7% solution in carbon disulfide): strong bands at 3550, 3420, 3020, 3005, 2950, 1597, 1494, 1450, 1370, 1325 (broad), 1160, 1095, 1065, 1028, 968. 762, 746, and 689 cm.$^{-1}$ The band at 968 cm.$^{-1}$ gives evidence that the double bond is *trans*.[12]

The residue that remained in the flask after distilling the alcohol was chromatographed on neutral alumina and eluted with 20% ether–80% pentane to give a yellow oil. The ultraviolet spectrum of this oil in 95% ethanol showed a strong maximum at 251.5 mμ and a weak maximum at 292 mμ; minima were observed at 291 and 232 mμ.

Dehydration of trans-1,3-diphenylbuten-1-ol-3. A. With acetic anhydride. Twenty grams (0.09 mole) of the alcohol was refluxed for 8 hr. with 10 g. of acetic acid and 20 g. of acetic anhydride. Thereafter, the solution was concentrated and the yellow residue (a gum) was chromatographed on neutral activated alumina. A white solid was obtained (96% yield) by eluting with 10% ether-pentane. Crystallization from 95% ethanol at room temperature provided 7.8 g. (42%) of a crystalline product which when further purified had a melting point of 137.0–138.0°.

Anal. Calcd. for $C_{32}H_{28}$: C, 93.16; H, 6.84; mol. wt. 412. Found: C, 92.95; H, 6.92; mol. wt. 424 (cryoscopic in benzene).

(17) F. R. Japp and N. H. J. Miller, *J. Chem. Soc.*, **47**, 11 (1885).

(18) Melting points were taken with total immersion Anschutz thermometers but otherwise not corrected. Analyses were carried out by Miss Heather King. Infrared spectra were determined on a Perkin-Elmer Model 21 instrument with sodium chloride prism and ultraviolet spectra on a Cary Recording Spectrophotometer, Model 11.

Infrared spectrum (10% solutions in carbon tetrachloride and carbon disulfide). In addition to the bands described in the discussion above, the following strong bands were observed: 3050, 3020, 2915, 1495, 1448–1455, 1075, and 1030 cm.$^{-1}$

The filtrate from the crystallization of the above dimer (Dimer I), when placed in the refrigerator overnight, deposited 5.9 g. (32%) of a white amorphous solid, m.p. 124–126°. One gram of this material was chromatographed on neutral activated alumina and eluted with 10% ether-pentane to give an 0.4 g. fraction of dimer melting at 124.5–127.5°. Several recrystallizations of this fraction from 95% ethanol provided a pure sample of the second dimer (Dimer II), m.p. 125.0–126.0°.

Anal. Calcd. for $C_{32}H_{28}$: C, 93.16; H, 6.84; mol. wt. 412. Found: C, 93.17; H, 6.87; mol. wt. 396 (Rast).

Additional dimer I was isolated from this chromatogram which brought the total yield of this compound to 50%. The mixed melting point of dimers I and II was 124–135°.

B. With iodine. trans-1,3,-Diphenylbuten-1-ol-3, 3.22 g. (0.002 mole), 35 mg. of iodine and 300 ml. of toluene were refluxed for 7 hr. The toluene solution was washed with saturated sodium bisulfite solution and water, and dried. After concentration of the solution, there remained a yellow residue which was chromatographed on neutral alumina and yielded 2.95 g. (98%) of a white solid. Crystallization from 95% ethanol at room temperature gave 1.23 g. (42%) of dimer I, m.p. 137–138°, and upon cooling, 0.90 g. (31%) of crude dimer II.

C. With phosphorus trichloride. To a solution of 5.0 g. (0.0223 mole) of the *trans* alcohol in 20 ml. of dry pyridine was added slowly 3.15 g. (0.0229 mole) of phosphorus trichloride while maintaining the temperature at 0–5°. The mixture was stirred for 30 min. and then 100 g. of ice was added. The organic material was extracted with 100 ml. of ether and the ethereal layer was washed thoroughly with water and dried. Removal of the ether provided a yellow oil which was chromatographed on neutral alumina to yield dimer I as the only apparent product.

Hydrogenation of dimer I. Catalytic reduction of 0.700 g. (0.002 mole) of dimer I with Baker's 10% palladium-on-carbon in 20 ml. of ethyl acetate resulted in the absorption of 1.97 moles of hydrogen per mole of dimer. The solution was filtered through Celite and the solvent removed. Crystallization of the oily residue from 95% ethyl alcohol gave 0.62 g. (88%) of transparent needles, m.p. 119–120°.

Anal. Calcd. for $C_{32}H_{32}$: C, 92.26; H, 7.74. Found: C, 92.04; H, 7.89.

Infrared spectrum (15% solutions in carbon tetrachloride and cyclohexane): strong bands at 3057, 3026, 2930, 2865, 1600, 1495, 1475, 1450, 1068, 1030, 745, and 693 cm.$^{-1}$ Ultraviolet spectrum (ethanol) similar to that of *tert.* butylbenzene: λ_{max} 268.5 (log ϵ 2.757), 264.5 (log ϵ 2.838), 259 (log ϵ 2.947), 253.5 (log ϵ 2.863) and 248.5 mμ (log ϵ 2.718); $\lambda_{infl.}$ 261 (log ϵ 2.907) and 243 mμ (log ϵ 2.521).

Catalytic dehydrogenation of dimer I. A mixture of 2.00 g. of dimer I and 400 mg. of 10% palladium-on-carbon was heated at 300° for 2 hr. The residue was taken up in ether and the catalyst removed by filtration. The filtrate was concentrated by heating under reduced pressure and the yellow residue chromatographed on neutral alumina. The first fraction was eluted with pentane and consisted of 347 mg. of crude ethyl benzene which was identified by its infrared and ultraviolet spectra. The material (730 mg.) eluted with 4% ether-pentane crystallized upon evaporation of the solvent, m.p. 173–175°. This material proved to be 1,3,5-triphenylbenzene by a comparison of melting points and spectra with authentic material prepared according to Bernhauer.[19]

With further evaporation of the solvent from the above filtrate there was deposited an amorphous solid (about 20 mg.), m.p. 96–99.5°. This material proved to be 1,2,4-triphenylbenzene with trace amounts of the symmetrical isomer from which it was inseparable. The ultraviolet spectrum (in ethanol) of this material is identical with that of authentic 1,2,4-triphenylbenzene,[17] m.p. 101.5–102°. It has a maximum at 249 mμ, a minimum at 228 mμ. and high absorption in the range 280–325 mμ; by contrast 1,3,5-triphenylbenzene displays a maximum at 252 mμ, a minimum at 225 mμ, and absorption that falls considerably more rapidly in the range 260–325 mμ. The infrared spectra of authentic 1,3,5- and 1,2,4-triphenylbenzene and of the material m.p. 96–99.5° were determined in potassium bromide disks. The latter had all of the bands of the 1,2,4-isomer and weak bands corresponding to the strongest unique peaks of the 1,3,5-isomer. Particularly significant were bands at 1473, 1442, 1385, 1006, 895, and 835 cm.$^{-1}$ which are shown by the 1,2,4-isomer but not by the 1,3,5-isomer. Peaks at 1493, 1410, 910, and 876 cm.$^{-1}$ show that the impurity is the 1,3,5-compound.

Dehydrogenation of dimer I with sulfur. One gram of dimer I and 155 mg. of sulfur were mixed and immersed in a Wood's metal bath at 125°. The temperature was raised until the evolution of hydrogen sulfide commenced (260°) and then increased slowly and maintained at 270° for 30 min. The amount of hydrogen sulfide evolved was 0.8 mole per mole of dimer. The residue was chromatographed several times on neutral alumina with no success in resolving the components. Concentration and crystallization from ether-pentane of the combined fractions from the unsuccessful chromatogram eventually gave 145 mg. of 1,3,5-triphenylbenzene, m.p. 175.5–176.6°. Crystallization of the residue obtained from this filtrate from methanol then gave 66 mg. of an amorphous sulfur-containing compound, m.p. 107–109°. An analytical sample was prepared by recrystallization from methanol with considerable loss to give colorless crystals, m.p. 110.5–111.5°.

Anal. Calcd. for $C_{18}H_{14}S$: C, 82.40; H, 5.38. Found: C, 82.77; H, 5.39.

Dehydrogenation of dimer I with chloranil. A solution of 2.00 g. (0.0048 mole) of dimer I and 3.00 g. (0.012 mole) of chloranil in 35 ml. of benzene was heated under reflux for 24 hr. The solution was then cooled, diluted with an equal volume of pentane, and concentrated after filtering the insoluble material. The resulting brown residue was chromatographed on alumina using 5% ether-petroleum ether (b.p. 30–60°) to elute the column. Upon evaporation of the solvent there remained 670 mg. (34%) of crude 2,3,5-triphenylstilbene, m.p. 176–179°. An analytical sample was obtained by three recrystallizations from ether to yield small white needles, m.p. 180.5–181.5°.

Anal. Calcd. for $C_{32}H_{24}$: C, 94.08; H, 5.92. Found: C, 93.96; H, 5.93.

Terminal methyl determination on dimer I, when carried out by conventional methods[20,21] gave values ranging from 0.97 to 1.44 methyl groups. This would be expected from styryl derivatives.[22] Dr. C. W. Koch[23] found a value of 0.2 by a variation of the Kuhn-Roth procedure which involves a 20-hr. digestion period with chromic anhydride–sulfuric acid solution. Essentially all of the benzoic acid is destroyed by this procedure.

Oxidation of dimer I *with potassium permanganate.* To a solution of 2.0 g. (0.002 mole) of dimer I in 50 ml. of pyridine, was added 4.08 g. (0.03 mole) of potassium permanganate in 50 ml. of water over a period of 3 hr. The mixture had to be heated to 45° where it reacted at a mod-

(19) K. Bernhauer, P. Müller, and F. Neiser, *J. prakt. Chem.* (2), **145**, 301 (1936).

(20) R. Kuhn and F. L'Orsa, *Z. angew. Chem.*, **44**, 847 (1931).

(21) W. F. Barthel and F. B. La Forge, *Ind. Eng. Chem., Anal. Ed.*, **16**, 434 (1944).

(22) E. J. Eisenbraun, S. M. McElvain, and B. F. Aycock, *J. Am. Chem. Soc.*, **76**, 607 (1954).

(23) We wish to thank Dr. Koch, University of California, Berkeley, for this determination.

erate speed. Solid sodium bisulfite was added to decompose the manganese dioxide and the solution was steam distilled to remove the pyridine. The residue was extracted with ether and the ether layer was extracted with dilute base. The basic extract was worked up in the usual manner to yield 560 mg. of crystalline benzoic acid, m.p. 123.2–124.2°. The mixed melting point with authentic benzoic acid was undepressed.

The neutral material from the oxidation was chromatographed on neutral alumina to separate 863 mg. of a yellow crystalline material. This was crystallized from methanol-ether mixtures for analysis, m.p. 206.0–207.2°.

Anal. Calcd. for $C_{32}H_{26}O_4$: C, 80.99; H, 5.52. Found: C, 81.05; H, 5.48.

The infrared spectrum suggested that this compound contained a hydroxyl function (3525 cm.$^{-1}$) and an *alpha-beta*-unsaturated ketone (1692 cm.$^{-1}$). Its identity could not be determined.

Oxidation experiments using more vigorous conditions always resulted in degradation of the dimer to benzoic acid and inseparable, unidentifiable oils.

Oxidation of dimer I *with acidic potassium permanganate.* To 1.00 g. (0.002 mole) of dimer I in 50 ml. of nitrobenzene was added over a period of 2 hr. a solution containing 11.3 g. of potassium permanganate, 13 ml. of concentrated sulfuric acid, and 90 ml. of water. After stirring this mixture for 4 hr. at room temperature, sodium bisulfite was added to remove the manganese dioxide; the solution was then made basic with 6*N* sodium hydroxide and steam distilled to remove the nitrobenzene. The residue was worked up in the usual way to give 25 mg. of crude benzoic acid, m.p. 115–118°. The neutral material was chromatographed on neutral alumina to give 50 mg. of a white solid. Crystallization from 95% ethanol provided 10 mg. of a white crystalline product, m.p. 187°.

Anal. Calcd. for $C_{17}H_{14}O$: C, 87.14; H, 6.02. Found: C, 86.98; H, 5.99.

The infrared spectrum indicated that this compound had the structure of an *alpha-beta*-unsaturated, five-membered ring ketone. The small amount of this material precluded further examination.

Ozonization of dimer I, *oxidative decomposition.* A solution of 4.12 g. (0.01 mole) of dimer I in 70 ml. of chloroform was ozonized with excess ozone. The chloroform solution was then shaken for 48 hr. with 30 ml. of water and 7.5 ml. of 30% hydrogen peroxide. Thereafter, the organic material was separated and extracted with 1% sodium hydroxide. Acidification of this basic solution and continuous extraction with ether for 16 hr. provided 248 mg. of a yellow solid. This solid was chromatographed on silicic acid to remove the yellow impurity, and sublimed to yield 61 mg. of benzoic acid, m.p. 121–122°, neutralization equivalent 126. The mixed melting point with authentic material was not depressed.

The neutral organic fraction from above was concentrated and chromatographed on neutral alumina.

Fraction 1 (360 mg.), eluted with ether, was a yellow oil from which 30 mg. of a white solid, m.p. 74.5–75.5°, was obtained when it was dissolved in 95% ethanol.

Anal. Calcd. for $C_{25}H_{22}O$: C, 88.72; H, 6.55. Found: C, 88.73; H, 6.43.

The infrared spectrum suggested that this compound contained a carbonyl group; however, the small amounts precluded a careful examination of its structure.

Fraction 2 (300 mg.), eluted with 1% methanol-ether, deposited a white crystalline solid upon evaporation of the solvent. Crystallization from ether yielded 72 mg. of 1,2-dibenzoylethane, m.p. 147.0–147.4°. Literature[24] m.p. 145–147°. A mixed melting point with authentic material was undepressed.

Anal. Calcd. for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92; mol. wt. 238. Found: C, 80.70; H, 6.24; mol. wt. 231 (Rast).

The ultraviolet spectrum, λ_{max} 279 mμ (log ϵ 3.330) and 244 mμ (log ϵ 4.423) was identical with that in the literature.[25]

Fraction 3 (883 mg.), eluted with 2% methanol-ether and fraction 4 (813 mg.), eluted with methanol, were yellow oils which resisted crystallization and purification. Both gave positive carbonyl tests with 2,4-dinitrophenylhydrazine.

Ozonization of dimer I; *reductive decomposition.* A solution of 4.12 g. of dimer I in 50 ml. of ethyl chloride was ozonized with an excess of ozone. The solvent was removed and 15 ml. of chloroform and 5 ml. of glacial acetic acid were added. The ozonide was decomposed with zinc dust. The solution was then filtered, washed with 2% sodium bicarbonate solution, and dried. There remained 4.44 g. of a yellow viscous oil which was chromatographed on neutral alumina.

Fraction 1 (300 mg.), eluted with ether, was a yellow oil. This was rechromatographed on neutral alumina to yield two major fractions; neither could be induced to crystallize. Each fraction was converted to its 2,4-dinitrophenylhydrazine derivative. The first compound was crystallized from ethanol with considerable loss of material to give 5 mg. of derivative, m.p. 184–186°.

Anal. Calcd. for $C_{28}H_{23}O_4N_4$: C, 70.13; H, 4.83. Found: C, 70.42; H, 4.83.

This analysis corresponded to a carbonyl compound with the formula $C_{22}H_{20}O$. Its structure was not determined.

It was necessary to chromatograph the second 2,4-dinitrophenylhydrazone on neutral alumina to obtain a product with an acceptable melting point. From the chromatograph was obtained 13 mg. of product which was crystallized from 95% ethanol for analysis, m.p. 99–101°.

Anal. Calcd. for $C_{29}H_{26}O_4N_4$: C, 70.43; H, 5.30. Found: C, 70.66; H, 5.27.

The above analysis corresponded to a carbonyl compound with the formula $C_{23}H_{22}O$; however, its structure was not elucidated.

Fraction 2 (125 mg.), eluted with 2% methanol-ether, proved to be 1,2-dibenzoylethane as determined by its melting point and mixed melting point with authentic material.

Fraction 3 (1.175 g.), eluted with 4% methanol-ether, was the same polymeric material as obtained in the oxidative decomposition and remained an inseparable mixture.

2,4-Diphenyl-3-butenoic acid.[7] 1,3-Diphenyl-2-propanol was prepared by reducing 1,3-diphenyl-2-propanone with magnesium and methanol[26] or with lithium aluminum hydride. This alcohol has been dehydrated to 1,3-diphenylpropene by several methods.[27–31] In our work it was dehydrated by heating with and then distilling from potassium acid sulfate, but the product was not easily purified and crude yields were only 44–79%; the product after redistillation had a b.p. of 184–185°/20 mm., n_D^{25} 1.5932.

The olefin was converted to its sodium derivative by reaction with amylsodium in *n*-pentane by a procedure used for phenylallylsodium,[32] and carbonation was accomplished by siphoning the slurry of organometallic compound onto excess

(24) P. S. Bailey and R. E. Lutz, *J. Am. Chem. Soc.*, **70**, 2412 (1948).

(25) L. P. Kuhn, R. E. Lutz, and C. R. Bauer, *J. Am. Chem. Soc.*, **72**, 5058 (1950).

(26) L. Zechmeister and P. Rom, *Ann.*, **468**, 117 (1929).

(27) W. Dieckmann and H. Kammerer, *Ber.*, **39**, 3046 (1906).

(28) P. Ramart and P. Amagat, *Ann. chim.* [10] **8**, 263 (1926).

(29) A. P. Golovchanskaya, *Zhur. Obshcheĭ Khim.*, **16**, 1243 (1946); *Chem. Abstr.*, **41**, 3082 (1947).

(30) F. E. Francis, *J. Chem., Soc.*, **75**, 865 (1899).

(31) M. Tout and M. Guyard, *Bull. soc. chim. France*, **14**, 1086 (1947).

(32) R. Y. Mixer and W. G. Young, *J. Am. Chem. Soc.*, **78**, 3379 (1956).

Dry Ice. The reaction mixture was worked up by conventional methods, but the yield of 2,4-diphenyl-3-butenoic acid, m.p. 123.5–124.5°, was only 9%. Recrystallization from ligroin (b.p. 90–95°) gave pure acid, m.p. 125–126°.

Anal. Calcd. for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92, neutral equivalent, 238.3. Found: C, 80.71; H, 6.06; neutral equivalent, 243. Ultraviolet spectrum (95% ethanol): λ_{max} 252 (log ϵ 4.352), 283.5 (log ϵ 3.318), 292.5 mμ (log ϵ 3.121).

This acid is relatively stable to a temperature of 150° for a short time, but after heating at 100–115° for 2 hr. in a capillary tube, the m.p. was 118–119°.

Methyl 2,4,-diphenyl-3-butenoate was prepared from the acid with diazomethane; after recrystallization from ethanol at low temperatures, the ester melted at 35–36°.

Anal. Calcd. for $C_{17}H_{16}O_2$: C, 80.92; H, 6.39. Found: C, 80.71; H, 6.37.

2,4-Diphenyl-3-buten-1-ol.[7] Methyl 2,4-diphenyl-3-butenoate was reduced with excess lithium aluminum hydride in ether, the reaction mixture worked up as usual and the product distilled, b.p. 175–185°/1.4 mm. The yield was 70%, but the distillate was a mixture containing about 82% of 2,4-diphenyl-3-buten-1-ol on the basis of combustion analysis. The infrared spectrum was that expected of such a mixture.

Attempts were made to remove the ester by saponification with aqueous methanolic potassium hydroxide or sodium ethylate, but neutral material recovered from the reaction still gave a low carbon analysis even though the ester group appeared to have disappeared on the basis of the infrared spectrum. The product was a viscous red oil which deposited a solid. The solid was purified by chromatography on neutral, activated alumina and recrystallization from alcohol, m.p. 137–138°. It was shown to be dimer I by analysis, ultraviolet absorption and a mixed melting point determination. The yield was about 10% based on 2,4-diphenyl-3-buten-1-ol in the reaction mixture used.

The residual red oil would not distill below 200° at 1 to 2 mm., and did not give a correct analysis for 2,4-diphenyl-3-buten-1-ol.

Crude 2,4-diphenyl-3-buten-1-ol from the lithium aluminum hydride reduction was treated with 3,5-dinitrobenzoyl chloride in pyridine and gave a 3,5-dinitrobenzoate in 27% yield, m.p. 125–126° after recrystallization from aqueous acetone.

Anal. Calcd. for $C_{23}H_{18}O_6N_2$: C, 66.02; H, 4.34. Found: C, 66.28; H, 4.23.

The small amount of the 3,5-dinitrobenzoate that was available was pyrolyzed under nitrogen, but neither 1,3-diphenyl-1,3-butadiene nor its dimer was obtained.

Crude 2,4-diphenyl-3-buten-1-ol was refluxed with 2.5*N* aqueous alcoholic sulfuric acid but no dimer was obtained.

Although the experiments described here are only preliminary, this method to 1,3-diphenyl-1,3-butadiene does not appear promising and further work in this direction is not planned.

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[Contribution from the Noyes Chemical Laboratory, University of Illinois]

2-Phenyl-1,3-butadiene and Related Compounds[1]

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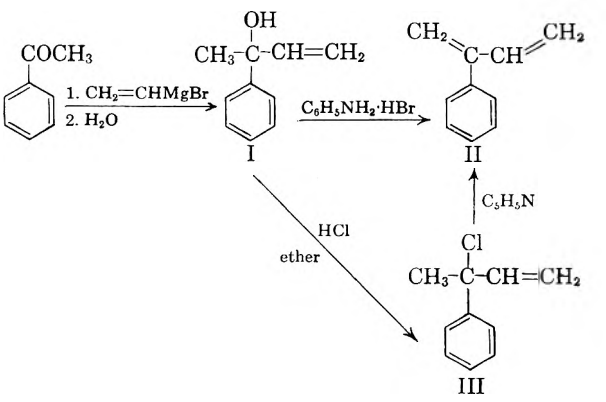
2-Phenyl-1,3-butadiene (II) has been prepared from acetophenone and vinylmagnesium bromide in a two-step synthesis. The synthesis and properties of several new and related compounds are given.

Recently, Normant discovered[2] that vinylmagnesium bromide could be prepared and used in reactions quite easily in tetrahydrofuran solvent. This work suggested a convenient route for the synthesis of 2-aryl-substituted dienes which are sometimes difficult to obtain in good yield by other methods. Thus, treatment of acetophenone with vinylmagnesium bromide gave methylphenylvinylcarbinol (I) in 75% yield. This carbinol (I) has been prepared previously by reaction[3] of acetophenone and the di-Grignard reagent of diacetylene, followed by hydrolysis and catalytic hydrogenation,[4] and by the action[5] of phenylmagnesium bromide on methyl vinyl ketone. However, the present method produced considerably better yields than previously reported. Dehydration of the carbinol (I) by slow distillation from aniline hydrobromide gave 2-phenyl-1,3-butadiene (II) in 61% yield. This represents an over-all yield of 46% from acetophenone for a two-step synthesis, and is possibly the best route presently available for preparing 2-phenyl-1,3-butadiene. All previous methods[6] involved numerous steps or poor yields or both. Treatment of methylphenylvinylcarbinol with an-



(1) The work discussed herein was supported by a grant from the National Science Foundation for polymer research.

(2) H. Normant, *Compt. rend.*, **239**, 1510 (1954).

(3) Yu. S. Zal'kind and A. P. Ivanov, *Zhur. Obshcheĭ Khim.*, **11**, 803 (1941); *Chem. Abstr.*, **36**, 3700 (1942).

(4) Kh. V. Bal'van, *Zhur. Obshcheĭ Khim.*, **24**, 501 (1954); *Chem. Abstr.*, **49**, 6174 (1955).

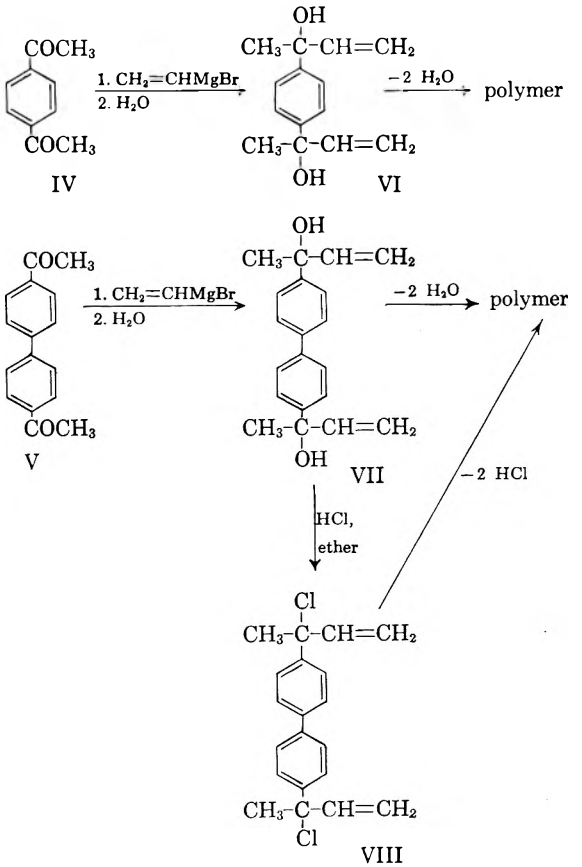
(5) A. I. Lebedeva and V. A. Shlyakova, *Zhur. Obshcheĭ Khim.*, **19**, 1290 (1949); *Chem. Abstr.*, **44**, 1054 (1950).

(6) J. E. Faraday, *Faraday's Encyclopedia of Hydrocarbon Compounds*, Chemindex Ltd., Manchester, England, 1954, Volume 5.

hydrous hydrogen chloride in ether produced methylphenylvinylchloromethane (III) in 50.5% yield. Dehydrohalogenation of this chloro-compound (III) with pyridine produced 2-phenyl-1,3-butadiene (II) in only 36% yield, however.

In an effort to extend this apparently general method to the synthesis of difunctional dienes, reactions were run on *p*-diacetylbenzene (IV) and *p,p'*-diacetylbiphenyl (V). Reaction of vinylmagnesium bromide with *p*-diacetylbenzene (IV) produced *p*-phenylenebis(methylvinylcarbinol) (VI) in 67% yield. A similar reaction with *p,p'*-diacetylbiphenyl (V) gave *p,p'*-biphenylenebis(methylvinylcarbinol) (VII) in 68% yield. These products were presumed to be mixtures of the expected stereoisomers which were not separated. All attempts to dehydrate the dicarbinols resulted in the formation of insoluble glassy polymers. Oxidation of *p*-phenylenebis(methylvinylcarbinol) (VI) with alkaline potassium permanganate gave terephthalic acid.

Treatment of *p,p'*-biphenylenebis(methylvinylcarbinol) (VII) with anhydrous hydrogen chloride in ether produced *p,p'*-biphenylenebis(methylvinylchloromethane) (VIII) in 67% yield. Attempts to dehydrohalogenate this compound were also unsuccessful. These unsuccessful reactions appear to be due to the high reactivity of the difunctional dienes which would be expected to be produced and to their tendencies to form polymeric mixtures.



In an earlier attempt to prepare 2,2'-*p*-phenylenedibutadiene from *p*-phenylenebis(succinic acid), terephthalaldehyde was condensed with malonic ester to give tetraethyl *p*-phenylenebis(methylenemalonate) (IX) in 38% yield. Further reactions similar to those described for the preparation of phenylsuccinic acid[7] led to unidentifiable products so the reaction scheme was abandoned. Since this ester (IX) had not been made previously, its preparation is described in the experimental section.

EXPERIMENTAL[8]

Methylphenylvinylcarbinol (I). A solution of vinylmagnesium bromide in 1200 ml. of tetrahydrofuran was prepared from vinyl bromide (214 g., 2.0 moles) and magnesium (48.6 g., 2.0 g.-atoms) as described by Seyferth and Stone.[9] Acetophenone (200 g., 1.67 moles) dissolved in 500 ml. of tetrahydrofuran was added at a rate to maintain gentle reflux and stirring was continued an additional hour. After hydrolysis with 500 ml. of a saturated aqueous solution of ammonium chloride, the organic layer was distilled. The tetrahydrofuran was removed on a steam bath and the residue distilled through a 12-in. Vigreux column to yield 184 g. (75%) of methylphenylvinylcarbinol, a colorless liquid of b.p. 73–74° (1.0 mm.), n_D^{20} 1.5338 [reported[4] b.p. 62° (0.5 mm.), n_D^{20} 1.5338].

Anal. Calcd. for $C_{10}H_{12}O$: C, 81.04; H, 8.16. Found: C, 81.08; H, 8.41.

The infrared spectrum (10% solution in chloroform) shows bands at 3570, 3400 cm.$^{-1}$ (hydroxyl[10]) and 1642 cm.$^{-1}$ (vinyl) in addition to the expected methyl and benzene bands. No carbonyl absorption was present.

p-Phenylenebis(methylvinylcarbinol) (VI). This compound was prepared in a manner similar to that for methylphenylvinylcarbinol. The following reagents were used: vinyl bromide (48.2 g., 0.45 mole) and magnesium (11.0 g., 0.45 g.-atom) in tetrahydrofuran (300 ml.), *p*-diacetylbenzene[11] (24.0 g., 0.15 mole) in tetrahydrofuran (100 ml.). The yield of colorless crystals, recrystallized from cyclohexane, was 22.0 g. (67%), m.p. 99–100°.

Anal. Calcd. for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.05; H, 8.44.

The infrared spectrum (10% solution in chloroform) shows bands at 3635 and 3470 cm.$^{-1}$ (hydroxyl[10]) and 1642 cm.$^{-1}$ (vinyl) in addition to the expected methyl and benzene bands. No carbonyl absorption was noted.

p,p'-Biphenylenebis(methylvinylcarbinol) (VII). This compound was prepared in the usual manner from vinyl bromide (16.0 g., 0.15 mole) and magnesium (3.64 g., 0.15 g.-atom) in tetrahydrofuran (300 ml.) and *p,p'*-diacetylbiphenyl[12] (11.0 g., 0.046 mole) in tetrahydrofuran (300 ml.). It was necessary to warm the solution of the diketone to prevent

(7) C. F. H. Allen and H. B. Johnson, *Org. Syntheses*, **30**, 83 (1950).

(8) The melting points are not corrected. We are indebted to Mr. Jozsef Nemeth of the Microanalytical Laboratory of the University of Illinois for the microanalyses of carbon and hydrogen, to Clark Microanalytical Laboratory, Urbana, Ill., for the microanalyses of chlorine, and to Mr. Paul McMahon of the University of Illinois for the infrared data.

(9) D. Seyferth and F. G. A. Stone, *J. Am. Chem. Soc.*, **79**, 515 (1957).

(10) In each case, the second hydroxyl band (*ca.* 3400 cm.$^{-1}$) disappeared on dilution of the chloroform solution, indicating it was due to intermolecular hydrogen bonding.

(11) R. Riemschneider, *Gazz. chim. ital.*, **77**, 607 (1947).

(12) L. M. Long and H. R. Henze, *J. Am. Chem. Soc.*, **63**, 1939 (1941).

crystallization and to add it while still warm. Recrystallization of the product from benzene–*n*-pentane (1:3) gave 9.2 g. of colorless crystals (68%), m.p. 117–118°.

Anal. Calcd. for $C_{20}H_{22}O_2$: C, 81.60; H, 7.53. Found: C, 81.66; H, 7.78.

The infrared spectrum (10% solution in chloroform) shows bands at 3562, 3400 cm.$^{-1}$ (hydroxyl[10]) and 1642 cm.$^{-1}$ (vinyl) in addition to the expected methyl and benzene bands. No carbonyl absorption was present.

Reaction of p-phenylenebis(methylvinylcarbinol) (VI) *with potassium permanganate.* A mixture of *p*-phenylenebis(methylvinylcarbinol) (1.00 g., 0.0046 mole), potassium permanganate (7.27 g., 0.046 mole), sodium hydroxide (1.00 g., 0.025 mole), and water (30 ml.) was heated under reflux for 24 hr. The mixture was cooled, and filtered from the manganese dioxide which was washed thoroughly with water. The filtrate was acidified with dilute sulfuric acid and the white precipitate obtained was filtered and washed with cold water. Recrystallization from glacial acetic acid yielded 0.46 g. of white crystals, m.p. above 300°.

An infrared spectrum (Nujol) of this acid was identical with a spectrum of authentic terephthalic acid.

A portion of this acid was converted to the ethyl ester, m.p. 42–44°. Mixed melting point with authentic diethyl terephthalate was 42–44°.

The 0.46 g. of product represents a 60% yield of terephthalic acid.

Methylphenylvinylchloromethane (III). A solution of methylphenylvinylcarbinol (10.0 g., 0.068 mole) in anhydrous ether (50 ml.) was cooled in an ice bath and anhydrous hydrogen chloride was bubbled through the solution for 3 hr. The ether and hydrogen chloride were removed at atmospheric pressure and the crude product dissolved in fresh ether (50 ml.). The ether solution was washed with dilute sodium carbonate and water and dried over anhydrous magnesium sulfate. Two distillations through a Vigreux column yielded methylphenylvinylchloromethane, a colorless liquid of b.p. 56–58° (0.5 mm.), n_D^{20} 1.5520. The yield was 5.7 g. (50.5%).

Anal. Calcd. for $C_{10}H_{11}Cl$: C, 72.09; H, 6.66; Cl, 21.25. Found: C, 71.88; H, 6.65; Cl, 21.17.

The infrared spectrum shows bands at 1629 cm.$^{-1}$ (vinyl) and 720 cm.$^{-1}$ (C-Cl) in addition to the expected methyl and benzene bands. No absorption above 3040 cm.$^{-1}$ was present (no hydroxyl).

p,p'-Biphenylenebis(methylvinylchloromethane) (VIII). A solution of *p,p'*-biphenylenebis(methylvinylcarbinol) (3.00 g., 0.010 mole) in anhydrous ether (100 ml.) was cooled and treated with anhydrous hydrogen chloride for 1 hr. The product was isolated as in the previous example. Recrystallization from benzene–*n*-pentane yielded colorless needles (2.28 g., 67%), m.p. 144.5–145°.

Anal. Calcd. for $C_{20}H_{20}Cl_2$: C, 72.50; H, 6.09; Cl, 21.41. Found: C, 72.34; H, 6.08; Cl, 20.95.

The infrared spectrum (Nujol) shows a band at 1634 cm.$^{-1}$ (vinyl) in addition to the expected methyl and benzene bands. No absorption above 2910 cm.$^{-1}$ was noted (no hydroxyl).

2-Phenyl-1,3-butadiene (II). (*a*) *Dehydration of methylphenylvinylcarbinol.* Methylphenylvinylcarbinol (40.0 g., 0.27 mole), aniline hydrobromide (4 g.), and hydroquinone (0.5 g.) were mixed in a 100-ml., round-bottomed flask connected to a 6-in. Vigreux column with distillation take-off. The pressure was reduced to 13 mm. and the flask heated in an oil bath, initially at 100° so that a very slow distillation took place. The reaction took 4 hr. and the oil bath temperature was ultimately raised to 150°. In the receiver, which was cooled in an ice salt bath, was collected a colorless liquid of b.p. 57–63° (13 mm.), n_D^{20} 1.5475 [reported,[13] b.p. 55–64° (15 mm.), n_D^{20} 1.5489]. The product contained a few droplets of water, the bulk of which was physically removed using a separatory funnel and the sample was dried by adding a few pellets of anhydrous calcium chloride and letting it stand for a few hours at 0°. The drying agent was filtered off and a colorless liquid obtained[14] (21.5 g., 61%) which reacted instantaneously in the cold with maleic anhydride to form the expected Diels-Alder adduct, 4-phenyl-Δ^4-tetrahydrophthalic anhydride, in 85% yield; m.p. 104.5–105° (lit. m.p. 105°[13,15]).

2-Phenyl-1,3-butadiene and 1,4-naphthoquinone, heated at 100° for 2 hr., yielded the expected 1,4-dihydro-3-phenyl-9,10-anthroquinone, colorless crystals of m.p. 143.5–144° (recrystallized from ethanol) (reported,[15] m.p. 144°).

The infrared spectrum of 2-phenyl-1,3-butadiene shows bands at 1687, 1625, 1590 cm.$^{-1}$ (conjugated double bonds), and 1600, 1577, 1497 cm.$^{-1}$ (phenyl) in addition to the expected C—H bands.

(*b*) *Dehydrohalogenation of methylphenylvinylchloromethane.* A solution of methylphenylvinylchloromethane (8.0 g., 0.05 mole), pyridine (40 ml.), and hydroquinone (0.5 g.) was heated under reflux for 1 hr., cooled, and poured into cold 10% sulfuric acid. The oily layer was ether extracted, washed with water and dried over anhydrous magnesium sulfate. Distillation yielded 2-phenyl-1,3-butadiene (2.2 g., 36%), b.p. 57–66° (13 mm.), n_D^{20} 1.5470.

Tetraethyl-p-phenylenebis(methylenemalonate) (IX). Terephthalaldehyde[16] (10.0 g., 0.075 mole), malonic ester (32.0 g., 0.20 mole), piperidine (0.5 ml.), and dry benzene (80 ml.) were heated under reflux for 48 hr. A trap was used to remove water from the reaction as it was formed. The benzene was distilled off at atmospheric pressure and the excess malonic ester removed under vacuum [95–100° (15 mm.)]. The residue, on cooling, solidified to a yellow mass, which was recrystallized from methanol. Colorless crystals of m.p. 135–136° were obtained. The yield was 12.0 g. (38%).

Anal. Calcd. for $C_{22}H_{26}O_8$: C, 63.15; H, 6.26. Found: C, 63.34; H, 6.42.

The infrared spectrum (10% solution in chloroform) shows bands at 1725 cm.$^{-1}$ (unsaturated ester carbonyl) and 1634 cm.$^{-1}$ (conjugated double bond) in addition to the expected benzene bands. No aromatic aldehyde bands were present.

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(13) O. Grummitt and H. Leaver, *J. Am. Chem. Soc.*, **74**, 1595 (1952).

(14) This product can be redistilled carefully with an 80% recovery of material. However, the physical constants do not change and for most normal reactions involving this compound, the redistillation is not necessary.

(15) C. C. Price, F. L. Benton, and C. J. Schmidle, *J. Am. Chem. Soc.*, **71**, 2860 (1949).

(16) J. M. Snell and A. Weissberger, *Org. Syntheses*, **Coll. Vol. III**, 788 (1955).

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

Preparation and Some Properties of Certain Fluorovinyl Iodides and Some Fluorinated Butadienes[1]

J. D. PARK, JOHN ABRAMO, MORRIS HEIN, D. N. GRAY, AND J. R. LACHER

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New fluorovinyl iodides, CF_2=CHI, CF_2=CClI, CF_2=CBrI, and CF_2=CI_2, were prepared and some of their reactions with various olefins studied. In all cases, a 1:1 linear adduct was formed, with the formation of small amounts of higher boiling fractions. A number of fluoro-1,3-butadienes were obtained from these adducts and their physical properties were tabulated.

This paper represents a continuation of our study on the preparation of certain fluorovinyl iodides[2] and some of their reactions under free radical and ionic conditions.

It was found that iodine monochloride added very readily to CF_2=CH_2, CF_2=CHI, CF_2=CHBr, and CF_2=CHCl but more slowly to CFCl=CFCl. The additions to CF_2=CH_2 and CF_2=CHI were very exothermic reactions, especially the latter, which was so vigorous that cooling was necessary during the course of the reaction.

The addition of iodine monochloride to these olefins is in agreement with the addition of alcohols under conditions favoring ionic reactions.[3-5] In our case, the negative chlorine becomes attached to the CF_2-group, which has a partial positive charge.

All of the olefins with the exception of CFCl=CFCl gave yields of adducts ranging from 83% to 95%. 1,2-Dichloro-1,2-difluoroethylene gave a yield of 23% with a secondary product, $CFCl_2$–$CFCl_2$, being formed from the reaction: $CFCl_2CFClI$ + ICl→$CFCl_2CFCl_2$ + I_2 or from $CF_2ClCFClI$ and free chlorine (formed from the dissociation of ICl into iodine and chlorine). Very little, if any, secondary products were formed with the other olefins.

CF_2ClCHI_2 and $CFCl_2CFClI$ obtained from the iodine monochloride additions are very unstable to light and are extremely strong lachrymators and so unstable that no further reactions were attempted. On the other hand, CF_2Cl—CH_2I has a pleasant odor and can be distilled at 92° with little or no decomposition.

The proof of structure of CF_2ClCH_2I, CF_2ClCHI_2, CF_2Cl—CHBrI, and CF_2Cl—CHClI, respectively, was established, chemically, by reaction with potassium hydroxide in mineral oil. In each case, a molecule of hydrogen chloride was removed with the formation of potassium chloride and CF_2=CHI, CF_2=CI_2, CF_2=CBrI, and CF_2=CClI, respectively. If the iodine monochloride had added the other way, to produce CF_2I-CH_2Cl (in the case of CF_2=CH_2), a molecule of hydrogen iodide would have been removed. In addition, CF_2Cl-CH_2I when treated with ethanolic potassium hydroxide yielded $CH_3CH_2OCF_2CH_2I$, the structure of which was proven by hydrolysis[6,7] of the ether with 96% sulfuric acid to the known ethyl iodoacetate. Similarly, $C_2H_5OCF_2CHClI$ upon hydrolysis yielded chloroiodoacetic acid.

Under free radical conditions the fluorovinyl iodides, CF_2=CHI, CF_2=CClI, CF_2=CBrI, and CF_2=CI_2 reacted with olefins in a manner such that the attacking free radical CF_2=CX· will add to a terminal CH_2-group, then a CFH-group and a CF_2-group, preferentially in that order as shown[2,8,9] previously in similar cases.

These additions ultimately resulted in the preparation of the following: 1,1-difluoro-2-chlorobutadiene; 1,1,2,4,4-pentafluoro-3-chlorobutadiene; 1,1-difluorobutadiene; and 1,1,4,4-tetrafluorobutadiene.

The reaction of CF_2=CClI and CF_2=CBrI apparently yielded Grignard reagents. These reacted with formaldehyde to yield CF_2=$CClCH_2OH$ and CF_2=$CBrCH_2OH$, respectively. However, we were unable to isolate any definite reaction products when the above Grignard reagents were treated separately with carbon dioxide and ethylene oxide.

The infrared spectra of all of the compounds prepared in this study were taken but are not reported in order to conserve space.

EXPERIMENTAL

The free radical addition reactions were carried out in Pyrex flasks which were sealed off at the neck and fitted

(1) Presented before the Fluorine Subdivision of the Division of Industrial and Engineering Chemistry, American Chemical Society meeting, Minneapolis, Minn., Sept. 1955. This paper represents parts of the theses submitted by D. N. Gray, J. Abramo, and M. Hein to the Graduate School, University of Colorado, in partial fulfillment of the requirements for the Ph.D. degree.

(2) J. D. Park, R. J. Seffl, and J. R. Lacher, *J. Am. Chem. Soc.*, **78**, 59 (1956).

(3) W. E. Hanford and G. W. Rigby, U. S. Patent **2,409,274**.

(4) W. T. Miller, Jr., E. W. Fager, and P. H. Griswold, *J. Am. Chem. Soc.*, **70**, 431 (1948).

(5) J. D. Park, D. K. Vail, K. R. Lea, and J. R. Lacher, *J. Am. Chem. Soc.*, **70**, 1550 (1948).

(6) J. A. Young and P. Tarrant, *J. Am. Chem. Soc.*, **71**, 2432 (1949).

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with stopcocks to permit the introduction and removal of the reactants and products. The ultraviolet light source was an Hanovia EH4 mercury arc tube.

1,1-Difluoro-2-iodoethylene (I). The dehydrochlorination of CF_2ClCH_2I (II) was carried out by a procedure similar to that previously reported[2] for the preparation of CF_2=CFI. It was found that better yields were obtained by running the reaction at about 200-mm. pressure.

The material was distilled over phosphorus pentoxide to yield 67 g. (65.4%) of a fraction boiling at 35.5° (622 mm.); n_D^{20} 2.171. Molecular weight determinations by the Regnault method: Calcd. for CF_2=CHI: 190. Found: 188.

Anal. Calcd. for C_2HF_2I: C, 12.64; H, 0.53; I, 66.8; F, 20. Found: C, 12.56; H, 0.58; I, 66.6; F, 19.8.

1,2-Dichloro-1,1-difluoro-2-iodoethane (III). The apparatus used in the addition of iodine monochloride to CF_2=CHCl was a 5 × 35 cm. Pyrex tube with a sintered glass frit at the bottom for dispersion of the incoming gas and the top mounted by a reflux condenser connected in series to a bubble counter and a trap cooled to −78° for the collection of unreacted starting material.

In a typical run, 325 g. (2 moles) of iodine monochloride was placed in the apparatus described above, and 184 g. (1.9 moles) of CF_2=CHCl passed through the glass frit from a steel cylinder at a rate such that some olefin came through the bubbler. The reaction, which is exothermic, required about 9 hr. The reaction product was washed with aqueous sodium bisulfite until colorless, then three more times with fresh water and finally dried over anhydrous sodium sulfate. Vacuum distillation in a Vigreux column yielded 442 g. (90%) of material boiling at 66–67° (100 mm.); n_D^{20} 1.4881; d_4^{20} 2.233.

Anal. Calcd. for $C_2HCl_2F_2I$: C, 9.2; F, 10.73. Found: C, 9.1; F, 10.58.

2-Chloro-1,1-difluoro-2-iodoethylene (IV). The dehydrochlorination of III was carried out in a 1-liter three-neck flask in a manner similar to that previously described[2] for CF_2=CFI. About 315 g. (0.82 mole) of III added dropwise to 90 g. (1.6 moles) of potassium hydroxide pellets suspended in 300 ml. of heavy mineral oil at 60° yielded 130 g. (78%) of III; b.p. 72–73° (628 mm.); n_D^{20} 1.4695; d_4^{20} 2.237.

Anal. Calcd. for C_2ClF_2I: C, 10.7; F, 16.9. Found: C, 11.0; F, 16.6.

1-Chloro-1,1-difluoro-2,2-diiodoethane (V) Into a 50-ml. three-neck flask, fitted with a dropping funnel, stirrer, and a reflux condenser, was placed 30 g. (0.16 mole) of I kept at 0°. Iodine monochloride was then added dropwise with stirring. The reaction was vigorously exothermic and was more easily controlled in another preparation by adding the olefin to ICl. The product was washed with aqueous $NaHSO_3$ and water, then dried with anhydrous sodium sulfate. Fifty-three g. of dried product was obtained. Distillation produced a 94% yield of V, b.p. 57.4–57.5° (8 mm.). The product is a very strong lachrymator and decomposes rapidly. A freshly redistilled sample was used for physical properties and analysis; b.p. 57.5° (8 mm.); n_D^{20} 1.5870; d_4^{20} 2.823.

Anal. Calcd. for $C_2HF_2ClI_2$: C, 6.82; F, 10.78. Found: C, 6.86; F, 10.99.

1,1-Dichloro-2,2-difluoroethylene (VI). A 50-ml. three-neck flask, equipped with a dropping funnel, a stirrer, and a reflux condenser, was charged with 20 g. powdered potassium hydroxide and 20 ml. $CFCl_2CF_2Cl$, the latter used as a medium for suspending the potassium hydroxide. Twenty-five g. of V was then added dropwise to the agitated mixture and the reaction initiated by bringing the solvent to a boil (43°). The addition of V was so adjusted to just keep the solvent ($CFCl_2CF_2Cl$) refluxing without external heat. A very hard salt cake was formed during the course of the reaction. Refluxing of the solvent was continued for 3 hr. after all the diiodide had been added. Distillation yielded 18.6 g. (83.5%) of VI, b.p. 133.5° (626 mm.); n_D^{20} 1.5869; d_4^{20} 2.961.

Anal. Calcd. for $C_2F_2I_2$: C, 7.6; F, 12.03. Found: C, 7.65; F, 11.95.

Reaction of CF_2Cl—CH_2I and CH_2=CH_2. A. *Thermal reaction.* The iodide II (119 g., 0.53 mole) was put into a 500-ml. Parr hydrogenation bomb and charged to 450 lbs. per square inch with ethylene. The bomb was rocked for 20 min. and the pressure observed to insure no leakage. The reaction mixture was heated to 280° where a drop in pressure was noted. Heating at 280° was continued for an additional 3 hr. after which the bomb was allowed to cool off.

The unreacted ethylene was discharged through a series of traps cooled in Dry Ice. The liquid was transferred to an Erlenmeyer flask and stored in the deep-freeze. Carbon black and iodine were found on the walls of the bomb. The liquid product, which was a solid in the deep-freeze, was distilled on a Todd column. About 13.6 g. (10%) was obtained which had the extrapolated boiling point for the desired product, $CF_2ClCH_2CH_2CH_2I$ (VII). The fraction boiling at 44.3–44.7° (7 mm.) was taken as the desired product.

This fraction, which was iodine colored, was decolorized with aqueous sodium sulfite, washed with water, and dried over "Drierite." The compound is unstable to light; b.p. 41.5° (5 mm.); 67.5° (23 mm.); n_D^{20} 1.4780; d_4^{20} 1.867.

Anal. Calcd. for $C_4H_6ClF_2I$: C, 18.88; H, 2.38; I, 49.88. Found: C, 18.80; H, 2.60; I, 50.09.

Also isolated from the reaction was about 10 g. of ethylene iodide. This solid was purified by crystallization from warm petroleum ether (60–80°), sublimation under vacuum, and recrystallization from the same solvent. Long, needlelike crystals were obtained, m.p. 81°.

Anal. Calcd. for $C_2H_4I_2$: C, 8.52; H, 1.42. Found: C, 8.58; H, 1.36.

B. *Photochemical reaction.* About 23 g. (0.1 mole) of II and 3.5 g. (0.19 mole) of CH_2=CH_2 were placed in a three-liter Pyrex flask and irradiated with ultraviolet light. The reaction was allowed to continue for 14 days. Distillation was carried out in a micro-distillation apparatus. The first fraction was the starting iodide. The next fraction was 3.3 g. (13%) of VII coming over at 41.3° at about 6-mm. pressure, n_D^{21} 1.4790 (iodine colored), d_4^{20} 1.867.

Photochemical reaction of CF_2=CHI and CH_2=CH_2. About 23 g. (0.1 mole) of I and 4.3 g. (0.15 mole) of CH_2=CH_2 were placed in a three-liter Pyrex flask and irradiated with an ultraviolet lamp for seven days. The resulting product was iodine colored. The reaction mixture was poured from the flask to a trap cooled in Dry Ice. Distillation through a Vigreux column afforded 10 g. (46%) of CF_2=CH—CH_2-CH_2I (VIII) distilling at 58° (81 mm.). The sample was decolorized with a drop of mercury before use. The product gave a positive test for unsaturation with $KMnO_4$ in acetone. B.p. 45.0–45.3° (40 mm.); 69.0–69.2° (116 mm.); n_D^{20} 1.4752; d_4^{20} 1.863.

Anal. Calcd. for $C_4H_5F_2I$: C, 22.04; H, 2.31; I, 58.22. Found: C, 22.05; H, 2.28; I, 58.50.

1,1-Difluoro-1,3-butadiene (IX). A 50-ml. three-neck flask was equipped with a dropping funnel, a stirrer, and a reflux condenser whose outlet led to a trap cooled in Dry Ice. Fourteen ml. of light mineral oil and 8 g. of powdered potassium hydroxide were put into the flask and the stirred potassium hydroxide slurry was heated to 95°. Six grams (0.051 mole) of VIII was added dropwise to the KOH slurry. After about 2 hr., some liquid was found to be condensing in the cold trap. Heating and stirring was continued for 5 more hr., whereupon about two milliliters of liquid was obtained in the cold trap.

The molecular weight of the product was determined using a Regnault bulb. Molecular weight for IX: Calculated, 90.1. Found, 90.1. B.p. −1° at 630-mm. Hg. Tarrant[10] has previously prepared this compound by another route and reported a b.p. of +3.5° (760 mm.).

(10) P. Tarrant, M. R. Lilyquist, and J. A. Attaway, *J. Am. Chem. Soc.*, **76**, 944 (1954).

TABLE I

PHYSICAL PROPERTIES OF COMPOUNDS PREPARED

Compound	n_D^{20}	d_4^{20}	MR_D Calcd.	MR_D Found	AR_F Obsd.	Mol. Wt. Calcd.	Mol. Wt. Found	B.P., °C./Mm. Hg
CF_2=CHI	1.4376	2.171	23.77	22.95	0.69	190	188	33.5/622
CF_2=CClI	1.4695	2.237	28.49	27.95	0.76			73/628
CF_2=CBrI	1.5059	2.5837	31.53	30.91	0.79			95.5/622.5
CF_2=CI_2	1.5869	2.961	36.57	35.84	0.74			133.5/626
CF_2ClCH_2I	1.4655	2.166	29.10	28.92	1.01			92.3/624
$CFCl_2$—$CFClI$	$1.5017^{22°}$	$2.265^{22°}$	38.84	38.45	0.91			44.4/17
$CF_2ClCHClI$	1.4881	2.233	33.83	33.66	0.94			66/100
$CF_2ClCHBrI$	1.5229	2.5464	36.87	36.62	0.98			70.5/51; 139.5/628
CF_2ClCHI_2	1.5870	2.823	41.90	42.06	1.18			57.5/8
$CF_2ClCH_2CH_2CH_2I$	1.4870	1.867	38.34	38.59	1.22			41.5/5; 67.5/23
CF_2=CH—$(CH_2)_2I$	1.4752	1.863	33.00	32.96	1.08			45–45.3/20; 61.2/85; 69.0/116
CF_2=$CHCH_2CF_2I$	1.4193	1.909	33.01	33.62	1.25			86.9/631.5
CF_2=$CHCF_2CFClI$	1.4331	2.086	37.87	38.20	1.17			112/635
CF_2=$CClCH_2CH_2I$	1.4958	1.9724	36.84	37.37	0.80			142/631
CF_2=$CClCH_2CF_2I$	1.4435	2.024	37.88	37.81	0.87			120/627
CF_2=$CClCHFCF_2I$	1.4342	2.115	37.87	37.74	1.07			59/90
CF_2=CHCH=CH_2						90.1	90.1	
CF_2=CHCH=CF_2						127	126	−33.4/158; −5.5/509; −1.8/584
CF_2=CClCF=CF_2						175	178	30–32/630
$C_2H_5OCF_2CH_2I$	1.4520	1.794	35.12	35.48	1.28			62.1/59
$C_2H_5OCF_2CHClI$	1.4760	1.885	39.98	40.46	1.34			67/20
CF_2=$CClCH_2OH$	1.4028	1.4267	21.97	21.97	1.1			43/20

Photochemical preparation of CF_2=CH—CH_2—CF_2I (X). In a manner similar to that described above, 33 g. (0.17 mole) of I and 20 g. (0.31 mole) of CF_2=CH_2 were irradiated with ultraviolet light in a five-liter flask for a period of 13 days. After this time, the contents of the flask were dissolved in ether and removed. Distillation was carried out in micro-equipment, after first removing the ether and unreacted I as one fraction. It is somewhat difficult to remove the last traces of ether from the higher boiling fractions. The fraction boiling at 42–44° (104 mm.) was taken as the desired product. Six grams (14% yield) of X was obtained. A test for unsaturation with $KMnO_4$ in acetone was positive. This product was decolorized with a drop of mercury before use. It is fairly stable to light. B.p. 86.9° (631.5 mm.); n_D^{20} 1.4193; d_4^{20} 1.909.

Anal. Calcd. for $C_4H_3F_4I$: C, 18.91; F, 29.92. Found: C, 18.87; F, 29.7.

1,1,4,4-Tetrafluoro-1,3-butadiene. A. *Dehydroiodination of* X. About 5.8 g. (0.023 mole) of CF_2=CH—CH_2CF_2I was added dropwise to a stirred potassium hydroxide slurry heated to 95° and worked up in a manner similar to that described for compound IX. Two grams (83%) of XI was obtained; this showed a positive test for unsaturation with $KMnO_4$ in acetone. Molecular weight determination by the Regnault method for CF_2=CHCH=CF_2: Calculated, 126. Found, 127, b.p. (isoteniscope) −33.4° (158 mm.); −5.5° (509 mm.); −1.8° at 584-mm. Hg. The infrared spectra of the above with that of an authentic sample of CF_2=CH—CH=CF_2 were found to be superimposable.

B. *Wurtz-type reaction with* I. Eight to nine grams of sodium sand was prepared in 75 ml. of dibutyl ether in a 500-ml. Morton flask, the ether being distilled from sodium. The flask was fitted with a pressure equalizing dropping funnel, a mercury-sealed stirrer and a Dry Ice–cooled Friedrich condenser. Thirty grams of I dissolved in 25 ml. butyl ether was added dropwise while the reaction mixture was kept at 0°. Sodium iodide appeared to be forming, but it was difficult to tell due to the finely divided sodium present. The mixture was allowed to warm up to room temperature during the addition of the olefin.

After a total reaction time of about 7 hr., the coolant in the Friedrich condenser was allowed to warm to 5–10° and about two grams of liquid was collected in a cold trap connected to the condenser. Upon heating the reaction mixture further, the entire contents turned black indicating decomposition. Ten per cent yield of XI was obtained. The product gave a positive test for unsaturation with $KMnO_4$ in acetone. Molecular weight of CF_2=CHCH=CF_2. Calculated, 126; Found, 128. The infrared spectrum was the same as that obtained from the elimination of HI from X.

Photochemical reaction of CF_2=CHI and CF_2=CFCl. About 38 g. (0.2 mole) of I and 33 g. (0.28 mole) of CF_2=CFCl were placed in a three-liter evacuated Pyrex flask and irradiated with ultraviolet light for 13 days. After this period of time, the liquid and gaseous products were pumped out through a liquid nitrogen trap to give a total of 55 g. of material. This was then allowed to warm up to room temperature and the gaseous products removed. About 16 g. of high boiling liquid which remained was distilled. The fraction boiling at 74.5–75.0° (144 mm.) was taken as the desired product, CF_2=CH—CF_2—CFClI (XII). In addition, a fraction (1.3 g.) distilling about 70° (8 mm.), n_D^{20} 1.4565 was obtained. This fraction was not identified. The yield of XII was 12.3%, based on I. All fractions were iodine colored and were decolorized with aqueous Na_2SO_3, washed with water, and dried over "Drierite." A test for unsaturation with $KMnO_4$ in acetone was positive, b.p. 112° (635 mm.); n_D^{20} 1.4331; d_4^{20} 2.086. This compound was considered too unstable to be sent for analysis.

Proof of the mode of addition of I to CF_2=CFCl was established by attempting to dehalogenate the product with Zn. If addition had occurred to give CF_2=CH—$CFClCF_2I$, dehalogenation would have produced CF_2=CH—CF=CF_2, a butadiene previously prepared in this laboratory.[2] However, no pentafluorobutadiene was obtained in this dehalogenation.

Reaction of CF_2=CHI and C_6H_6. Benzene and I were reacted photochemically in a five-liter flask for 13 days in an attempt to prepare C_6H_5CH=CF_2. During the course of the reaction a yellow-brown film was deposited on the inside of the flask. At the end of the reaction a considerable amount of free iodine was left in the flask. In the distillation, after removal of starting materials, about 0.5 ml. of a compound, distilling at 66° (61 mm.), and having an n_D^{20} of 1.4840, was

obtained. This fraction showed a positive test for unsaturation with $KMnO_4$ in acetone. Prober[11] reports a b.p. of 65–66° (61–62 mm.); and an n_D^{20} of 1.4925 for $C_6H_5CH{=}CF_2$ prepared by another route.

Attempted coupling of C_6H_5MgBr and $CF_2Cl{-}CFClI$. Phenyl magnesium bromide (3*M* solution) was added dropwise to a stirred ethereal solution of $CF_2Cl{-}CFClI$ and a noticeable reaction took place with the deposition of a salt. However, no coupling product was obtained. Only phenyl iodide was isolated along with $CF_2{=}CFCl$. Similar results were obtained when the reaction was carried out at 0° and at −78°.

Photochemical reaction of $CF_2{=}CClI$ with $CH_2{=}CH_2$. About 45 g. (0.2 mole) of IV and 0.2 mole of ethylene were charged to a 5-liter Pyrex flask, sealed, and irradiated for 30 days. At the end of this period a good deal of iodine was present in the flask. The products of the reaction were obtained by pouring out the liquid and removing the vapors from the flask by suction. Distillation of the materials from the flask gave 11 g. of unreacted IV and 27 g. (71%) of the desired $CF_2{=}CCl{-}CH_2CH_2I$ (XIII), b.p. 142–143° (631 mm.); d_4^{20} 1.972; n_D^{20} 1.4958.

Anal. Calcd. for $C_4H_4F_2ClI$: C, 19.0%; F, 15.05%. Found: C, 18.95%; F, 15.1%.

1,1-Difluoro-2-chloro-1,3-butadiene. About 27 g. of XIII was treated with a suspension of mineral oil in a manner outlined in the preparation of IX. About 1 ml. of material was obtained. Attempts to obtain more product were unsuccessful. Enough material was available for an infrared spectrum which had the doublet associated with butadienes in the double bond region of the spectrum.[12]

Photochemical reaction of $CF_2{=}CClI$ with $CF_2{=}CHF$. About 45 g. of IV and about 0.2 mole of $CF_2{=}CHF$ were put into the 5-liter Pyrex bulb and irradiated with ultraviolet light for 18 days. After this period the products which were highly colored were removed from the flask. Distillation on a micro-distillation apparatus yielded 14 g. (69%) of $CF_2{=}CClCHFCF_2I$ (XIV) boiling at 58–59° (90 mm.). The iodine in the product was removed by shaking with a few drops of mercury and the physical properties were determined immediately after this treatment. n_D^{20} 1.4342; d_4^{20} 1.115.

Anal. Calcd. for C_4HClF_5I: C, 15.6; F, 31. Found: C, 15.46; F, 30.86.

1,1,3,4,4-Pentafluoro-2-chloro-butadiene. About 28 g. of XIV was added dropwise to a suspension of potassium hydroxide in mineral oil in a manner similar to that described for compound IX. Evacuation of the reaction system through a liquid nitrogen trap yielded 8 ml. of material. Pot to pot distillation of the reaction products in a vacuum system left about 0.5 ml. of product which was used for a molecular weight determination (Regnault method) and infrared spectrum. Mol. wt. Calcd. for $CF_2{=}CCl{-}CF{=}CF_2$: 178. Found: 175, b.p. 30–32° (628 mm.).

Anal. Calcd. for C_4F_5Cl: C, 26.9; F, 53.2. Found: C, 27.1; F, 53.

Infrared shows the doublet in double bond region of spectrum which is associated with butadiene.[12]

Photochemical reaction of $CF_2{=}CClI$ with $CF_2{=}CH_2$. A 5-liter Pyrex bulb was charged with 45 g. (0.2 mole) of IV and 0.2 mole of $CF_2{=}CH_2$ and irradiated with an ultraviolet light for 30 days. At the end of this period the products were highly colored with iodine. The contents of the flask were emptied and subjected to distillation in a micro-distillation assembly. About 14 g. of IV was recovered along with 19 g. of material boiling at 120° (627 mm.) which was the desired $CF_2{=}CCl{-}CH_2{-}CF_2I$ (XVI). Physical properties were determined after shaking the product with a few drops of mercury. n_D^{20} 1.4435; d_4^{20} 2.024. (AR_F = 1.1).

Anal. Calcd. for $C_4H_2F_4ClI$: C, 16.66%; F, 26.35%. Found: C, 16.23%; F, 26.35%.

Preparation of Grignard reagent with $CF_2{=}CClI$. About 3 g. (0.13 mole) of magnesium turnings were washed with absolute ether and placed in a 300-ml. three-neck flask. The flask was provided with a reflux condenser, stirrer, and dropping funnel. After adding 100 ml. of absolute ether to the flask about 2 ml. of IV was added and the reaction started by warming the magnesium turnings in the flask with a pinpoint flame. A total of 22 g. of IV was added over a 2-hr. period at a rate such that reflux was maintained. The ethereal solution was quite dark at this point. The mixture was hydrolyzed with 100 ml. of 3*N* sulfuric acid and the gaseous products condensed in a trap cooled to −78°. Molecular weight determination (Regnault Method) gave a value of 95. Calcd. for $CF_2{=}CHCl$ is 98.5.

Reaction of $CF_2{=}CClMgI$ with formaldehyde. Preparation of the Grignard reagent was carried out in a 500-ml. Morton flask provided with a stirrer, 0° reflux condenser, and a dropping funnel with a pressure equalizing arm. About 5 g. of magnesium turnings were washed with absolute ether, placed in the Morton flask, and covered with 100 ml. of ether. The Grignard reaction was initiated in the usual way and a total of 42 g. (0.19 mole) of IV was added dropwise over a 3-hr. period, while the ethereal solution of the Grignard reagent was stirred vigorously, and cooled with an ice bath. Seven grams of paraformaldehyde was depolymerized by heating and the gaseous formaldehyde was led into the reaction mixture through a section of 10-mm. glass tubing set just above the surface of the ether. During the addition of the formaldehyde, enough heat is generated to cause refluxing of the ether. After the formaldehyde was added, the mixture was allowed to come to room temperature and stirred for an additional 3 hr. At the end of this period the reaction mixture was poured on cracked ice and acidified with 100 ml. of 20% sulfuric acid. The ether layer was separated and the aqueous layer was extracted with three 100-ml. portions of ether. The ether fractions were combined, and dried over anhydrous potassium carbonate over night. The ether was stripped off with a vacuum pump leaving a tarry liquid which was subjected to vacuum distillation through a Vigreux column. About 14 g. (54%) of a colorless liquid, b.p. 42–43° (20 mm.) was obtained. This liquid which was the desired $CF_2{=}CClCH_2OH$ reacted with sodium metal, gave a positive test for unsaturation with aqueous potassium permanganate, and an acid reaction to litmus. n_D^{20} 1.4028; d_4^{20} 1.427.

Anal. Calcd. for $CF_2{=}CClCH_2OH$: C, 28; F, 29.6. Found: C, 28.1; F, 29.2.

Attempted coupling of $CF_2Cl{-}CH_2I$. A 1-liter three-neck flask was provided with a stirrer, dropping funnel, and a reflux condenser. This assembly was charged with 160 ml. of acetic anhydride, 160 ml. of methylene chloride, and 65 g. (1 mole) of zinc dust. About 226 g. (1 mole) of II was added slowly. No reaction occurred at room temperature; however, heating with a microburner caused some dehalogenation as shown by the presence of a low boiling liquid in the traps which was $CF_2{=}CH_2$ and would result from the dehalogenation of the starting material. None of the desired $CF_2ClCH_2CH_2CF_2Cl$ was obtained.

Attempted reaction of $CF_2ClCFClI$ with $CF_2{=}CHCl$. A 500 ml.-Parr bomb was sealed, cooled in an isopropyl alcohol–Dry Ice bath and evacuated. The bomb was checked for leaks by sealing the bomb and letting it stand for 10 min. and checking for any loss in vacuum by means of a mercury manometer connected to the bomb. The bomb was then charged with 150 g. (0.55 mole) of $CF_2ClCFClI$ and 55 g. (0.55 mole) of $CF_2{=}CHCl$. After warming to room temperature, the bomb was heated to 200° while being rocked. About 500 p.s.i. showed on the gauge during the 8-hr. rocking period. At the end of the period the bomb was allowed to cool and the unreacted olefin was collected in a series of traps cooled to −78°. Almost all of the unreacted olefin was collected. Apparently, no reaction took place.

(11) M. Prober, *J. Am. Chem. Soc.*, **75**, 968 (1953).

(12) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, 1st ed., Wiley & Sons, Inc., N. Y., 1954, p. 35.

Attempted Grignard reactions with CF_2=CClMgI. The Grignard reagent was synthesized with IV on a 0.2*M* basis as described previously. The reagent was then allowed to react with 0.2*M* quantities each of ethylene oxide, carbon dioxide, perfluorobutyronitrile, and lithium perfluorobutyrate, respectively. However, no reaction product was isolated in each case.

Attempted reaction of CF_2ClCFClI with SO_2. A 500-ml. stainless steel Parr bomb was sealed and checked for leaks by evacuating, sealing, and checking for loss of vacuum with a mercury manometer. About 160 g. (0.55 mole) of CF_2ClCFClI containing 0.1 g. of benzoyl peroxide was charged to the bomb. After cooling the bomb to −78° about 30 g. of sulfur dioxide was allowed to pass in. The bomb was then heated to 100° and left at this temperature over night. Distillation of the products from the bomb yielded only the starting CF_2ClCFClI.

Attempted Grignard formation with CF_2ClCFClI. About 23 g. (0.2 mole) of CF_2Cl—CFCl was added to 5 g. of magnesium covered with 100 ml. of tetrahydrofuran dried over sodium. The reaction was initiated in the usual way and the rest of the iodide was added dropwise over a 1-hr. period. The magnesium was consumed at the end of this period and a low boiling liquid had condensed in the trap attached to the reflux condenser. A molecular weight determination on this gave a value of 114, theory for CF_2=CFCl is 116. Hydrolysis of the reaction mixture with 20% sulfuric acid did not yield other products. Apparently the only reaction which had occurred was that of dehalogenation.

Attempted Grignard reaction with CF_2=CHI. In an attempt to prepare the Grignard reagent, CF_2=CHMgI, I was treated with an equivalent amount of magnesium in sodium dried diethyl ether. The reaction was run under conditions identical to those in which perfluorovinyl iodide, CF_2=CFI, was shown to react quite rapidly.[2] After a period of 16 hr., it was visibly evident that none or very little of the magnesium had reacted.

1,1-Difluoro-1-chloro-2-bromo-2-iodoethane (XVII). The preparation and purification of XVII was carried out with CF_2=CHBr and ICl in a manner similar to that previously described[2] for the preparation of CF_2Cl—CFClI. Yield 83%, b.p. 70.5° (51 mm.); 139.5–140° (628 mm.); n_D^{20} 1.5229; d_4^{20} 2.5464.

Anal. Calcd. for $C_2HBrClF_2I$: C, 7.85; F, 12.44. Found: C, 7.9; F, 12.3.

1,1-Difluoro-2-bromo-2-iodoethylene (XVIII). About 30 g. of powdered potassium hydroxide suspended in 90 ml. of CF_2Cl—$CFCl_2$ was placed in a 100-ml. three-neck flask equipped with stirrer, dropping funnel, and reflux condenser. About 46 g. (0.15 mole) of XVII was added dropwise to the above suspension in the course of an hour. Heat was maintained as the reflux boiling point of CF_2Cl—$CFCl_2$. Stirring was continued for an additional 2 hr., after which the reaction products were decanted and stored over "Drierite." Distillation of the products yielded 31.5 g. (78%) of XVIII with the following properties. B.p. 95.5° (622.5 mm.); n_D^{20} 1.5059; d_4^{20} 2.5837.

Anal. Calcd. for C_2BrF_2I: C, 8.93; F, 14.13. Found: C, 8.81; F, 14.05.

Preparation of CF_2=CBrMgI. About 4 g. (0.165 mole) of magnesium turnings and 43 g. of XVIII were reacted according to the procedure outlined for the preparation of CF_2=CClMgI. Hydrolysis of the Grignard reagent with 4*N* sulfuric acid yielded a gas of molecular weight (Regnault method) of 145. Calcd. for CF_2=CHBr is 143.

Reaction of CF_2=CBrMgI with formaldehyde. The Grignard reagent was treated with formaldehyde in a manner similar to that described for the preparation of CF_2=CCl-CH_2OH. A yield of 20 g. (56%) of CF_2=$CBrCH_2OH$ was obtained. B.p. 35.5–36° (5 mm.); n_D^{20} 1.4469; d_4^{20} 1.8966.

Anal. Calcd. for $C_3H_3BrF_2O$: C, 20.83; H, 1.73; F, 21.94. Found: C, 20.78; H, 1.88; F, 21.79.

Attempted reactions with CF_2=CBrMgI. The Grignard reagent was allowed to react with solid carbon dioxide and ethylene oxide, respectively. No reaction product was isolated in either case.

1,1-Difluoro-2-iodoethyl ethyl ether (XIX). Thirty grams of potassium hydroxide dissolved in 100 ml. of absolute ethanol was placed in a 300-ml. three-neck flask fitted with a reflux condenser, stirrer, and dropping funnel. Under reflux, 68 g. (0.3 mole) of II was added during a period of 30 min. The heat generated from the reaction was sufficient to maintain refluxing of the alcohol. Stirring was continued for an additional 2 hr. The product being unstable produced some free iodine in solution.

Water was added to the ethanol solution and two layers formed were separated, washed, and dried over sodium sulfate.

Distillation on the platinum-spiral Todd column showed that everything except a small amount of very high boiler distilled at 62.1° (59 mm.). 54 g. (76.5%) of XIX was obtained, b.p. 62.1° (59 mm.); n_D^{20} 1.4520; d_4^{20} 1.794.

This ether is a strong lachrymator and very unstable to light.

Further proof of its structure was established by hydrolyzing this ether to the known ester, $CH_2ICOOCH_2CH_3$, b.p. 73–74° (16 mm.); n_D^{19} 1.5043. Beilstein reports a b.p. 73° (16 mm.) and $n_D^{12.5}$ 1.5079.

1,1-Difluoro-2-chloro-2-iodoethyl ethyl ether (XX). About 52 g. of III was added dropwise to 100 ml. of 12% ethanolic potassium hydroxide in a manner similar to that described for the preparation of XIX. Distillation of this compound at 20 mm. gave 16 g. (30%) of product boiling at 66–67°. The compound was quite lachrymatory and liberated iodine on standing. The iodine color was removed by shaking the compound with a few drops of mercury and physical properties were immediately determined. n_D^{20} 1.4760; d_4^{20} 1.885.

The hydrolysis of $C_2H_5OCF_2CHClI$ was carried out in the following manner. About 16 g. of XX was charged to a 150-ml. three-neck flask provided with a stirrer, reflux condenser, and a dropping funnel. Stirring was started and 50 ml. of 90% sulfuric acid was added dropwise. After the addition of the sulfuric acid was completed the mixture was heated at 95° on a water bath and stirred for an additional hour. A white solid which was silicon dioxide was found in the water trap attached to the reflux condenser indicating that the CF_2 group was being hydrolyzed.

The reaction mixture was then poured into 200 ml. of water. Extraction of the aqueous mixture with ether was followed by extraction of the ether with 5% sodium hydroxide solution. Neutralization of the aqueous solution was followed by ether extraction. Evaporation of the ether solution left about 3 g. of solid. Recrystallization from cyclohexane gave a white solid melting at 89.5–90° (Willstatter[13] reports an m.p. of 90° for $CHClICO_2H$).

The ether solution which should contain the ester, CHClI—$CO_2C_2H_5$ was treated with anhydrous ammonia. Evaporation of the ether left a solid which was recrystallized from cyclohexane. M.p. 140° (literature[13] reports 140° for CHClI—$CONH_2$).

Acknowledgment. We wish to thank the Minnesota Mining and Manufacturing Co., St. Paul, Minn., and the Monsanto Chemical Co., St. Louis, Mo., for partial support of this work in the form of grants-in-aid.

We further wish to thank E. I. du Pont de Nemours & Co., Inc., Wilmington, Del., for the vinylidene fluoride donated to us through the courtesy of Dr. E. G. Young.

BOULDER, COLO.

(13) R. Willstatter and H. F. Hattenroth, *Ber.*, **37**, 1775 (1904).

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE ROHM & HAAS CO.]

Homogeneous Metal Salt Catalysis in Organic Reactions. III. The Preparation of Allyl Ethers by Allyl Transfer Reactions[1,2]

WARREN H. WATANABE, LAWRENCE E. CONLON,[3] AND JESSE C. H. HWA

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There is described a reaction between an alcohol and an allyl ether or allyl alcohol which provides a simple one-step synthesis of allyl ethers. The catalysts used are mercuric salts of strong acids, or combinations of mercuric salts such as mercuric acetate with strong acids. Several modifications of this reaction are described; yields range from about 50% to near-quantitative. A possible reaction scheme is proposed.

In a recent publication we described the reaction of a vinyl ether, $CH_2{=}CH{-}OR$, with an alcohol, $R'OH$, in the presence of a weak acid salt of mercury to effect a vinyl transfer, leading to a new vinyl ether, $CH_2{=}CH{-}OR'$, and ROH. It was postulated that this reaction proceeded through a symmetrical intermediate, labile to weak acid, of the form $\begin{matrix} RO \\ R'O \end{matrix}\!\!>\!CHCH_2HgX$, which could break down either to starting material or to products, thus explaining the equilibrium character of this reaction.

A second type of symmetrical intermediate, closely analogous to that above, but one which is derived from the allyl ether system, was then conceived. This postulated intermediate was $ROCH_2CHCH_2OR'$, expected to be labile to strong acid, with HgX in the 2-position, which would make possible a reaction of allyl transfer. We now report the successful confirmation of this prediction by the discovery of novel methods of preparation of allyl ethers.

The reactions studied were the following:

$$CH_2{=}CHCH_2OR + R'OH \rightleftharpoons CH_2{=}CHCH_2OR' + ROH \quad (1)$$

$$CH_2{=}CHCH_2OH + ROH \longrightarrow CH_2{=}CHCH_2OR + H_2O \quad (2)$$

A third reaction,

$$(CH_2{=}CHCH_2)_2O + 2ROH \longrightarrow 2CH_2{=}CHCH_2OR + H_2O \quad (3)$$

was also studied separately since allyl ether is readily available and is a convenient source of allyl goups. In detail, it is most probably a combination of the first two reactions. Thus it may proceed by formation first of the desired alkyl allyl ether and allyl alcohol, then by reaction of allyl alcohol as in (2).

Catalysts. For the three reactions, certain mercuric salts of strong acids, or mercuric salts in the presence of strong acids, were specific catalysts. No other inorganic salts that were tested, either in the presence or absence of strong acid, nor strong acid alone, proved to have catalytic activity when used at the concentrations at which the mercuric salts were effective. Neither reaction (1) nor the modification (3) have hitherto been reported in the literature. Reaction (2), however, is a known method for the preparation of allyl ether,[4] but large amounts of strong acids are required; and in the one reported case in which a metal was used (cuprous chloride, with hydrochloric acid, ammonium chloride, and copper metal[5]), the concentration of catalyst used was greater than that required of the mercuric salts. Thus the cuprous salt was used at about 0.2 mole per mole of allyl alcohol, whereas in this work mercuric salt on the order of 0.01–0.05 mole per mole of allyl compound was sufficient. Since in reactions (2) and (3) inactivation of catalyst through reduction to metallic mercury occurred rapidly, this amount was usually added in several increments.

A survey of a variety of mercuric salt or mercuric salt-acid combinations showed mercuric acetate-boron trifluoride etherate in equimolar combination to give the cleanest reaction and best yields. This combination was therefore used as our catalyst of choice throughout the reaction study. Interestingly, mercuric bromide or mercuric phosphate, although salts of strong acids, were not found to be active.

Reaction Conditions. Reaction (1) was effected simply by mixing the reactants, adding catalyst, and distilling off the new allyl ether. This technique, is, however, highly restricted, since most of the alkyl allyl ethers with alkyl groups containing more than four carbon atoms have boiling points very close to those of their parent alcohols, and separation of the allyl ether from the alcohol by distillation is exceedingly difficult. When this method is possible, however, the yield is high.

Reactions (2) and (3) avoid this limitation, since they may be driven to completion either by

(1) For the previous paper in this series, see W. H. Watanabe, *J. Am. Chem. Soc.*, **79**, 2833 (1957).

(2) Presented at the 133rd Meeting of the American Chemical Society, San Francisco, Calif., April 15, 1958.

(3) Present address, Shawinigan Resins Corp., Springfield, Mass.

(4) Senderson, *Compt. rend.*, **181**, 699 (1925); E. Moffett, *J. Am. Chem. Soc.*, **56**, 2009 (1934).

(5) P. Kurtz, *Ann.*, **572**, 23 (1951).

removal of water or by removal of the product if it is lower-boiling than the water-allyl alcohol or water-solvent azeotrope. The general method used was to mix the reactants, add catalyst and a solvent such as benzene, which forms an azeotrope with water, and reflux the mixture through a continuous water separator. The progress of the reaction could be followed by the appearance of water, and increments of catalyst were added when necessary. Yields by this method were on the order of 50%. Typical results are given in Table I.

TABLE I

YIELDS IN THE PREPARATION OF ALLYL ETHERS

Allyl Ether Prepared From	Allylating Agent	Reaction	Yield, %
Methyl alcohol	Allyl ethyl ether	1	85
Methyl alcohol	Allyl alcohol	2	94
Methyl alcohol	Allyl ether	3	67
Allyl alcohol	Allyl alcohol	2	46
n-Butyl alcohol	Allyl alcohol	2	55
n-Octadecyl alcohol	Allyl alcohol	2	47
n-Octadecyl alcohol	Allyl ether	3	71
Cyclohexanol	Allyl alcohol	2	42
Cyclohexanol	Allyl ether	3	58
Benzyl alcohol	Allyl alcohol	2	51

Discussion. While no detailed study of mechanism was undertaken, we consider it probable that, as in the vinyl transfer reaction,[6] these allyl transfer reactions occur by reversible alkoxymercuration. The over-all reactions may be:

$$CH_2{=}CHCH_2OR + R'OH + HgX_2 \rightleftharpoons CH_2{=}CHCH_2OR' + ROH + HgX_2$$

The normal direction of addition would be expected to be in the sense of (4a),[7] but such additions are reversible in strong acid[8] and it is necessary only that a small proportion of reaction pass through (II) for allyl transfer to occur.[9] The requirement that strong acid be generated or be added in order to cause allyl transfer is experimentally substantiated by the fact that mercuric acetate alone is ineffective.

Catalyst decomposition, which is marked when R = H, appears to be associated with the formation of acrolein and the reduction of the mercuric salt to free mercury, and thus probably arises from the normal addition intermediate (I).

4a: $XHgCH_2CHCH_2OR + HX$ (OR′) — I

4b: $R'OCH_2CHCH_2OR + HX$ (HgX) — II

EXPERIMENTAL

Since some toxic material, presumed to be acrolein, is liberated as a by-product when allyl alcohol or allyl ether are used as allylating agents, it is recommended that these reactions be carried out in a hood.

Catalytic studies. One mole of allyl alcohol was refluxed for a minimum of 1 hr. with 1.0 g. or more of the metal salt through a Dean-Stark continuous water separator. If water collected in the separator, the salt was considered active; of no water formed, the reaction mixture was cooled, 0.5–1.0 g. concentrated sulfuric acid was added, and reflux resumed. If no water formed within 1 hr., the salt was considered inactive. By this test the following salts were inactive: nickel bromide, nickel sulfate, cobalt acetate, cadmium acetate, zinc acetate, manganous chloride, aluminum chloride, and antimony trichloride. Cuprous chloride alone, or in the combination used by Kurtz, was not active at the concentration tested. Mercuric salts which were inactive included mercuric acetate, mercuric benzoate, mercuric bromide, mercuric phosphate, and crystalline mercuric sulfate. Finely ground mercuric sulfate, mercuric acetate plus sulfuric acid, mercuric acetate plus boron trifluoride etherate, and mercuric oxide plus boron trifluoride all showed high activity.

A comparison of mercuric acetate-sulfuric acid and mercuric acetate-boron trifluoride etherate showed the latter to be preferable: in 10 hr., 11.5 g. mercuric acetate with 3 g. of sulfuric acid in 3 moles allyl alcohol gave a 53% conversion to allyl ether and a 97% conversion to metallic mercury; in 3 hr., 11.5 g. mercuric acetate with 3 g. boron trifluoride (20% in ether) in 3 moles allyl alcohol gave a 63% conversion to allyl ether and 82% conversion to metallic mercury.

Preparation of allyl methyl ether. Further catalyst studies. This is an example of reaction (1). To a mixture of 34.4 g. (0.4 mole) allyl ethyl ether and 51.2 g. (1.6 moles) methyl alcohol (boiling point of mixture 56.8°) was added 3.83 g. (*ca.* 3 mole % on ether) mercuric acetate and 1.0 g. (*ca.* 90 mole % on mercury) concentrated sulfuric acid, and the mixture brought to reflux. After 40 min. the vapor temperature had settled at 42.8°. Careful fractionation over a 4-hr. period produced 26.4 g. material, b.p. 42.8–43.5°, n_D^{25} 1.3729, 92% pure by bromine number, giving a yield of 85%. During this distillation the cloudy precipitate originally present in the reaction mixture slowly turned orange-red and remained as such throughout the fractionation. No metallic mercury was formed.

A portion of this product was carefully treated with phosphoric anhydride at room temperature until reaction ceased, and fractionally distilled: b.p. 42–42.3°, n_D^{25} 1.3759 (lit.,[10] b.p. 42.5–43°, n_D^{25} 1.3778–1.3803), d_4^{25} 0.7568.

(6) W. H. Watanabe and L. E. Conlon, *J. Am. Chem. Soc.*, **79**, 2828 (1957).

(7) E. Biilmann, *Ber.*, **33**, 1642 (1900); J. Sand and K. A. Hofmann, *Ber.*, **33**, 1359 (1900); K. A. Hofmann and J. Sand, *Ber.*, **33**, 2700 (1900).

(8) R. Adams, F. L. Roman, and W. N. Sperry, *J. Am. Chem. Soc.*, **44**, 1781 (1922); for further references see J. Chatt, *Chem. Revs.*, **48**, 7 (1951).

(9) A splitting of allyl ether to allyl alcohol in the presence of water, nitric acid, and mercuric acetate is implied in the results of R. K. Summerbell, G. Lestina, and H. Waite, *J. Am. Chem. Soc.*, **79**, 234 (1957). This would be the case where R = $CH_2{=}CHCH_2$ and R′ = H in the mechanism above.

(10) J. C. Irvine, J. L. A. Macdonald, and C. W. Soutar, *J. Chem. Soc.*, **107**, 337 (1915).

Anal.[11] Calcd. for C_4H_8O: C, 66.63; H, 11.18. Found: C, 66.71; H, 11.22.

Continued distillation of the residue from the original preparation gave a 92% recovery of excess methyl alcohol and a 57% yield of ethyl alcohol.

To an identical mixture of allyl ethyl ether and methyl alcohol, only the mercuric acetate was added and reflux carried out for 1 hr. The boiling point remained at 56.8°. When 1.0 g. sulfuric acid was added, reaction occurred, as in the above example. Another such mixture of allyl ethyl ether and methyl alcohol was refluxed for 2 hr. with 1.0 g. sulfuric acid alone, but no reaction occurred. Reflux for an additional 3 hr. after the addition of 1.0 g. boron trifluoride etherate similarly gave no reaction. Upon addition of 1.9 g. mercuric acetate, reaction occurred, giving allyl methyl ether (n_D^{25} 1.3730) with less than 1 hr. reflux. Reflux of another such mixture of allyl ethyl ether and methanol with 4 g. of 0.72*M* sodium methoxide in methanol for 1.2 hr. gave no reaction.

Examples of reaction (2). Preparation of allyl cyclohexyl ether. A mixture of 99 g. (1 mole) cyclohexanol, 70 g. (1.2 moles) allyl alcohol, 57 g. benzene, 1.5 g. of 45% solution of boron trifluoride in ether, and 4.6 g. (0.04 mole) mercuric acetate was heated under reflux, and the reflux condensate collected in a Dean-Stark water separator. After reflux for 1 hr., 1.6 g. of the boron trifluoride solution and 4 g. mercuric acetate were added and reflux continued for an additional 2 hr. The reaction mixture was then flash-distilled at 0.1 mm. into a receiver cooled with Dry Ice-acetone, and the distillate washed four times with 50 ml. portions of water, dried, and fractionated. An 86.2 g. yield of material, b.p. 81–89°/36–37 mm., found by bromine number analysis to be 84% pure, was obtained. The yield was thus 42% based on cyclohexanol. The crude product was dissolved in an equal volume of benzene, 5 g. boric acid added, and azeotropic distillation carried out until no further water separated out. The pure allyl cyclohexyl ether was then obtained by fractional distillation: b.p. 81–83.5°/38–39 mm., n_D^{25} 1.4483, d_4^{25} 0.8830.

Anal. Calcd. for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 76.51; H, 11.49.

(11) Microanalyses by Mr. C. W. Nash and associates.

By essentially identical procedures *allyl ether* was prepared in 46% yield: b.p. 94–94.8°, n_D^{25} 1.4134, d_4^{25} 0.8027.

Anal. Calcd. for $C_6H_{10}O$: C, 73.43; H, 10.27. Found: C, 73.43; H, 10.13.

The same method gave *allyl n-butyl ether*, b.p. 64–65°/120 mm., n_D^{25} 1.4029, d_4^{25} 0.7794 (lit.[12] b.p. 117.8–118°/763 mm., n_D^{20} 1.4057, d_4^{20} 0.7829), in 55% yield.

The same method gave *allyl octadecyl ether* in 47% yield: b.p. 146–153°/0.15–0.20 mm., m.p. 26–27°.

Anal. Calcd. for $C_{21}H_{42}O$: C, 81.21; H, 13.63. Found: C, 81.10; H, 13.62.

Allyl benzyl ether was also prepared in 51% yield by this method: b.p. 71–71.5°/5 mm., n_D^{25} 1.5052, d_4^{25} 0.9548.

Anal. Calcd. for $C_{10}H_{12}O$: C, 81.04; H, 8.16. Found: C, 81.43; H, 8.60.

Example of reaction (3). The preparation of allyl octadecyl ether. A solution of 135 g. (0.5 mole) *n*-octadecyl alcohol in 85 g. benzene was prepared and in this solution there were dissolved, in order, 46.6 g. (0.4 mole) allyl ether, 2.0 g. mercuric acetate, and 1.0 g. of a 45% solution of boron trifluoride in ether. The solution was heated under reflux, and the condensate led through a continuous water separator. After 3 hr., 3 g. of an aqueous layer had separated and the solution had turned quite dark. An additional 2.0 g. mercuric acetate and 1.0 g. boron trifluoride solution were added and reflux continued until another 1.5 g. of an aqueous layer had separated.

In order to remove unreacted alcohol, 5 g. boric acid was next added and reflux resumed until no further water appeared. The reaction mixture was then stripped by heating to 97° under 0.35 mm. pressure, and the residue then fractionally distilled to give 110.2 g. allyl octadecyl ether, b.p. 146–152°/0.30 mm., a yield of 71% based on octadecyl alcohol.

Acknowledgment—We wish to acknowledge the technical assistance of Mr. Charles D. Stills in a portion of this work.

(12) E. A. Talley, A. S. Hunter, and E. Yanovsky, *J. Am. Chem. Soc.*, **73**, 3528 (1951).

PHILADELPHIA, PA.

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF CALIFORNIA]

Reactions of Succinyl Dichloride with Organometallic Reagents[1]

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The reaction of diethylcadmium with succinyl dichloride gives no 3,6-octanedione but yields instead γ-ethyl-γ-caprolactone, succinic anhydride, and both pseudo and normal ethyl esters of γ-ketocaproic acid. These products are shown to be consistent with the view that succinyl dichloride is a normal open-chain structure, but γ-ketocaproyl chloride is a cyclic structure (γ-chloro-γ-caprolactone). The reaction of ethylmagnesium bromide with succinyl dichloride also yields products consistent with the above-cited structures. Although the cadmium reaction with succinyl dichloride appears of no value for practical preparative purposes, the Grignard reaction with this dichloride furnishes a useful synthesis of γ-keto acids. The mechanism of the Grignard reaction with acid chlorides in presence of ferric chloride is discussed, and it is suggested that the key step involved, which leads to high yields of ketones, is extraction of halogen from the acid chloride by ferric chloride.

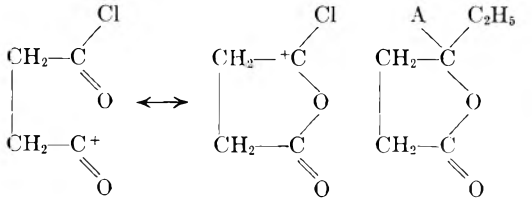
In view of recent evidence[2] that succinyl dichloride exists as the normal open-chain diacid dichloride and that γ-keto acid chlorides exist at room temperature as cyclic structures (γ-chloro-γ-lactones), it is of interest to determine whether the reactions of succinyl dichloride with Grignard and cadmium reagents yield products consistent with such structures. These reagents are selected

(1) This investigation was supported in part by a research grant (E-86) from the National Institutes of Health, U. S. Public Health Service. A part of these data was presented at the 127th meeting of the American Chemical Society, Cincinnati, Ohio, March 30, 1955.

(2) J. Cason and E. J. Reist, *J. Org. Chem.*, **23**, 1492 (1958).

because the Grignard reagent is believed to react with an acid chloride by addition to carbonyl,[3] whereas the cadmium reagent is believed[4] to react by initial extraction of chlorine from the acid chloride. Of further interest is the reaction of succinyl dichloride with the Grignard reagent in the presence of anhydrous ferric chloride. This reaction has been recently demonstrated[5,6] to constitute an effective preparation of ketones, and certain proposals concerning the mechanism of the reaction have been presented. Examination of these reactions of succinyl dichloride is the subject of the present report.

Reactions with diethylcadmium. According to the mechanism which has been described[4] for reaction of a cadmium reagent with an acid chloride, the initial reaction product from succinyl dichloride would be the cyclic acylonium ion represented in two resonance forms in I. Attack by the



carbanion from the cadmium reagent (or by some other species equivalent to the carbanion) at the position of the charge in form Ib would yield the cyclic form (II) of γ-ketocaproyl chloride. Attack at the position of charge in form Ia would yield the open-chain form of γ-ketocarproyl chloride; however, this has been shown[2] to cyclize rapidly at room temperature to the cyclic form, II. Since the cadmium reagent reacts relatively slowly with acid chlorides at room temperature,[7] it follows that the ultimate product of the reaction with diethylcadmium should be γ-ethyl-γ-caprolactone (III), arising from reaction of II with diethylcadmium. Examination of this reaction has indeed shown that none of the product expected (3,6-octanedione) from the normal diacid dichloride structure could be isolated, while γ-ethyl-γ-caprolactone was obtained, although in yields of only 13–15%.

The product obtained in largest amount (20–45% yields) from reaction of diethylcadmium with succinyl dichloride was ethyl γ-ketocaproate, isolated as a mixture of the normal open-chain ester and cyclic pseudo ester, IV. Ester formation in the cadmium reaction has been demonstrated[8] to result from reaction of the acid chloride with ether in presence of the Lewis acids in the reaction mixture; however, when as much ether as possible is distilled after formation of the cadmium reagent and the reaction with the acid chloride is carried out after addition of benzene (as was the case in the present work), ester formation is ordinarily of the order of magnitude of 5%. The large amount of ester in the present instance could arise from an unexpectedly high order of reactivity of the cyclic acid chloride, II, with ether; however, this was found to be not the case. A cadmium reaction with γ-ketocaproyl chloride yielded only 6% or less of ethyl γ-ketocaproate and about 17% of lactone III. Since about 20% recovery of γ-ketocaproic acid was realized from the reaction, it would appear that acid chloride II is relatively inert towards reaction with either ether or the cadmium reagent, in line with expectations arising from steric considerations and the structure II.

In the hope that the bulkier di-*n*-butyl ether would reduce the yield of ester, one reaction between succinyl dichloride and diethylcadmium was carried out in that ether as solvent. In this instance, the yield of *n*-butyl γ-ketocaproate proved to be about 40%, and the yield of lactone III dropped to about 5%. The higher yield of butyl ester may be ascribed to the fact that the ether was sole solvent for the reaction, whereas benzene was the principal solvent in reactions utilizing diethyl ether.

Since acid chloride II is unreactive towards ether in presence of the cadmium reagent, no high order of reactivity would be expected for the cyclic ion, I. The only rationale which appears able to account for the high ratio of ester is a cyclic transition state involving succinyl dichloride. The driving force behind a reaction involving such a transition state would be the lower energy of cyclic products with five-atom rings and distribution of steric interferences between two centers of reaction. A form such as V would yield the product, VI, which is a cyclic structure for an ester acid chloride, a form not encountered in a rather careful investigation of such compounds.[9] An intermediate such as VI would be expected to either lose ethyl chloride to yield succinic anhydride or react with the cadmium reagent to give the pseudo ester, IV. Succinic anhydride was isolated from the reaction in 15% yield, and the ethyl γ-ketocaproate was somewhat less than one-half pseudo ester, recognized by its infrared absorption at 5.64 μ and by the high index of refraction of the ester from the cadmium reaction. Since pseudo ester is rearranged to normal ester with acid catalysis,[10]

(3) C. E. Entemann and J. R. Johnson, *J. Am. Chem. Soc.*, **55**, 2900 (1933).

(4) J. Cason, *J. Org. Chem.*, **13**, 227 (1948).

(5) W. C. Percival, R. B. Wagner, and N. C. Cook, *J. Am. Chem. Soc.*, **75**, 3731 (1953).

(6) R. T. Morrison and M. Wishman, *J. Am. Chem. Soc.*, **76**, 1059 (1954).

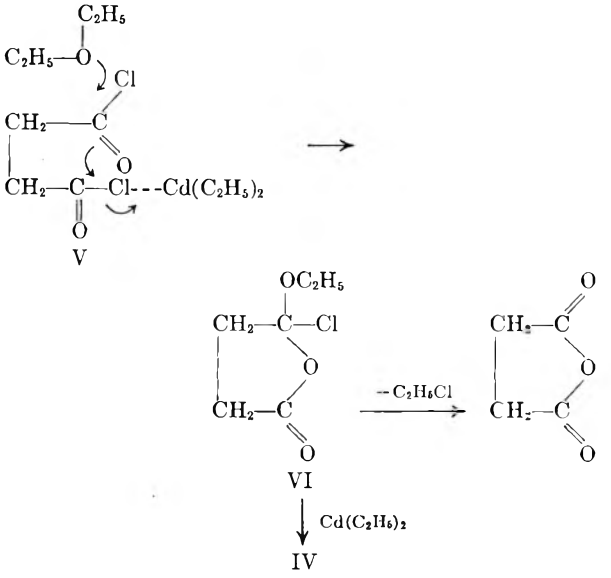
(7) J. Cason, *J. Am. Chem. Soc.*, **68**, 2078 (1946).

(8) J. Cason, *Chem. Revs.*, **40**, 15 (1947).

(9) J. Cason and R. D. Smith, *J. Org. Chem.*, **18**, 1201 (1953).

(10) D. P. Langlois and H. Wolff, *J. Am. Chem. Soc.*, **70**, 2624 (1948).

isolation of normal ester would be expected on account of Lewis acids in the reaction mixture; however, presence of any psuedo ester must be interpreted as evidence of its formation in the initial reaction. For comparison purposes, a modification of the procedures of Langlois and Wolff[10] was used to prepare the pseudo esters of both levulinic and γ-ketocaproic acids.



Thus, the available information concerning the high ratio of ester formation from succinyl dichloride may be correlated on the basis of a cyclic transition state such as V, in which there may be involved other Lewis acids than the organocadmium reagent (both cadmium chloride and magnesium halides are present in the reaction mixtures). Such a transition state would be expected to be less favored in the case of glutaryl dichloride, where the ring would contain six atoms, and this behavior has been observed in investigations of glutaryl dichloride (see following paper).

Reactions with ethylmagnesium bromide. The Grignard reaction with succinyl dichloride gave significantly different ratios of products under three different conditions investigated. The products isolated are summarized in Table I, in which are also included for comparison the products obtained from the cadmium reaction. The striking difference in products attests the different mechanisms of these two reactions.

Although there were used nearly two moles of Grignard reagent per mole of succinyl dichloride, it may be noted that the principal reaction product at 0° is γ-ketocaproyl chloride, isolated as γ-ketocaproic acid after hydrolysis. Isolation of this product is ascribed to the low reactivity[11] of the

TABLE I

YIELDS[a] IN REACTIONS OF SUCCINYL DICHLORIDE WITH ORGANOMETALLIC REAGENTS

Compounds Isolated	Yield[b] from Diethyl-cadmium	Yield from Ethylmagnesium Bromide		
		0°	−40°	−40°, FeCl₃
Ethyl γ-keto-caproate	20–45%	4%	—	—
γ-Ethyl-γ-caprolactone (III)	13–15%	6%	4–10%	12%
γ-Ketocaproyl chloride[c] (II)	—	54%	8%	14%
3,6-Octanedione[d]	—	3–7%	2–7%	23%
3-Ethyloctane-3-ol-6-one[e]	—	—	13–19%	—

[a] Yield figures are approximate since they were determined by isolation, and some of the isolations were troublesome. A range is indicated where significant variations were observed in different runs. In some reactions, other unidentified fractions were isolated; *cf.* Experimental. [b] In one run, after solvent had been distilled from the product the residue was allowed to stand overnight before fractional distillation. There crystallized a 15% yield of succinic anhydride; after recrystallization, m.p. 119–120°, no depression on admixture with an authentic sample of succinic anhydride. In the other runs, this substance was probably hydrolyzed during the work-up. [c] Isolated as γ-ketocaproic acid, after hydrolysis. [d] Isolated as 2-methyl-3-ethyl-2-cyclopentenone, after cyclization by alkali. [e] Isolated largely as the dihydrofuran resulting from dehydration of the hemiacetal. The yield of this material in the −40° run was probably considerably higher than indicated, for considerable quantities of higher-boiling material were obtained, and the properties of this material indicated that it is a dimer of the dehydration product of the hydroxy ketone (*cf.* Experimental).

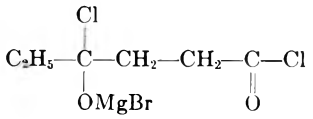
halogen in the cyclic form (II) towards the Grignard reagent, hence slow conversion at 0° to γ-ethyl-γ-caprolactone (III). A low order of reactivity of the carbonyl group in II is also expected on account of the high yields of lactones obtained[12] in reaction of a Grignard reagent with ethyl levulinate. The insignificant yield of ethyl γ-ketocaproate is consistent with the high reactivity of the Grignard reagent (in comparison with the cadmium reagent), which renders diethyl ether unable to compete effectively for reaction with acid chloride. This is observed in all Grignard reactions except those with highly hindered acid chlorides where extraction of halogen by a Lewis acid becomes a significant reaction path.

The small yield of 3,6-octanedione (or its further reaction products) can be rationalized only on the basis that the initial product of the Grignard re-

(11) Recovery of γ-ketocaproyl chloride from the Grignard reaction with succinyl dichloride, and failure to recover this acid chloride from the cadmium reaction, as reported in Table I, should not be interpreted as demonstrating a higher order of reactivity of the cadmium reagent towards an acid chloride. A recent investigation [J. Cason and R. J. Fessenden, *J. Org. Chem.*, 22, 1326 (1957)] has shown that the cadmium reagent is far less reactive than the Grignard reagent. The cadmium reaction reported in Table I was continued for 3 hours at 40° and for an additional 2 hours under reflux in benzene solvent. Even under these conditions, when γ-ketocaproyl chloride was used as starting material in the reaction with diethylcadmium, 20% of it failed to react.

(12) J. Cason, P. B. Brewer, and E. L. Pippen, *J. Org. Chem.*, **13**, 239 (1948).

action, VII, loses magnesium halide more rapidly than it reacts with another mole of Grignard reagent, and also the resultant γ-keto acid chloride

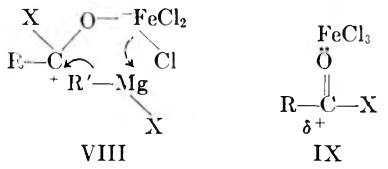


VII

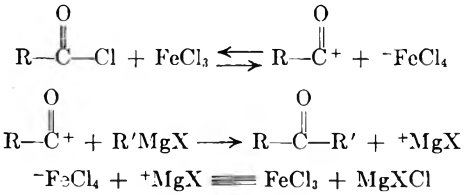
closes to the γ-chloro-γ-lactone (II) more rapidly than it reacts with Grignard reagent. An alternate explanation that structure II is formed directly *via* a cyclic transition state such as V, wherein Grignard reagent takes the place of ether and magnesium halide takes the place of cadmium reagent, seems invalidated by the large drop in yield of acid chloride II when the temperature is lowered to −40°. This observation also renders unlikely the direct conversion of VII to II by displacement of halogen from the carbonyl group in VII. Such an intramolecular reaction involving a five-atom ring would hardly be expected to have a higher energy of activation than reaction of the acid chloride with Grignard reagent.

The drop in yield of acid chloride II when the temperature is lowered to −40° can only be ascribed to this substance not being formed at the lower temperature, for it would certainly survive if formed. Acid chloride II may fail to form either because intermediate VII becomes stabilized at this temperature or because the open-chain γ-ketocaproyl chloride reacts with Grignard reagent at −40° more rapidly than it cyclizes. Since the latter seems unlikely on grounds cited in the preceding paragraph, intermediate VII probably survives for a sufficient time to allow reaction with additional Grignard reagent to give the dimagnesium derivative. The dimagnesium derivative must lose magnesium halide at a significant rate at −40° to give 3,6-octanedione, for the major product of the low temperature reaction (in addition to a higher-boiling, unidentified fraction) is the keto alcohol resulting from further reaction of 3,6-octanedione.

Mechanism of the Grignard reaction in presence of ferric chloride. The only reaction reported in Table I which gives 3,6-octanedione as the major product is the low temperature Grignard reaction in presence of ferric chloride. The yield of dione is more than three times that obtained in absence of ferric chloride. Since none of the keto alcohol, from further reaction of the dione, could be isolated, it must be concluded that ferric chloride does not simply promote the Grignard reaction with a carbonyl group, but rather that it has a specific effect in favoring reaction with an acid chloride. Previous investigators have suggested[6] that the effect of ferric chloride arises from its participation in a cyclic transition state (VIII) of the type suggested by Swain and Boyles[13] for reaction of a ketone with a Grignard reagent. An alternate suggestion[5] differed somewhat, in that there was visualized an intermolecular reaction between the ferric chloride complex, IX, and a carbanion (or equivalent) from the Grignard reagent. These explanations have in common a failure to differentiate between carbonyl in an acid chloride and in other structures such as a ketone. Since our data show that ferric chloride promotes discrimination in favor of an acid chloride, a satisfactory mechanism must include this factor, and must also involve regeneration of ferric chloride which is used in catalytic amounts. A mechanism which seems consistent with the experimental observations is that presented in the following equations:



VIII IX



This mechanism embodies the essential features of the mechanism proposed[4] for reaction of the cadmium reagents, except that ferric chloride functions as a stronger Lewis acid which will extract halogen at lower temperatures than those at which cadmium reagents are effective. The reality of this mechanism may be checked by investigation of a compound which gives rise to rearrangement if the acylonium ion is formed.[9] It has already been demonstrated[9] that ferric chloride at room temperature does promote rearrangement attributed to extraction of halogen from an acid chloride to give the acylonium ion. The only facts not established are reactivity of ferric chloride in this regard at −40°, and ability of ferric chloride to compete with the Grignard reagent in reaction with an acid chloride. Such an investigation is presently under way in these laboratories.

EXPERIMENTAL[14]

The pseudo methyl ester of levulinic acid was prepared for determination of its infrared spectrum. The procedure of Langlois and Wolff[10] was used; however, the semicarbazone

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

(14) Melting points are corrected and boiling points are uncorrected. Distillations, unless otherwise specified, were through a half-meter column of the simple Podbielniak type which has been described in detail (J. Cason and H. Rapoport, *Laboratory Text in Organic Chemistry*, Prentice-Hall, Inc., New York, 1950, pp. 237–243). Infrared spectra were recorded on a Baird double beam spectrophotometer. Microanalyses are by the Microanalytical Division, Department of Chemistry, University of California.

of the normal ester could not be completely precipitated, even on addition of a large volume of diethyl ether. Distillation yielded a sample of pure pseudo ester, however, b.p. 93–95°/15 mm., n_D^{25} 1.4330, single carbonyl band in the infrared spectrum at 5.64 μ. From the distillation residue could be isolated semicarbazone of the normal ester, m.p. 175° (dec.).

Pseudo ethyl ester of γ-ketocaproic acid. This ester was obtained in very poor yield when pyridine was used as base in the reaction; however, a satisfactory procedure using sodium carbonate was developed.

The acid chloride of γ-ketocaproic acid was prepared from 26 g. of acid by the procedure previously described.[2] To a mixture of 60 ml. of absolute ethanol and 25 g. of anhydrous sodium carbonate, the acid chloride was added dropwise with vigorous shaking as the *p*H was held above 6 and the temperature was held below 30°. After the addition had been completed during a 5-hr. period, shaking was continued for an additional hour, after which 100 ml. of ether was added. After removal of salt by filtration and of solvent by distillation, there was obtained a residue of 24.9 g. of crude ester. To this ester were added 40 ml. of absolute ethanol, 14.4 g. of semicarbazide hydrochloride and 12 g. of sodium acetate, then the mixture was shaken for 25 hr. After addition of a large volume of dry ether the precipitated material was removed by filtration. Removal of solvent at reduced pressure from the filtrate left 16 g. of residue which was distilled to yield a product, b.p. 91–94°/9 mm., cloudy with a trace of inorganic material. After standing overnight, the clear supernatant liquid was decanted to give a colorless product, n_D^{18} 1.4400.

Anal. Calcd. for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.67; H, 8.76.

The infrared spectrum exhibited a single carbonyl band at 5.64 μ.

The normal ethyl ester of γ-ketocaproic acid was obtained either by reaction of diethylcadmium with γ-carbethoxybutyryl chloride[2] or by esterification of the keto acid with ethanol in presence of sulfuric acid; b.p. 92°/9 mm., n_D^{25} 1.4233. The infrared spectrum exhibited a single carbonyl band at 5.80 μ.

Reaction of diethylcadmium with succinyl dichloride.[15] (*A*). In 425 ml. of anhydrous diethyl ether, there was prepared in the usual manner, under an atmosphere of nitrogen, a Grignard reagent from 98 g. (0.90 mole) of redistilled ethyl bromide and 21.6 g. (0.90 g.-atom) of magnesium. The solution of Grignard reagent was cooled to 0°, 90 g. (0.50 mole) of powdered anhydrous cadmium chloride was added in several portions during about 2 min., then the cooling bath was removed and the solution stirred 10 min. before it was stirred under reflux until a negative Gilman test for Grignard reagent was obtained (usually about 30 min.). After a negative test for Grignard reagent had been obtained ether was distilled until rate of distillation became slow, then 300 ml. of anhydrous thiophene-free benzene was added, and an additional 100 ml. of solvent was distilled. Finally, 350 ml. of additional dry benzene was added and the solution was cooled with stirring to 5–14° with an ice bath. A solution of 50 g. (0.325 mole) of succinyl dichloride in 150 ml. of benzene was added during about 2 min. The stirred mixture was allowed to warm to 38–40° and held at this temperature for 3 hr., after which it was heated under reflux for an additional 2 hr. After addition of ice and 12*N* sulfuric acid and extraction of the aqueous phase with benzene, the total benzene solution was washed with sodium carbonate solution twice and with water three times. Distillation from a Claisen flask of the material recovered from the benzene solution yielded 30.3 g. of colorless liquid, b.p. about 60°/1 mm. Fractionation of this product through the column at 9 mm. pressure yielded the fractions tabulated below:

Fraction	Weight, g.	Boiling Point	n_D^{25}
1	1.62	72–82°	1.4562
2	2.41	82–90°	1.4467
3	13.31	90–93°	1.4296
4	4.00	93–103°	1.4356
5	5.07	103.5–104°	1.4476
6	0.47	103.5°	1.4469

Fraction 3 gave an analysis in agreement with that of an ethyl ester of γ-ketocaproic acid (center cut used for analysis).

Anal. Calcd. for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.52; H, 8.93.

The infrared spectrum of frac. 3 exhibited two carbonyl bands, at 5.64 μ and at 5.80 μ. The index of refraction indicates somewhat less than 50% pseudo ester in the mixture. A semicarbazone, prepared by a common method[16] from frac. 3, had m.p. 106.0–106.5°; the semicarbazone of ethyl γ-ketocaproate has been reported[17] as melting at 106°.

Fraction 6 (center cut of frac. 5) gave an analysis in agreement with that of γ-ethyl-γ-caprolactone.

Anal. Calcd. for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.32; H, 9.80.

The infrared spectrum of this fraction showed a single carbonyl band at 5.68 μ, the expected position[18] for a γ-lactone. Frac. 5 was insoluble in water but dissolved in 10% aqueous sodium hydroxide; acidification of the alkaline solution yielded starting material. A *hydroxy hydrazide* of the lactone was prepared from hydrazine by the procedure of Blaise[19] and recrystallized from ethyl acetate to yield a white product of m.p. 75–76°.

Anal. Calcd. for $C_8H_{18}N_2O_2$: C, 55.14; H, 10.41; N, 16.08. Found: C, 55.68; H, 10.11; N, 16.05.

The infrared spectrum of the hydroxy hydrazide, taken in a Nujol mull on account of insolubility in the common spectral solvents, exhibited a single carbonyl band at 6.10 μ. Thus, the structure must be that of a hydroxy hydrazide, as has been reported by others,[20] not the cyclic structure assumed by Blaise.[19]

In one run similar to that described above, solvent was removed from the benzene extracts and the residue was allowed to stand overnight. A crystallizate weighing 5 g. separated, and after recrystallization had m.p. 120°, no depression on admixture with an authentic sample of succinic anhydride.

(*B*). To 4.32 g. (0.18 g.-atom) of magnesium and 50 ml. of anhydrous di-*n*-butyl ether, stirred under an atmosphere of nitrogen, there was added a solution of 19.6 g. (0.18 mole) of freshly distilled ethyl bromide in 50 ml. of di-*n*-butyl ether at such a rate (about 1-hour addition time) that the temperature was held at about 40°. After the mixture had been stirred for an additional hour, there was added 10.0 g. (0.10 mole) of anhydrous cadmium chloride, then stirring was continued for another hour at about 80°. Since the Gilman test for Grignard reagent was still positive after this period, an additional 10 g. of cadmium chloride was added. After 15 min. additional stirring at 80°, the test for Grignard reagent had become negative. The reaction mixture was cooled to about 55°, and there was added during about one min. a solution of 10 g. (0.065 mole) of succinyl dichloride

(15) Succinyl dichloride used in reactions described in this paper was prepared by the method reported in ref. (2).

(16) R. L. Shriner and R. C. Fuson, *Identification of Organic Compounds*, John Wiley and Sons, Inc., New York, 1948, pp. 170, 171.

(17) M. Maire, *Bull. soc. chim. France*, [4], **3**, 285 (1908).

(18) R. S. Rasmussen and R. R. Brattain, *J. Am. Chem. Soc.*, **71**, 1073 (1949).

(19) E. E. Blaise, *Compt. rend.*, **140**, 790 (1905).

(20) R. M. Joyce, W. E. Hanford, and J. Harmon, *J. Am. Chem. Soc.*, **70**, 2529 (1948); J. B. Umland and S. A. Witkowski, *J. Org. Chem.*, **22**, 346 (1957).

dissolved in 50 ml. of di-*n*-butyl ether. The temperature of the reaction mixture rose to about 90° during 3 min., while becoming rather viscous and dark. Heating with stirring was continued for an additional 3 hr. at 75–80°, then the mixture was cooled and worked up as described for the reaction in diethyl ether. Fractional distillation at 9 mm. pressure yielded the following fractions:

Fraction	Weight, g.	Boiling Point	n_D^{25}
1	0.29	69–106°	1.4507
2	0.52	106–108°	1.4445
3	0.59	108–115°	1.4382
4	2.81	115–117°	1.4296
5	1.93	117°	1.4303

The boiling point and index of refraction of frac. 2 indicate that it consists largely of γ-ethyl-γ-caprolactone.

Fraction 4 has an analysis in agreement with that of a butyl ester of γ-ketocaproic acid.

Anal. Calcd. for $C_{10}H_{18}O_3$: C, 64.60; H, 9.68. Found: C, 64.38; H, 9.53.

The *semicarbazone*, prepared by a common method,[16] had m.p. 97.5–98.5°.

Anal. Calcd. for $C_{11}H_{21}N_3O_3$: C, 54.33; H, 8.69; N, 17.28. Found: C, 54.61; H, 8.40; N, 17.28.

Reaction of ethylmagnesium bromide with succinyl dichloride. There is described a representative run under each of the three conditions investigated.

(*A*) *At 0°.* To 120 g. (0.78 mole) of succinyl dichloride dissolved in 300 ml. of dry benzene, arranged for stirring under an atmosphere of nitrogen and cooled to 0°, there was added dropwise a solution in 600 ml. of ether of Grignard reagent prepared from 36 g. (1.5 g.-atoms) of magnesium and 180 g. (1.65 moles) of freshly distilled ethyl bromide. It had been found in earlier runs that use of ether alone as solvent was unsatisfactory on account of rapid precipitation of a complex which stopped the stirrer. The rate of addition of Grignard reagent was adjusted so that the temperature of the reaction mixture could be maintained in the range −5° to +5°. Soon after addition began, the reaction mixture turned brick red; as addition proceeded, the color gradually changed to orange. After addition had been completed the reaction mixture was stirred at 0° for 2 hr., then decomposed with ice and 12*N* sulfuric acid. The aqueous and organic phases were separated, the organic phase was washed once with water, then this phase was placed on a mechanical shaker for 10 hr.[21] with a saturated aqueous sodium carbonate solution. After the shaking period, the aqueous alkaline layer was separated and the organic phase was washed with water.

The sodium carbonate extract was acidified to Congo Red with 12*N* sulfuric acid, then continuously extracted with ether for 24 hr. Removal of ether from the extract left a residue of 60.6 g., which yielded on distillation 50 g. of γ-ketocaproic acid, b.p. 140°/10 mm., which solidified slowly on cooling. The semicarbazone of this acid had m.p. 164.0–164.2° and gave no melting point depression on admixture with the semicarbazone of an authentic sample of γ-ketocaproic acid.

The original aqueous phase obtained after decomposition of the Grignard complex was also continuously extracted with ether for 24 hr. This extract yielded an additional 2 g. of γ-ketocaproic acid, b.p. 120°/4 mm., and 3 g. of ethyl-γ-ketocaproate, b.p. 90°/10 mm., infrared spectrum identical with that of the normal ethyl ester of γ-ketocaproic acid.

The organic phase from which the keto acid was extracted with carbonate contained neutral material which was not readily separated by direct distillation; however, the products obtained after alkali treatment could be partially separated. The residue remaining after removal of solvent was heated under reflux for 4 hr. with excess 10% aqueous sodium hydroxide. The cooled basic solution was extracted five times with ether, and each extract was washed once with water. Removal of solvent from the dried extract and distillation yielded 2.65 g. of impure 2-methyl-3-ethyl-2-cyclopentenone, b.p. 81–83°/10 mm., n_D^{25} 1.4600 (lit.,[22] b.p. 90°/15 mm.) The infrared spectrum showed bands at 5.93 and 6.01 μ, indicative of an α,β-unsaturated ketone, while the ultraviolet spectrum gave similar indication with a band of λ_{max} 235.5 mμ, ε 5400. As shown in the characterization of this compound in section (*C*) below, the extinction coefficient and index of refraction of this sample indicate that it is only about 40% cyclic ketone.

The basic solution remaining after extraction of the saponification mixture was acidified to Congo Red with 12*N* sulfuric acid, then extracted five times with ether. Distillation of the material recovered from this extract yielded 6 g. of γ-ethyl-γ-caprolactone, b.p. 107°/10 mm., n_D^{25} 1.4466. The infrared spectrum contained one carbonyl band at 5.69 μ.

When a reaction was carried out as described above except that there were used only 1.5 moles of ethyl bromide per mole of succinyl dichloride, the yield of γ-ketocaproic acid was reduced to 44%. Further reduction of ethyl bromide to 1.2 moles resulted in only 39% yield of γ-ketocaproic acid.

(*B*) *Grignard reaction at −40°.* The Grignard reaction was carried out in the general manner described under (*A*), except at lower temperature; and there were used as reactants 1 mole of magnesium and of ethyl bromide, 0.5 mole of succinyl dichloride. Addition of the Grignard solution to the dichloride, dissolved in 200 ml. of ether, was begun at −70°, but it was soon found necessary to allow the reaction mixture to warm up to the range −35° to −40° in order to prevent the precipitated complex from stopping the stirrer. After completion of the addition, which required about 3 hr., the mixture was decomposed with ice (the mixture was acidic without addition of acid).

After separation of the aqueous and organic phases from the reaction, the aqueous phase was extracted four times with ether. The ether extracts were washed once with water, then stirred under reflux for 1 hr. with 400 ml. of saturated aqueous sodium carbonate solution. The cooled ether phase was separated and extracted once more with saturated sodium carbonate solution and once with water. The aqueous phases were combined and acidified to Congo Red with 12*N* sulfuric acid, then extracted four times with ether. Distillation of the product recovered from the dried ether extracts yielded 5 g. of γ-ketocaproic acid, b.p. 115°/2 mm. The semicarbazone of this acid had m.p. 165–166° and gave no depression on mixing with an authentic sample.

Content of the *neutral fraction* remaining after carbonate extraction was evaluated by work-up in two ways. *Method (a), direct distillation.* The organic phase remaining after extraction with sodium carbonate was dried over magnesium sulfate, the solvent was removed by distillation, and the residue was distilled to yield the following fractions:

Fraction	Weight, g.	B.P./pressure	n_D^{25}
1	1.42	30–64°/20 mm.	—
2	11.24	64–68°/20 mm.	1.4422
3	2.41	69–109°/20–9 mm.	1.4527
4	1.80	109–111°/9 mm.	1.4589
5	1.85	111–148°/9–4 mm.	1.4705
6	1.35	*ca.* 148°/9–0.5 mm.	1.4823

(21) Simple extraction in a separatory funnel with carbonate yields a small amount of keto acid, and subsequent extractions continue to yield small amounts of acid. This behavior is ascribed to the fact that the material actually in the ether solution is γ-chloro-γ-caprolactone, which is hydrolyzed to the keto acid. This is supported by the observation that attempted distillation of the residue from the unextracted ether solution leads to evolution of hydrogen chloride and tar formation.

(22) E. E. Blaise, *Compt. rend.*, **158**, 709 (1914); H. Pringsheim and J. Leibowitz, *Ber.*, **56**, 2037 (1923).

Fraction 2 has a boiling point consistent with that expected for 2,2,5-triethyl-2,3-dihydrofuran (dehydration product of hemiacetal of 3-ethyl-3-hydroxy-6-octanone); however, elementary analysis was not in agreement with this formula, and it seems probable that this fraction is an azeotrope of the dihydrofuran with a small amount of the keto alcohol and/or the hemiacetal. Redistillation of frac. 2 gave material boiling sharply at 72°/28 mm., n_D^{25} 1.4390, infrared spectrum unchanged. The infrared spectrum exhibited weak carbonyl bands at about 5.9 and 6.0 μ, and the ultraviolet spectrum showed no significant absorption except for a rapid rise in absorption as the wavelength was decreased to 210 mμ (characteristic of a carbon-carbon double bond not conjugated). A usual method[16] for preparing semicarbazones gave a reasonable yield from frac. 2 of a derivative whose analysis was in agreement with that calculated for the *semicarbazone of 3-ethyl-3-hydroxy-6-octanone.*

Anal. Calcd. for $C_{11}H_{23}N_3O_2$: C, 57.61; H, 10.11; N, 18.32. Found: C, 57.55; H, 10.05; N, 18.12.

Shortly after recrystallization from water, this semicarbazone had m.p. 90–92° (literature,[23] m.p. 95°), but on standing the m.p. dropped to 79–82° (one recrystallized sample, which had been dried for several days, had m.p. 79.5–80.5°). The low-melting form was converted to the high-melting form by heating at 85–90° for 3–4 hr., and on standing at room temperature changed back to the low-melting form. This behavior suggests polymorphism in the semicarbazone; however, there is also the possibility of a change in structure related to keto alcohol and hemiacetal.

Fracs. 3 and 4 should contain any lactone or dione formed in the reaction; however, no pure components could be isolated until after the alkali treatment described below. The high-boiling material is also described below.

Method (b), alkali treatment prior to distillation. In a run carried out as described above, solvent was removed from the organic phase remaining after carbonate extraction to leave a residue of 35.2 g., which was heated under reflux with 10% aqueous sodium hydroxide for 4 hr. The cooled alkaline solution was extracted four times with ether, and the extracts were washed with water.

The total aqueous phases were acidified to Congo Red with 12*N* sulfuric acid and extracted four times with ether. There was recovered from this extract 3.0 g. of γ-ethyl-γ-caprolactone, b.p. 108–109°/12 mm., n_D^{25} 1.4470.

Material recovered from the extracts of neutral material was distilled to yield the following fractions:

Fraction	Weight, g.	B.P./pressure	n_D^{25}
1	1.95	<65°/20 mm.	1.4470
2	14.45	65°/20 mm.	1.4393
3	4.42	65–151°/20–4 mm.	1.4620
4	7.30	151–153°/4 mm.	1.4716

The characteristics of *frac. 2* were the same as described for this fraction in Method (a); these included analysis, infrared spectrum, and semicarbazone formation.

Fraction 3 contained very little material boiling in the range of 3-ethyl-2-methyl-2-cyclopentenone (93–97°/20 mm.); however, in another run there was isolated 3.8 g. (7% yield) of this product (for characterization, refer to run with ferric chloride). As indicated in Table I, the ratio of the several products obtained in this reaction was rather variable; this is ascribed partly to the uncertain reaction conditions resulting from the barely stirrable mixtures arising from complex precipitation, partly to the uncertainty introduced from the azeotropic material in frac. 2, and partly to the significant amount of high-boiling uncharacterized material described in the next paragraph.

Fraction 4 appears to be some type of dimer of the primary reaction products. No reaction with 2,4-dinitrophenylhydrazine or semicarbazide was observed. The infrared spectrum showed a broad, weak band in the carbonyl region near 6 μ, and a strong band in the ether region (8.9 μ). Redistillation yielded a component boiling sharply at 152–153°/4 mm., with unchanged infrared spectrum. The ultraviolet spectrum showed no absorption except the end absorption characteristic of a carbon-carbon double bond. Elementary analysis (C, 76.99; H, 11.57) is in fair agreement with $C_{20}H_{36}O_2$, the formula for a dimer of 2,2,5-triethyl-2,3-dihydrofuran.

(C) Grignard reaction at −40° in presence of ferric chloride. A reaction was carried out as described under section (*B*) using the same quantities of reagents, except that 1.5 g. (0.009 mole) of anhydrous ferric chloride was added to the succinyl dichloride solution before addition of Grignard reagent was begun. Addition was started at −65°, but during the course of the 2 hr. required for addition, the temperature was allowed to rise as high as −45° in order to prevent stopping of the stirrer by precipitated complex. After addition was complete, stirring was continued for an additional 5 min., then the reaction mixture was decomposed by pouring onto ice (mixture acid to Congo Red).

The aqueous and organic phases of the reaction mixture were separated, and the organic phase was washed first with water then three times with saturated aqueous sodium carbonate solution (shaking 5–10 min. with each wash), finally with water. The total aqueous carbonate extracts were acidified to Congo Red with 12*N* sulfuric acid and extracted four times with ether. The ether extracts were washed once with water and dried over anhydrous magnesium sulfate. From this extract was recovered 9.5 g. of γ-ketocaproic acid, b.p. 140–160°/10 mm., slowly solidifying on cooling. The semicarbazone, after crystallization from water, had m.p. 167–168° and showed no depression on mixing with an authentic sample of the semicarbazone of γ-ketocaproic acid.

From the extract of neutral material, remaining after carbonate extraction, there was recovered 26.5 g. Since no constant-boiling fractions could be separated by direct distillation, the distilled fractions (weight 22.5 g.) were combined and heated under reflux for 4 hr. with 450 ml. of 10% aqueous sodium hydroxide solution. The cooled basic solution was extracted four times with ether, and the ether extracts were washed once with water. The neutral material recovered from the ether extracts was distilled to yield 14.0 g. of 2-methyl-3-ethyl-2-cyclopentenone, b.p. 85°/10 mm., n_D^{23} 1.4810.

Anal. Calcd. for $C_8H_{12}O$: C, 77.37; H, 9.74. Found: C, 76.52; H, 10.09.

The infrared spectrum of the cyclopentenone showed strong bands at 5.9 and 6.05 μ, as expected for an α,β-unsaturated ketone. This was confirmed by the ultraviolet spectrum: λ_{max} 235 mμ, ϵ 13,500.

The *semicarbazone,* prepared as usual,[16] had m.p. 217–218° (dec.).

Anal. Calcd. for $C_9H_{15}N_3O$: C, 59.64; H, 8.34; N, 23.18. Found: C, 60.16; H, 8.61; N, 23.28.

The combined aqueous alkaline phases, remaining after saponification and extraction of neutral material, were acidified to Congo Red with 12*N* sulfuric acid and extracted three times with ether. Distillation of the material recovered from the ether extracts yielded 8.65 g. of γ-ethyl-γ-caprolactone, b.p. 108–110°/10 mm., n_D^{25} 1.4460.

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(23) Huan, *Compt. rend.*, **188**, 1175 (1929).

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF CALIFORNIA]

Reactions of Glutaryl Dichloride with Organometallic Reagents[1]

JAMES CASON AND ELMER J. REIST

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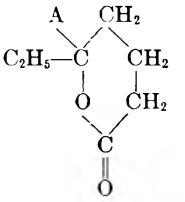
The infrared spectrum of glutaryl dichloride indicates that the substance is largely or entirely in a normal open-chain form. Reactions of glutaryl dichloride with diethylcadmium or with ethylmagnesium bromide yield products consistent with the view that this di-acid dichloride is of open-chain structure, but δ-ketoenanthyl chloride is of a cyclic structure (δ-chloro-δ-enantholactone). Formation of small amounts of 3,7-nonanedione in the cadmium reaction (in contrast with no yield of diketone in the cadmium reaction with succinyl dichloride) indicates the lesser stability of the six-atom ring with exocyclic double bond; also, δ-ethyl-δ-enantholactone was found to equilibrate readily with the isomeric γ- or δ-unsaturated acid. The striking preference of keto acid chlorides for the cyclic structure, however, is illustrated by the fact that the principal product of the Grignard reaction at 0° was found to be the cyclic δ-ketoenanthyl chloride, a result analogous to that obtained with succinyl dichloride. Grignard reactions, either with or without ferric chloride, could not be carried out satisfactorily below about −20° on account of precipitation of complexes; however, results at −20° indicated operation of the same factors observed in reactions of succinyl dichloride at −40°.

Investigation[2] of the reactions of succinyl dichloride has shown that the products may be formulated on the basis of the view[3] that this di-acid dichloride is a normal open-chain structure but γ-keto acid chlorides rapidly form a cyclic structure (γ-chloro-γ-lactone), even at temperatures as low as 0°. The present report is concerned with the structure and reactions of glutaryl dichloride, wherein the cyclic structures would have six-membered rings, a form less favored[4] than the five-membered ring in instances where there is an exocyclic double bond.

The infrared spectrum of glutaryl dichloride was found to exhibit a single carbonyl band at 5.60 μ, the normal location for a low molecular weight acid chloride and that observed[3] for succinyl dichloride. There was no indication of a second carbonyl band which might be ascribed to a cyclic form of the acid chloride. Quantitative determination of carbonyl absorption by glutaryl dichloride, calculated per mole of carbonyl present in the open-chain form, gave values in excellent agreement with those[3] for caprylyl chloride and pimelyl dichloride; however, the quantitative values are of little direct utility in supporting the open-chain structure of glutaryl dichloride, on account of the high absorption of a cyclic acid chloride with a six-membered ring. Whereas an open-chain acid chloride, such as caprylyl chloride, exhibits an ϵ_{max} of about 370, the cyclic δ-ketoenanthyl chloride (I) has λ_{max} at 5.65 μ, with ϵ_{max} of about 900. In view of this strong absorption at 5.65 μ in structure I, however, it does follow that absence of a second absorption band in glutaryl dichloride indicates little, if any, of the cyclic structure.



I, A = Cl
II, A = OC_2H_5 (not isolated)
III, A = C_2H_5

Reaction with diethylcadmium. Examination of the products obtained in the cadmium reaction with glutaryl dichloride, as summarized in Table I, reveals two differences from the results with succinyl dichloride.[2] Succinyl dichloride yielded none of the open-chain dione, and the principal product was keto ester, partly the cyclic pseudo ester (five-membered ring analogous to formula II). These differences are consistent with the greater ease of formation of cyclic products with the five-atom ring. Failure of the ester to result in significant amounts may be ascribed to involvement of the cyclic transition state previously suggested,[2] for the ends of a five-atom chain are in position to cyclize with greater frequency than are the ends of a six-atom chain. For example,[5] δ-chlorosulfides and δ-chloroamines cyclize to the heterocycles at a rate seventy to seventy-five times faster than do the corresponding ε-chlorosulfides and ε-chloroamines. In addition, cyclic compounds involved in the present instance would contain the carbonyl group, and correlations developed in connection with the concept of I-strain[4] have shown the exocyclic double bond to be less favored in the case of six-atom rings. By the same token, if there is involved in the cadmium reaction with δ-ketoenanthyl chloride the previously proposed[2] cyclic transition state shown in two resonance forms in IV, reaction to give the open-chain 3,7-nonanedione would be more favored when the cyclic product (lactone III) has the six-membered ring. Although the yield of dione from glutaryl dichloride is low, no

(1) This investigation was supported in part by a research grant (E-86) from the National Institutes of Health, U. S. Public Health Service.

(2) J. Cason and E. J. Reist, *J. Org. Chem.*, **23**, 1668 (1958).

(3) J. Cason and E. J. Reist, *J. Org. Chem.*, **23**, 1492 (1958).

(4) H. C. Brown, *J. Org. Chem.*, **22**, 439 (1957).

(5) G. M. Bennett, F. Heathcoat, and A. N. Mosses, *J. Chem. Soc.*, 1929, 2567; H. Freundlich and A. Krestovnikov, *Z. Physik. Chem.*, **76**, 79 (1911).

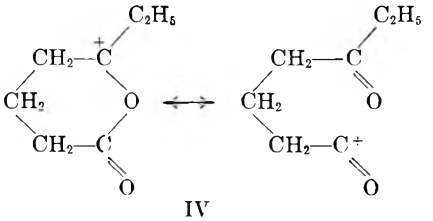
dione could be isolated in the cadmium reaction with succinyl dichloride.[2]

TABLE I

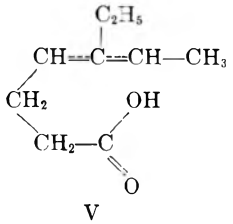
YIELDS[a] IN REACTIONS OF GLUTARYL DICHLORIDE WITH ORGANOMETALLIC REAGENTS

Compounds Isolated	Yield[b] from Diethyl-cadmium	Yield from Ethyl-magnesium Bromide		
		0°	−20°	−20°, $FeCl_3$
δ-Ethyl-δ-enantho-lactone[c] (III)	15–20%	11%	14%	17%
δ-Ketoenanthyl chloride[d] (I)	30–40	50	24	17
3,7-Nonanedione[e]	6–10	*ca.* 6	*ca.* 14	*ca.* 18
3-Ethylnonan-3-ol-7-one[a]	—	*ca.* 5	*ca.* 8	*ca.* 7

[a] Yield figures are approximate in all instances, for they were determined from isolation, and in some instances the isolations were troublesome. Yields preceded by *ca.* are subject to an additional uncertainty, in that mixtures of dione and hydroxy ketone were analyzed by infrared spectroscopy. Identity of the hydroxy ketone was not established with certainty. [b] Range of yields in the cadmium reaction is that observed in different runs. No yield of ethyl δ-ketoenanthate is indicated, although minor amounts of this ester were probably obtained (*cf.* Experimental). Considerable quantities of cyclic acid chloride were recovered in the cadmium reaction because the reaction was continued for only 2.5 hr. at 40°, with no additional heating under reflux as was done in reactions of succinyl dichloride reported separately.[2] This procedure was adopted in order to demonstrate the presence of the cyclic acid chloride as an intermediate. [c] Isolated in part as the isomeric unsaturated acid. [d] Isolated as δ-ketoenanthic acid, after hydrolysis. [e] Isolated in part as the cyclic aldol product, 2-methyl-3-ethyl-2-cyclohexenone.



IV

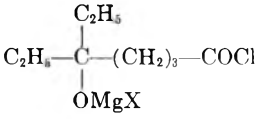


V

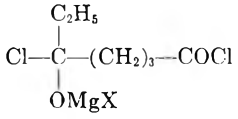
The persistence of the cyclic acid chloride (I), even when the six-atom ring is involved, attests the remarkable preference of the keto acid chlorides for the cyclic structure. In the instance of the 5-atom rings,[2] where the cyclic structure for the keto acid chloride was the only form encountered, the cyclic pseudo ester (analogous to II) was unstable with respect to the normal ester, in presence of acid. When the methods used for preparation of the pseudo esters of γ-keto acids were applied to δ-ketoenanthyl chloride (I), no pseudo ester could be isolated; the product exhibited the infrared spectrum of the normal ester. This result was not entirely unexpected on account of the failure to isolate ester from the cadmium reaction.

The lesser stability of six-atom rings caused some difficulty in isolation and characterization of δ-ethyl-δ-enantholactone (III), in both cadmium and Grignard reactions. Equilibration occurs between the lactone and the isomeric γ- or δ-unsaturated acid (V) in presence of mineral acid or during long heating in fractional distillation. By extraction with sodium carbonate, acid and lactone could be separated. Careful washing of the two components and rapid distillation yielded pure samples of acid showing a single carbonyl band at 5.87 μ and of lactone showing a single carbonyl band at 5.79 μ. The reported[6] region for carbonyl absorption in δ-lactones is about 5.75 μ.

Reactions with ethylmagnesium bromide. In the Grignard reaction at 0° with succinyl dichloride, the dominant formation (only product in yield greater than about 5%) of the cyclic form of γ-ketocaproyl chloride was attributed to the very rapid cyclization of the open-chain form of this acid chloride. With glutaryl dichloride, the cyclic keto acid chloride (I) remained the principal product; however, the yield of other products became about twice that observed with succinyl dichloride. This indicates occurrence of the predicted lower rate of cyclization of the open-chain form of δ-ketoenanthyl chloride. Reaction of the open-chain keto acid chloride at the acid chloride grouping would lead initially to 3,7-nonanedione, while reaction at the keto group (more reactive than the acid chloride) would give structure VI as the



VI



VII

initial product. Direct cyclization of this intermediate would lead to lactone III, while further reaction of the acid chloride grouping would lead to the hydroxy ketone, which was present in small amount.

In the Grignard reaction with succinyl dichloride, a dramatic drop in yield of cyclic acid chloride was observed when the reaction temperature was lowered to −40°. Mechanical difficulties (precipitation of unstirrable sludges) prevented lowering the temperature below about −20° in the case of glutaryl dichloride; so the change in products was less pronounced; however, even at −20°, there is observed a significant decrease in yield of cyclic acid chloride, and a proportional increase in products resulting from reaction of either the initial reaction intermediate, VII, or the open-chain keto

(6) E. E. van Tamelen and M. Shamma, *J. Am. Chem. Soc.*, **76**, 2315 (1954).

acid chloride. Thus, stabilization of the intermediate VII is indicated (for discussion of this point refer to ref. 2).

Failure to secure a significant increase in the yield of 3,7-nonanedione in presence of anhydrous ferric chloride is ascribed to the inability to secure a sufficiently low reaction temperature ($-70°$ has been previously recommended[7]); however, a small increase in yield of dione was observed.

As was the case in the reactions of succinyl dichloride, the only procedure of preparative significance is the Grignard reaction at 0°. This probably constitutes the most convenient preparation of γ- and δ-keto acids, respectively.

EXPERIMENTAL[8]

Glutaryl dichloride. Although it has been reported[9] that glutaryl dichloride may be prepared in 80% yield by treatment of glutaric acid with a fivefold excess of thionyl chloride, our maximum yield was about 68% and large amounts of glutaric anhydride were obtained. The use of catalytic amounts of pyridine, found essential in the preparation of succinyl dichloride,[3] gave excellent results.

(*A*) *Without pyridine.* A mixture of 100 g. (0.76 mole) of glutaric acid and 300 ml. (3.8 moles) of thionyl chloride was heated under reflux for 2.5 hr. After the excess thionyl chloride had been removed under reduced pressure the product was fractionated at 7 mm. pressure to yield 61 g. (47%) of glutaryl dichloride, b.p. 89°, and 40 g. (46%) of glutaric anhydride, b.p. 138°, m.p. 52°, no depression in melting point on admixture with an authentic sample of glutaric anhydride.

(*B*) *With pyridine catalyst.* A mixture of 40 g. (0.3 mole) of glutaric acid, 0.5 ml. of pyridine, and 120 ml. (1.5 moles) of thionyl chloride was heated under reflux for 3 hr. Distillation yielded 43 g. (84%) of glutaryl dichloride, b.p. 92–93°/10 mm.

Reaction of diethylcadmium with glutaryl dichloride. According to the procedure described[2] for reaction of diethyl cadmium with succinyl dichloride, a cadmium reagent was prepared *via* the Grignard reagent from 100 g. (0.84 mole) of distilled ethyl bromide and allowed to react with 40 g. (0.24 mole) of glutaryl dichloride. Reaction time was 2.5 hr. at 40°.

After decomposition of the reaction mixture by addition of ice and extraction of the aqueous phase with three portions of ether, the combined organic phases were washed first with water, then stirred overnight[10] with 450 ml. of saturated aqueous sodium carbonate solution. The sodium carbonate extract was acidified and extracted with four portions of ether. Removal of ether left a yellow solid which was recrystallized from ether–petroleum ether to yield 10 g. (29%) of white δ-ketoenanthic acid, m.p. 48.0–48.5°, no depression in melting point on admixture with an authentic sample[3] of δ-ketoenanthic acid.

The neutral material remaining after carbonate extraction was fractionated to yield the following fractions.

Fraction	Weight, g.	B.P. (10 mm.)
1	2.03	75–115°
2	1.79	115–125°
3	6.68	125–130°
4	2.15	(column stripped)

Ethyl δ-ketoenanthate would boil near 110° at this pressure, but no significant constant-boiling fraction was noted during distillation of Fraction 1.

Fraction 2, which solidified on standing, was recrystallized from hexane to yield white 3,7-nonanedione, m.p. 53.0–53.5° (literature,[11] m.p. 53°).

Anal. Calcd. for $C_9H_{16}O_2$: C, 69.13; H, 10.33. Found: C, 69.32; H, 10.44.

The infrared spectrum exhibited a narrow intense carbonyl band at 5.84 μ.

The *bisdinitrophenylhydrazone* of the diketone was prepared by a common method.[12] This derivative was so insoluble that it was purified by heating under reflux for 1 hr. in 95% ethanol, then filtering the product from the hot solution and washing with hot ethanol, m.p. 183–184°.

Anal. Calcd. for $C_{21}H_{24}N_8O_8$: C, 49.03; H, 4.68; N, 21.69. Found: C, 48.96; H, 4.90; N, 22.24.

Fractions 3 and 4 did not yield any pure components, even after refractionation; so they were combined and heated under reflux for 3 hr. with 50 ml. of 10% aqueous sodium hydroxide. Neutral material was extracted from the cooled alkaline solution with three portions of ether, and the ether extracts were washed with water. Evaporation of ether left 0.37 g. of residue whose infrared spectrum exhibited bands at 5.88 and 6.03 μ and was identical with the spectrum of the aldol product obtained by treating 3,7-nonanedione with alkali.

Anal. Calcd. for $C_9H_{14}O$: C, 78.21; H, 10.29. Found: C, 78.83; H, 10.62.

The ultraviolet spectrum had λ_{max} at 244.5 mμ, ε 10,450. For 2-methyl-2-cyclohexenone (one less substituent on the double bond), there has been reported[13] λ_{max} 234 mμ, ε 9,660.

The semicarbazone, prepared by a usual procedure,[12] had m.p. 213.5–214° (dec.).

Anal. Calcd. for $C_{10}H_{17}N_3O$: C, 61.51; H, 8.78; N, 21.52. Found: C, 61.30; H, 9.20; N, 21.38.

The alkaline solution, from which the cyclic ketone was extracted, was acidified and heated briefly, to yield a mixture of lactone III and the isomeric unsaturated acid. From this mixture a pure sample of lactone was obtained, while a pure sample of unsaturated acid was obtained in the Grignard reaction at 0° (see below).

The mixture of lactone and acid was extracted with ether, and the acid was re-extracted into aqueous sodium carbonate solution. The ether solution of *lactone* was washed twice with water and dried, then ether was evaporated and the lactone distilled to yield 2.10 g. of colorless liquid, b.p.

(7) W. C. Percival, R. B. Wagner, and N. C. Cook, *J. Am. Chem. Soc.*, **75**, 3731 (1953).

(8) Melting points are corrected and boiling points are uncorrected. Distillations, unless otherwise specified, were through a half-meter column of the simple Podbielniak design which has been described in detail (J. Cason and H. Rapoport, *Laboratory Text in Organic Chemistry*, Prentice-Hall, Inc., New York, 1950, p. 237). Infrared spectra were recorded on a Baird double beam spectrophotometer. Microanalyses are by the Microanalytical Division, Department of Chemistry, University of Calif.

(9) S. Skraup and S. Guggenheimer, *Ber.*, **58**, 2493 (1925).

(10) In another run, the organic extract was shaken in a separatory funnel with four successive portions of saturated aqueous sodium carbonate solution, then stirred overnight with an additional portion of carbonate solution. Work-up of the first four extracts yielded about two-thirds of the keto acid, while the remaining third was recovered from the overnight extraction.

(11) E. E. Blaise, *Compt. rend.*, **173**, 314 (1921).

(12) R. L. Shriner and R. C. Fuson, *Identification of Organic Compounds*, John Wiley and Sons, Inc., New York, 1948, pp. 170, 171.

(13) E. W. Warnhoff and W. S. Johnson, *J. Am. Chem. Soc.*, **75**, 494 (1953).

123°/10 mm., n_D^{25} 1.4614, single carbonyl band in the infrared spectrum at 5.79 μ.

Anal. Calcd. for $C_9H_{16}O_2$: C, 69.13; H, 10.33. Found: C, 69.19; H, 10.52.

Acidification of the carbonate extract of the lactone solution yielded 4 g. of colorless liquid, b.p. 130°/9 mm., n_D^{25} 1.4552. This index of refraction indicates a lactone content of about 30%, and the infrared spectrum indicates a mixture of lactone and acid.

Reaction of ethylmagnesium bromide with glutaryl dichloride. (*A*) *At 0°.* In a procedure parallel to that described for the reaction of succinyl dichloride,[2] reactants were 0.5 mole of distilled ethyl bromide, 0.5 g.-atom of magnesium turnings and 0.25 mole of glutaryl dichloride. Reaction time at 0°, after completion of addition, was 2 hr.

After the reaction mixture had been decomposed with ice and 12*N* sulfuric acid, the aqueous layer was separated and then extracted with three portions of ether. After the combined organic phases had been washed with water, they were stirred overnight with 450 ml. of saturated aqueous sodium carbonate solution. The material recovered from the carbonate extract, after acidification, proved to be a mixture of lactone III, unsaturated acid V, and δ-ketoenanthic acid. This mixture was distilled until there had been removed a top fraction of b.p. 98–140°/6 mm., weight 2.0 g., whose infrared spectrum was characteristic of the mixtures of lactone III and acid V frequently encountered in this investigation. The distillation residue, weight 16.0 g., solidified on cooling; crystallization from ether–petroleum ether yielded white crystals of m.p. 48.0–48.5°, no depression in melting point on admixture with an authentic sample of δ-ketoenanthic acid.

Fractional distillation of the neutral material remaining after carbonate extraction yielded no homogeneous components except for 1.5 g. of δ-ketoenanthic acid;[14] so the recombined fractions were heated under reflux for 3 hr. with 80 ml. of 10% aqueous sodium hydroxide. The products of alkali treatment were separated by the procedure described above under the cadmium reaction to yield 4.0 g. of ketonic material, b.p. 100–110°/18 mm.; 0.5 g. of lactone III; and 1.9 g. of the mixture of lactone III and unsaturated acid V, b.p. 120–121°/5 mm., n_D^{25} 1.4548.

The lactone-acid mixture (1.9 g. described above) was shaken out with a mixture of saturated aqueous sodium carbonate solution and ether, and the carbonate layer was carefully acidified to Congo Red with 12*N* sulfuric acid, then extracted with three portions of ether. The ether extracts were washed twice with water, dried over magnesium sulfate, then distilled to yield 1.0 g. of pure *unsaturated acid* (V), b.p. 117–118°/4.5 mm., n_D^{25} 1.4522, single carbonyl band in the infrared at 5.87 μ.

Anal. Calcd. for $C_9H_{16}O_2$: C, 69.13; H, 10.33; equiv. wt., 156. Found: C, 69.13; H, 10.31; equiv. wt., 153.

The ketonic material (4.0 g. described above) obtained in this reaction and other Grignard reactions exhibited an infrared spectrum which indicated a mixture of 2-methyl-3-ethyl-2-cyclohexenone (aldol product from 3,7-nonanedione) with about an equal amount of a saturated ketone. Repeated fractionation of this material yielded a product, b.p. 96–98°/10 mm., containing only small amounts of the cyclohexenone (as characterized by the intense infrared band at 6.03 μ). The infrared spectrum of this material was quite similar to that of 3,7-nonanedione except that the relative intensity of the carbonyl band at 5.84 μ was less and there was a weak broad band at 2.8 μ, characteristic of the hydroxyl group. The substance was inert to boiling 10% aqueous sodium hydroxide. Characterization of this material as 3-ethylnonan-3-ol-7-one seems reasonably safe, and further verification was not sought since its positive identification is not significant to the objectives of the present investigation.

(*B*) *Grignard reaction at −20°.* Grignard reagent from 0.5 mole of ethyl bromide in 165 ml. of ether was added to 0.24 mole of glutaryl dichloride dissolved in 100 ml. of ether. Addition was initiated at −50°, but it was soon necessary to allow the reaction to warm to about −20° in order to avoid plugging of the stirrer. Addition was completed in about 1.5 hr., then the reaction was stirred a few minutes as the temperature was allowed to rise to room temperature. Decomposition was with ice and 12*N* sulfuric acid.

Carbonate extraction of the reaction mixture and work-up as described for the run at 0° yielded 1.92 g. of lactone-unsaturated acid mixture, b.p. 105–143°/6 mm., and 8.14 g. of δ-ketoenanthic acid, b.p. 143–145°/6 mm., m.p. 46–48°.

The neutral material remaining after carbonate extraction was fractionally distilled at 10-mm. pressure to yield the following components:

Fraction	Weight, g.	B.P., °C.	n_D^{25}
1	1.23	83–98	1.4630
2	5.23	98–100	1.4557
3	0.81	100–117	
4	1.50	117–119	
5	0.33	119–133	
6	3.11	133–135	1.4593
7	0.55	(column stripped at 1 mm.)	

Fraction 2 has an infrared spectrum indicating an approximately equimolar mixture of 2-methyl-3-ethyl-2-cyclohexenone and 3-ethylnonan-3-ol-7-one (refer to investigation of run at 0°).

Fraction 4 solidified readily, m.p. 53°, no depression on admixture with an authentic sample of 3,7-nonanedione.

Fraction 6 has an infrared spectrum characteristic of the mixture of lactone III and acid V (refractive index indicates about 75% lactone).

(*C*) *Grignard reaction at −20° in presence of ferric chloride.* A reaction using 0.25 mole of glutaryl dichloride was carried out as described under (*B*) except that 0.75 g. of anhydrous ferric chloride was added to the ether solution of acid chloride.

Carbonate extraction of the products yielded 2.12 g. of lactone-unsaturated acid mixture, b.p. 120–144°/6 mm., and 4.13 g. of δ-ketoenanthic acid, b.p. 144–145°/6 mm., m.p. 48.0–48.5°.

Distillation of the neutral material at 10-mm. pressure yielded the following fractions:

Fraction	Weight, g.	B.P., °C.
1	1.61	40–92
2	3.35	92–95
3	2.42	95–110
4	2.79	110–118
5	0.90	118–132
6	2.53	132–134
7	1.29	134–145
8	1.89	(column stripped at 1 mm.)

The infrared spectrum of *Fractions 2 and 3* indicated an approximately equimolar mixture of 2-methyl-3-ethyl-2-cyclohexenone and 3-ethylnonan-3-ol-7-one.

(14) This material had b.p. 143–145°/6 mm., m.p. 48–48.5°, no depression in melting point on admixture with an authentic sample of δ-ketoenanthic acid. Small quantities of δ-ketoenanthic acid were isolated at this point in all the runs with ethylmagnesium bromide. It is not clear why this material fails to appear in the fraction extracted with carbonate.

Fraction 4 is 3,7-nonanedione, m.p. 51–53°, no depression on admixture with an authentic sample. An additional 0.2 g. of dione was recovered from Fraction 5 by crystallization from ether–petroleum ether. The infrared spectra of the remainder of this fraction and of *Fractions 6 and 7* indicated a mixture of lactone and unsaturated acid.

Fraction 8 crystallized on standing, m.p. 48.0–48.5° after precipitation from ether–petroleum ether, no depression of melting point on admixture with an authentic sample of δ-ketoenanthic acid.

BERKELEY, CALIF.

[COMMUNICATION NO. 1748 FROM THE KODAK RESEARCH LABORATORIES]

Derivatives of Benzoylresorcinol

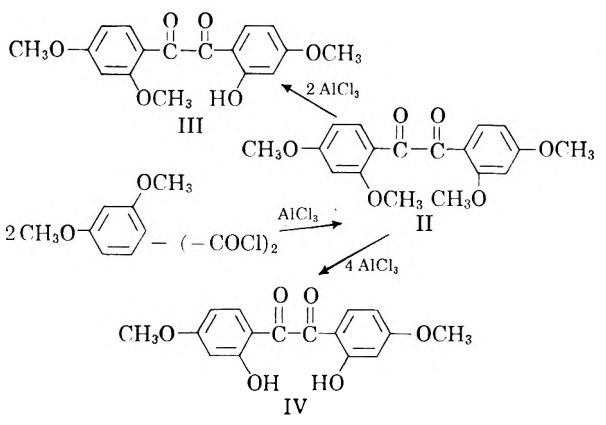
J. A. VANALLAN

Received May 22, 1958

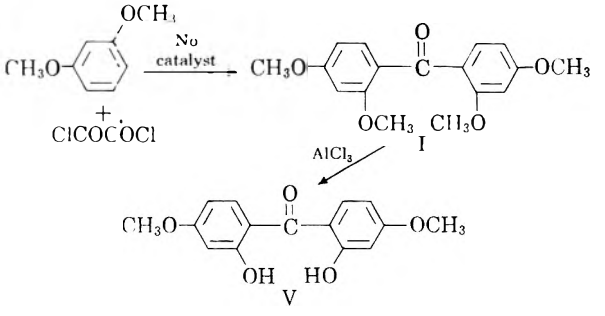
A new synthesis of 2,2′-dihydroxy-4,4′-dimethoxybenzophenone is described. The substance stated by Staudinger to be 2,2′,4,4′-tetramethoxybenzophenone has been shown to be 2,2′,4,4′-tetramethoxybenzil. The ultraviolet absorption spectra of these materials are discussed.

In extending the investigation of derivatives of benzoylresorcinol,[1] we had occasion to synthesize a compound described[2] as 2,2′,4,4′-tetramethoxybenzophenone (I). The ultraviolet absorption spectrum of this latter substance was at variance with that expected from our earlier work, so it was decided to re-examine this substance.

When *m*-dimethoxybenzene was allowed to react with oxalyl chloride in carbon disulfide[2] or ethylene chloride, with aluminum chloride as a catalyst, a substance melting at 129–130° was obtained, confirming Staudinger's result. However, methoxyl determination, Grignard analysis, and elementary analyses led to the conclusion that the substance melting at 129–130° was 2,2′,4,4′-tetramethoxybenzil (II). To test this hypothesis, II was oxidized with alkaline hydrogen peroxide to 2,4-dimethoxybenzoic acid, a reaction typical of benzils. Selective demethylation of II with two and four equivalents of aluminum chloride gave 2-hydroxy-2′,4,4′-trimethoxybenzil (III) and 2,2′-dihydroxy-4,4′-dimethoxybenzil (IV), respectively. The structures of III and IV are assigned on the basis of the Grignard analysis, on the known propensity of *o*-methoxyl groups to be demethylated, and the similarity of their ultraviolet curves to II.



It was noted that, on mixing oxalyl chloride and *m*-dimethoxybenzene, the solution became reddish yellow and hydrogen chloride was slowly evolved; heating accelerated this evolution of gas. In order to determine the nature of this reaction, the components were heated for a few hours, and the reaction mixture was distilled. The distillate was recrystallized from ethanol to give a substance having a melting point of 135–136° which, from its elementary analysis, methoxyl determination, and Grignard analysis, is 2,2′,4,4′-tetramethoxybenzophenone (I). Its mixed melting point with II is 110–113°, and its 2,4-dinitrophenylhydrazone (m.p. 150°) differs from that of II (m.p. 185°). Moreover, demethylation of I with aluminum chloride gives 2,2′-dihydroxy-4,4′-dimethoxybenzophenone (V), identical with that obtained from *m*-dimethoxybenzene and phosgene in the presence of aluminum chloride.[3]



The melting point of I has been reported as 130°[4] and as 137.2–139°.[5] It is evident, therefore, that the substance Staudinger describes as 2,2′,4,4′-

(1) J. A. VanAllan and J. F. Tinker, *J. Org. Chem.*, 19, 1243 (1954).

(2) H. Staudinger, E. Schlenker, and H. Goldstein, *Helv. Chim. Acta*, 4, 334 (1921).

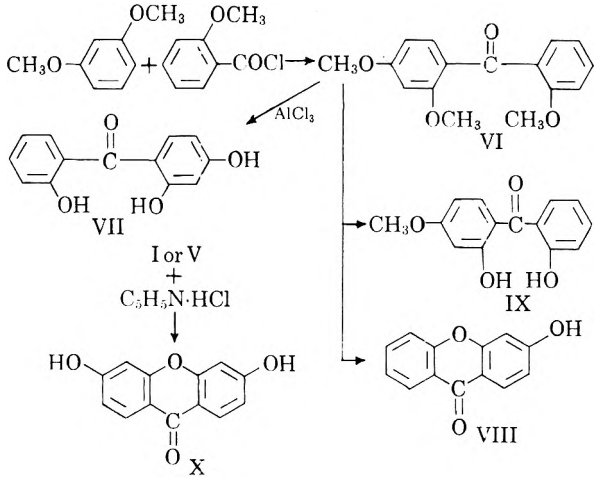
(3) General Aniline and Film Corp., Brit. Patent 706,151 (1954).

(4) J. Tambor, *Ber.*, 43, 1882 (1910).

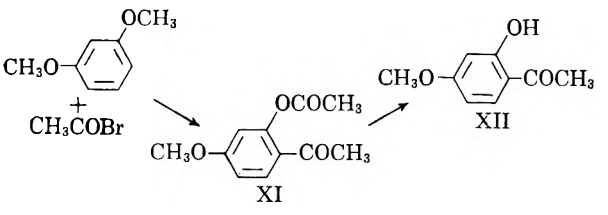
(5) G. Wittig and V. Pockels, *Ber.*, 72, 89 (1939).

tetramethoxybenzophenone is most certainly 2,2′,4,4′-tetramethoxybenzil.

To determine the generality of the reaction of organic acid halides with *m*-dimethoxybenzene, *o*-methoxybenzoyl chloride was allowed to react with *m*-dimethoxybenzene. The reaction proceeded smoothly, with the evolution of hydrogen chloride, to give a 91% yield of 2,2′,4-trimethoxybenzophenone (VI), which was demethylated with aluminum chloride in benzene to 2,2′,4-trihydroxybenzophenone (VII). If VI was demethylated using pyridine hydrochloride, the major portion of the product was 3-hydroxyxanthone (VIII), together with some 2,2′-dihydroxy-4-methoxybenzophenone (IX). Similarly, if V is demethylated using pyridine hydrochloride, the major portion of the product is 2,7-dihydroxyxanthone (X). The identities of VIII and X were confirmed by making their known acetyl derivatives. The formation of X from I is further confirmatory evidence for the structure of I.



Heating acetyl bromide and *m*-dimethoxybenzene for 3 hours at the boiling point of the mixture results in the formation of 2-acetoxy-4-methoxybenzophenone (XI) in 38% yield. The structure of the latter was established by hydrolyzing it to 2-hydroxy-4-methoxyacetophenone (XII), the identity of which was confirmed by comparison of its phenylhydrazone and 2,4-dinitrophenylhydrazone with those of authentic samples. Acetyl chloride failed to react with *m*-dimethoxybenzene under the same conditions.



Discussion of ultraviolet spectra. In Fig. 1 (also Table I) it is shown that these hydroxylated benzophenones have spectra characteristics of the

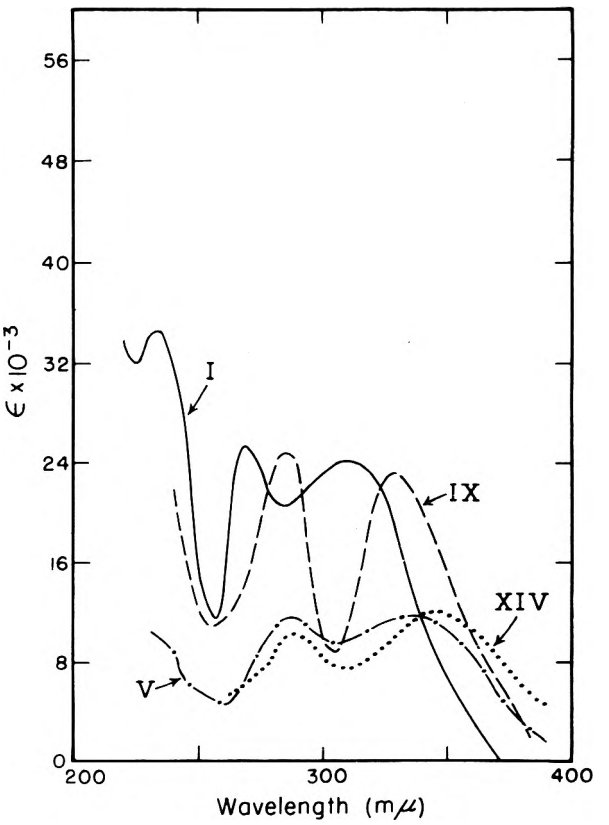
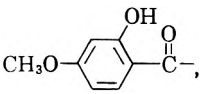


Fig. 1. Ultraviolet absorption spectra in methanol of: 2,2′,4,4′-tetramethoxybenzophenone (I) ———; 2,2′-dihydroxy-4,4′-dimethoxybenzophenone (V) ·–·–·–; 2,2′-dihydroxy-4-methoxybenzophenone (IX) – – – –; 2,2′,4,4′-tetrahydroxybenzophenone (XIV) .....

benzoylresorcinols, as shown by comparison with the known 2,2′,4,4′-tetrahydroxybenzophenone (XIV). In Fig. 2, the spectra of the benzils just described are shown. The similarity of these two series is apparent at once, which is interpreted to mean that there is little resonance coupling through the *o*-diketo group. The intensity of absorption of the benzils is significantly higher than the benzophenones, which is consonant with the concept that the groupings,



in the benzils are acting, to some extent, additively.

A large decrease in intensity and a slight shift to longer wave lengths are observed in both series when 2,2′-methoxy groups are demethylated to the corresponding hydroxy groups. This is believed to be a consequence of conjugate chelation[1] which is possible between the carbonyl and hydroxy groups in both systems.

EXPERIMENTAL

2,2′,4,4′-Tetramethoxybenzophenone (I). A mixture of 75 g. (70 ml., 0.55 mole) of *m*-dimethoxybenzene and 33 g.

TABLE I
PROPERTIES OF BENZOPHENONE AND BENZIL DERIVATIVES

Compound No.	λ	Log ε	λ	Log ε	Empirical Formula	Calcd. C	Calcd. H	Calcd. H[b]	Calcd. Addn.[b]	Calcd. CH_3O	Found C	Found H	Found H[b]	Found Addn.[b]	Found CH_3O
VI	279	4.43	312	4.40	$C_{16}H_{16}O_4$	70.6	5.9	—	—	34.2	71.0	5.9	—	—	31.7
I	278	4.45	312	4.42	$C_{17}H_{18}O_5$	67.6	6.0	0.0	1.0	41.2	67.7	5.8	0.1	0.9	41.3
IX	285	4.40	329	4.36	$C_{14}H_{12}O_4$	68.9	4.9	—	—	—	68.5	4.9	—	—	—
V	284	4.12	340	4.12	$C_{15}H_{14}O_5$	65.8	5.1	2.0	1.0	22.6	65.5	5.2	2.0	1.3	22.6
VII	288	4.40	329	4.38	$C_{13}H_{10}O_4$	67.5	4.3	—	—	—	67.7	4.1	—	—	—
XIV	287	4.01	348	4.17	Ref. 1	—	—	—	—	—	—	—	—	—	—
II	272	4.57	312	4.49	$C_{18}H_{18}O_6$	65.5	5.4	—	2.0	37.5	65.6	5.3	—	1.6	36.9
III	284	4.60	325	4.53	$C_{17}H_{16}O_6$	64.6	5.2	—	—	—	64.5	5.1	0.2	2.5	—
IV	284	4.32	328	4.25	$C_{16}H_{14}O_6$	63.6	4.6	—	—	20.5	64.1	4.5	2.1	1.8	21.1
Ie[a]	—	—	—	—	$C_{23}H_{22}O_8N_4$	57.5	4.6	—	—	—	57.5	4.6	—	—	—
IIe	—	—	—	—	$C_{24}H_{22}O_9N_4$	56.4	4.3	—	—	—	56.9	4.7	—	—	—
XIIe	—	—	—	—	$C_{15}H_{14}O_6N_4$	52.2	4.1	—	—	9.0	52.0	3.9	8.8	—	—

[a] 2,4-Dinitrophenylhydrazone derivative of compound is signified by "e" following the Roman numeral. [b] These data were obtained by Grignard analysis, the "H" indicating the number of moles of active hydrogen generated by one mole of compound and the addition the number of moles of Grignard reagent consumed by addition to the carbonyl groups of the compound.

(24 ml., 0.24 mole) of oxalyl chloride was slowly heated to 170–180°. Vigorous evolution of hydrogen chloride ensued, and the mixture became bright red. After refluxing 1.5 hr., the reaction mixture was distilled to give 25 ml. of *m*-dimethoxybenzene, b.p. 98–100°/6 mm., 30 ml. of a fraction 200–210°/0.4 mm. which was recrystallized from alcohol to give 28 g. (38%) of I, m.p. 135–136°. 2,4-Dinitrophenylhydrazone of I, m.p. 150°, was recrystallized from a mixture of butanol and methanol. See Table I for analytical results. The distillation residue was boiled with alcohol and the yellow insoluble portion was recrystallized first from butanol and then from xylene to give bright yellow crystals of a substance, m.p. 193–195°, having the same empirical formula as I.

Anal. Found: C, 67.4; H, 5.4.

This latter substance was not investigated further.

2,2',4,4'-Tetramethoxybenzil (II). A well-stirred mixture of 35 ml. of *m*-dimethoxybenzene, 12.9 g. (9.0 ml.) of oxalyl chloride, and 200 ml. of ethylene chloride was cooled to 0° and 30 g. of aluminum chloride slowly added, the temperature being kept below 15°; the mixture became highly colored. Stirring was continued for 1 hr. at 15–20°; the temperature was then raised to 60° for 0.5 hr. After cooling, the aluminum chloride complex was decomposed with cold, dilute hydrochloric acid. The organic layer was separated, washed with water and dilute sodium hydroxide, dried, and distilled. A forerun of 5 ml. of *m*-dimethoxybenzene was recovered. The product distilled between 240–260°/1 mm. and was twice recrystallized from ethanol to give 19 g. of white, platelike crystals of II, m.p. 129–130°. The 2,4-dinitrophenylhydrazone, m.p. 185°, was crystallized from benzene-methanol.

2,2'-Dihydroxy-4,4'-dimethoxybenzil (IV). A solution of 6.0 g. (0.02 mole) of II in 80 ml. of ethylene chloride was treated with 11 g. (4+ equivalents) of aluminum chloride. The mixture was heated on the steam bath for 2 hr. and decomposed with cold, dilute hydrochloric acid. The organic layer was separated and extracted with 10% sodium hydroxide solution. Acidification of the alkaline phase produced a white precipitate which was collected on a filter and dried; the yield was 6.0 g., m.p. 136–139°. One recrystallization from butanol gave 4 g. and raised the m.p. to 149–150°.

2-Hydroxy-2',4',4'-trimethoxybenzil (III). If the amount of aluminum chloride is reduced to 5.32 g. (2 equivalents) in the preparation just described, a 14% yield of III (m.p. 145–146°) is obtained.

2,2'-Dihydroxy-4,4'-dimethoxybenzophenone (V). Demethylation of I to V was accomplished in 59% yield by using the procedure described for IV.

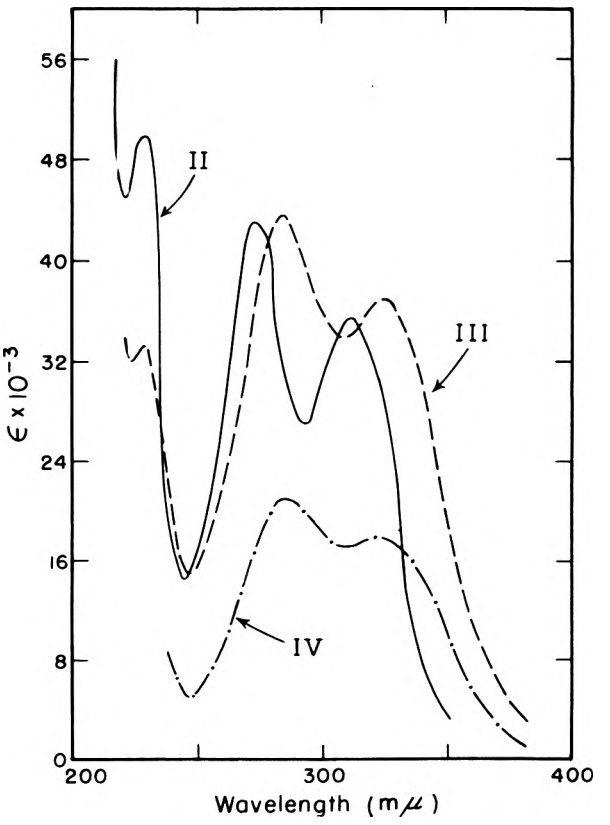


Fig. 2. Ultraviolet absorption spectra in methanol of: 2,2',4,4'-tetramethoxybenzil (II) ———; 2-hydroxy-2,2'-dihydroxy 4,4'-dimethoxybenzil (IV) -·-·-·

2,2',4-Trimethoxybenzophenone (VI). A solution of 28 g. (0.2 mole) of 2-methoxybenzoyl chloride in 40 ml. of *m*-dimethoxybenzene was heated to reflux temperature. A vigorous reaction ensued, and the heat source was removed until the reaction had subsided. The mixture was then heated until the evolution of hydrogen chloride had stopped (about 1 hr.) and then distilled; 18 ml. of *m*-dimethoxybenzene, b.p. 95–100°/5 mm., was recovered. The temperature then rose quickly and a fraction, b.p. 180–200°/15 mm., was collected; this fraction 47.5 g. (88.6%), n_D^{25} 1.608, is essentially VI.

2',2,4-Trihydroxybenzophenone (VII). Thirteen and six-

tenths grams of VI was dissolved in 80 ml. of ethylene chloride and 20 g. of aluminum chloride was added. The mixture was heated on the steam bath for 2 hr., then decomposed with dilute hydrochloric acid. The aqueous layer was drawn off and the organic layer washed with water, then with dilute sodium hydroxide solution. The alkaline solution was acidified and extracted with ethylene chloride. The ethylene chloride was removed *in vacuo* and the residual oil crystallized from benzene to give 4.1 g. of VII, m.p. 128°.

3-Hydroxyxanthone (VIII) *and 2,2'-dihydroxy-4-methoxybenzophenone* (IX). Pyridine hydrochloride (70 g.) and 21.0 g. of V were gently refluxed for 4 hr., then poured into water, and the precipitate, A, was collected on a filter. The solid, A, was added to 100 ml. of water and made alkaline with 50% sodium hydroxide solution; the solution was filtered and acidified; the precipitated solid amounts to 7.0 g. This crude material was suspended in 25 ml. of warm acetic anhydride and a drop of sulfuric acid added. Heating was continued until solution was complete. After cooling, the precipitate was collected and then recrystallized from benzene to give 7.0 g. of 3-acetoxyxanthone,[6] VIIIa, m.p. 160°. Saponification of 19.0 g. of VIIIa gave 15 g. of 3-hydroxyxanthone, m.p. 242°. 3,6-Diacetoxyxanthone,[7] m.p. 203–204°, from xylene was prepared from I in a manner similar to that just described.

(6) St. v. Kostanecki and R. Rutishauer, *Ber.*, **25**, 1648 (1892).

(7) R. Meyer and A. Conzetti, *Ber.*, **32**, 2103 (1899).

2-Acetoxy-4-methoxyacetophenone (XI). *m*-Dimethoxybenzene (57 g., 0.54 mole) and 60 ml. of acetyl bromide were refluxed for 3 hr. and distilled. A fraction (32 g., 38% yield) was collected, b.p. 155–160°/5 mm., which is essentially XI, n_D^{20} 1.550.

Anal. for $C_{11}H_{12}O_4$. Calcd.: C, 63.3; H, 5.8. Found: C, 63.8; H, 5.8.

The 2,4-dinitrophenylhydrazone of XI was prepared in the usual manner, but in the process, the acetyl group is lost, m.p. 230°, from dioxanebutanol.

2-Hydroxy-4-methoxyacetophenone (XII). 2,4-Dimethoxyacetophenone (18 g.) in 70 ml. of benzene was treated with 29 g. of aluminum chloride. A vigorous reaction ensued. After the reaction had subsided, the mixture was heated on the steam bath for 0.5 hr., then decomposed with iced hydrochloric acid. The benzene layer was extracted with dilute alkali, and the alkaline layer was acidified to give an oil. This, on distillation, gave 8 g. of XII, b.p. 145–147°/5 mm., which solidified, m.p. 46–48°, phenylhydrazone, m.p. 107–108°. Saponification of XI with alcoholic potassium hydroxide also gave XII, as proved by the identity of its phenylhydrazone, m.p. 107–108°, with that prepared above. The 2,4-dinitrophenylhydrazone (m.p. 230°) of XII is identical to that of XI.

Acknowledgment. We are indebted to D. W. Stewart of these Laboratories for the ultraviolet spectra reported.

ROCHESTER 4, N. Y.

[CONTRIBUTION FROM THE EDGAR C. BRITTON RESEARCH LABORATORY OF THE DOW CHEMICAL CO.]

Aromatic Phosphorodichloridites and Phosphorodichloridothioates. I. Aryl Phosphorodichloridites

HENRY TOLKMITH

Received April 22, 1958

A series of aryl phosphorodichloridites were prepared in yields of 84 to 98% by treating phenols with PCl_3 at a mole ratio of about 1:6 at reflux under atmospheric pressure and then completing this reaction by addition of catalytic amounts of anhydrous magnesium chloride.

For the preparation of the aryl phosphorodichloridites no satisfactory method was known at the outset of this investigation, although the first member of this series of compounds was described in 1883.[1] There were two synthetic methods mentioned in the literature:[1,2]

$$ArOH + PCl_3 \longrightarrow ArOPCl_2 + HCl \quad (1)$$

$$(ArO)_3P + 2PCl_3 \rightleftharpoons 3ArOPCl_2 \quad (2)$$

Phenol and its homologs were reported to react readily with phosphorus trichloride in equimolar proportions in the absence of catalysts or hydrochloric acid acceptors, at about 20–60°. However, during the actual course of reaction 1 substantial amounts of bis- and tris-esters were regularly produced.[1,3–6]

The reaction involving *p*-chlorophenol was reported to require a large excess of phosphorus trichloride in order to produce even small yields of *p*-chlorophenyl phosphorodichloridite.[4]

Even recently the yields for aryl phosphorodichloridites were reported to be not better than 25–50% of theory.[6,7]

Reaction 2 was reported to require a reaction temperature of 150° and to give only a 47% yield of phenyl phosphorodichloridite.[2] All previous in-

(1) E. Noack, *Ann.*, **218**, 87 (1883).

(2) J. B. Conant, V. H. Wallingford, and S. S. Gandheker, *J. Am. Chem. Soc.*, **45**, 764 (1923).

(3) R. Anschutz and W. O. Emery, *Ann.*, **239**, 309 (1887).

(4) W. Strecker and Ch. Grossmann, *Ber.*, **49**, 85 (1916).

(5) W. Broeker, *J. prakt. Chem.* (2) **118**, 287 (1928).

(6) G. R. Cebrian, *Arch. inst. farmacol. exptl. (Madrid)*, **8**, 61 (1956).

(7) J. C. Bill and B. A. Hunter, U. S. Patent **2,732,365** (1956).

vestigators mentioned that the thermal instability of aryl phosphorodichloridites at temperatures above 150° made it additionally difficult to obtain these compounds in even moderate yields.

Our development work was concentrated on reaction 1 and revealed that this reaction, apparently because of its equilibrium character, required conditions which reduced the hydrochloric acid concentration in the reaction mixture to a minimum. Operation under reduced pressure, causing reduction of reaction temperature, made it more difficult to complete the conversion of less reactive phenols. A final reaction temperature of about 80° and operation under atmospheric pressure were found to be desirable to complete the reactions within a reasonable time.

It was found necessary to use an excess of phosphorus trichloride. A substantially smaller excess gave greatly reduced yields, in agreement with literature and patent examples.[7,8] As substantially larger excess of phosphorus trichloride was not found to increase the yield.

The reaction rate of various phenols in reaction 1 was found to decrease with increaseing dissociation constants of the phenols. With 2,4,5-trichlorophenol this rate was so low that the reaction with 5 moles of phosphorus trichloride at 80° did not go to completion within 24 hr. We found that the presence of anhydrous magnesium chloride, known as a catalyst for this type of reaction,[8] brought the conversion of 2,4,5-trichlorophenol essentially to completion within less than 10 hr. This catalyst was found to affect the reaction rate of other phenols in a similar manner. The presence of catalyst was necessary in all reactions involving orthohalogenated phenols, in order to produce maximum yields in minimum reaction times. The proper timing of catalyst addition was found to be of importance. The presence of catalyst in the reaction mixture during the entire reaction time gave noticeably smaller yields than presence of catalyst during the reaction of the second half of the phenol only.

In the absence of catalyst and in the presence of sufficient excess of PCl_3 halophenols reacted without side reaction according to reaction 1 exclusively but their reaction did not proceed to the point of complete conversion of the phenol. $MgCl_2$ as a catalyst promoted not only reaction 1 but also undesired side reactions involving di- and trisubstitution. Maximum yields were obtained when $MgCl_2$ was added after the noncatalytic part of the reaction of phenols with PCl_3 had come almost to a standstill.

Reaction 1 could be expected to be complete after evolution of one mole of hydrochloric acid per mole of phenol used. Owing to contamination of hydrochloric acid with some phosphorus trichloride, the accurate determination of the point at which exactly one mole of hydrochloric acid was formed was rather difficult. A more practical way to find the necessary reaction time was to continue the reaction until the reaction mixture contained only traces of unreacted phenol, as determined by infrared analysis. The method developed did not work well with 2,6-disubstituted phenols owing to steric hindrance.

The aryl phosphorodichloridites prepared were vacuum-fractionated twice for purification. The pure compounds were isolated as heavy, colorless, water-clear liquids. They were found to be soluble without decomposition in those organic solvents which did not contain carbonyl groups or reactive hydrogen. The results obtained were as shown in Table I.

We investigated the hydrolysis of aryl phosphorodichloridites briefly. The reaction with liquid water at room temperature was found to be rather violent with all phosphorodichloridites prepared. Reaction with moist air at room temperature was found to involve at least two different steps:

$$ArOPCl_2 + 2H_2O \longrightarrow ArOP(OH)_2 + 2HCl \quad (3)$$

and

$$ArOP(OH)_2 + H_2O \longrightarrow ArOH + H_3PO_3 \quad (4)$$

The two types of hydrolysis product formed, aryl phosphite and free phenol, were identified by the infrared-absorption bands of phosphite-hydroxyl and phenolic hydroxyl, located at 3.8 ± 0.3μ and 2.9 ± 0.1μ, respectively. Hydrolysis of phenyl phosphorodichloridite ($C_6H_5OPCl_2$) and *m*-ethylphenyl phosphorodichloridite (*m*-C_6H_3-$C_6H_4OPCl_2$) was found to proceed according to reaction 3 while hydrolysis of chloroaryl phosphorodichloridites involved reaction 4 also. The rate of reaction 4 apparently was the higher the greater the dissociation constant of the phenol involved.

EXPERIMENTAL

Equipment. A 3-neck, round-bottom flask fitted with a thermometer and glass stirrer was used. Attached to the flask was a dropping funnel for addition of those phenols which were liquid at room temperature. (Solid phenols were added in small, crushed portions.) The flask was connected with a reflux condenser which in turn was connected with a saddle-packed water-scrubber. This permitted estimation of hydrogen chloride as formed in the reaction.

Quality of starting products. Phosphorus trichloride was freshly redistilled from a commercial product. The phenols employed were purified products, as indicated in Table II.

Procedure. The flask was charged with phosphorus trichloride. Then the phenol was added portion-wise with agitation at mole ratios as given in Table I over a period of about 3 hr. at temperatures below +20° in the case of liquid phenols and 25–30° in the case of solid phenols. After a clear solution was obtained the mixture was slowly warmed to reflux at atmospheric pressure. Alkylated phenols were more reactive than halogenated phenols and gave best yields when at least half of the phenol was converted at a reaction temperature of less than 30° before the temperature was raised to mild reflux (about 80° in the mixture). Re-

(8) C. L. Moyle, U. S. Patents 2,170,833 (1939), 2,220,113 and 2,220,845 (1940).

TABLE I

Aryl—$OPCl_2$

Aryl	Mole Ratio Aryl OH: PCl_3	Reaction Time, Hr.	Yield (% Theory)	P-Analysis, % Theor.	P-Analysis, % Found	d_4^{20}	n_D^{20}	B.P. °/C. at 10 Mm.
C_6H_5—	1:6	10	84	15.89	15.87	1.3539	1.5588	90
m-C_2H_5—C_6H_4—	1:5	11	93.4	13.89	13.93	1.2590	1.5474	115
2-Cl-4-*t*-C_4H_9—C_6H_3—	1:5	10	93.5	10.85	10.91	1.2870	1.5510	154
2-Br-4-*t*-C_4H_9—C_6H_3—	1:5	12	91.1	9.39	9.47	1.4669	1.5676	165
o-Cl—C_6H_4—	1:5	10	98	13.50	13.45	1.4686	1.5736	111–112
p-Cl—C_6H_4—	1:5	9	85		13.48	1.4714	1.5749	113–113.5
2,4-Cl_2—C_6H_3—	1:6	12	88		11.7	1.5651	1.5860	134
2,5-Cl_2—C_6H_3—	1:6	12	86	11.74	11.67	1.5672	1.5869	138
3,4-Cl_2—C_6H_3—	1:5 to 1:20	10 to 20	83 to 87		11.65	1.5736	1.5894	136
2,4,5-Cl_3—C_6H_2—	1:5 to 1:7	10 to 20	90.3 to 90.7	10.38	10.35	1.6556	1.6007	154–155
2,4,6-Cl_3—C_6H_2—	1:6	280[a]	11.0		10.39	1.6563	1.6012	156

[a] Reaction still incomplete.

TABLE II

Phenol	Physical Properties
C_6H_5OH[9]	F.p., +40.8°
m-C_2H_5—C_6H_4OH[9]	B.p., 75–77°/10 mm.
2-Cl-4-C_4H_9—C_6H_3OH[10]	F.p., +12.4°
2-Br-4-C_4H_9—C_6H_3OH[10]	F.p., +7.8°
o-Cl—C_6H_4OH[9]	F.p., +9.4°
p-Cl—C_6H_4OH[9]	M.p., 42–43°
2,4-Cl_2—C_6H_3OH[9]	M.p., 44–45°
2,5-Cl_2—C_6H_3OH[11]	M.p., 56.5–57.5°
3,4-Cl_2—C_6H_3OH[12]	M.p., 64–66°
2,4,5-Cl_3—C_6H_2OH[9]	M.p., 64–65°
2,4,6-Cl_3—C_6H_2OH[9]	M.p., 69–70°

action mixtures containing orthohalogenated phenols were less reactive and directly heated to reflux. The course of the reaction was followed by titration of hydrogen chloride dissolved in the scrubber water. The reaction was not considered complete until the scrubber water showed almost neutral *p*H.

In order to obtain high yields it was found necessary to complete all reactions involving halogenated phenols in the presence of anhydrous magnesium chloride (0.01 mole per mole of phenol used). Originally, this catalyst was added to the clear phenol–phosphorus trichloride solution before warm-up. Better yields were obtained by addition of magnesium chloride after about one-third of the theoretical amount of hydrochloric acid was found in the scrubber water.

The total amount of hydrogen chloride evolved was found to be 124–143% of theory, depending upon the temperature of cooling water going into the condenser. The excess amount of hydrochloric acid found was produced by some phosphorus trichloride being evaporated along with the hydrogen chloride.

To find the point of complete phenol conversion, samples of reaction mixture were taken after the scrubber water had turned almost neutral. When infrared analysis showed the presence of less than 1% of free phenol in the reaction mixture, after removal of excess phosphorus trichloride at low temperature under vacuum, the reaction was considered to be complete.

Main product isolation. The reaction mixture was transferred without filtration to a glass still equipped with thermometer and glass stirrer. Unreacted phosphorus trichloride was taken off by distillation with agitation under atmospheric pressure until the temperature of the reaction mixture had risen to 140–145°. The crude concentrate obtained, remaining liquid at room temperature in all runs undertaken, was then distilled under a pressure of less than 15 mm.

Purification. The main products obtained were fractionally redistilled twice at a pressure of 10 mm. through a fractionation column of 15 cm. length and 3 cm. diameter, packed with Berl saddles. The results obtained were those given in Table I.

MIDLAND, MICH.

(9) Purified commercial product.

(10) L. E. Mills and C. M. Galloway, U. S. Patents **2,221,807** and **2,221,808** (1940).

(11) E. Noelting and E. Kopp, *Ber.*, **38**, 3510 (1905).

(12) Badische Anilin and Soda-Fabrik; German Patent **156,333** (1903).

[CONTRIBUTION FROM THE EDGAR C. BRITTON RESEARCH LABORATORY OF THE DOW CHEMICAL CO.]

Aromatic Phosphorodichloridites and Phosphorodichloridothioates. II. *O*-Aryl Phosphorodichloridothioates

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O-Aryl phosphorodichloridothioates are formed from phenols and $PSCl_3$ in the presence of catalysts or HCl-acceptors in yields of less than 75%. Sulfuration of *O*-aryl phosphorodichloridites with $PSCl_3$ produces *O*-aryl phosphorodichloridothioates in yields of 75–92%. Noncatalytic sulfuration with elemental sulfur gives yields of 86–90% but does not produce pure compounds. Reaction with sulfur in the presence of catalytic amounts of activated carbon and molar amounts of $PSCl_3$ give yields of 70–95% of pure compound. The composite reaction of *O*-aryl phosphorodichloridites and PCl_3 with sulfur gives pure compounds in about 85% yield. The same reaction in the presence of molar amounts of an aryl phosphorodichloridothioate of the same structure as the one to be prepared gives pure compounds in yields of 93–98%.

In the past *O*-aryl phosphorodichloridothioates have been prepared in two ways:

$$\text{ArylOH} + PSCl_3 \longrightarrow \text{ArylOPSCl}_2 + HCl \quad (a)$$

$$\text{ArylOPCl}_2 + S \longrightarrow \text{ArylOPSCl}_2 \quad (b)$$

Reaction (a), in the absence of catalysts or HCl-acceptors, was reported to produce no *O*-phenyl phosphorodichloridothioate.[1] In the presence of aqueous sodium hydroxide, or with sodium phenate in place of phenol, the yields were found to be low, owing to unavoidable side reactions involving hydrolysis and overesterification.[2] Reaction (b) was reported to give *O*-aryl phosphorodichloridothioates at temperatures of about 200° but no yields were given.[1,3] Both reactions were studied in various modifications to find methods which would produce high yields of phosphorodichloridothioate.

The following reactions also were investigated:

$$\text{ArylOPCl}_2 + PSCl_3 \longrightarrow \text{ArylOPSCl}_2 + PCl_3 \quad (c)$$

$$m\ \text{ArylOPCl}_2 + n\ PCl_3 + (m+n)S \longrightarrow m\ \text{ArylOPSCl}_2 + n\ PSCl_3 \quad (d)$$

A. Synthesis from phenols and $PSCl_3$. Reaction (a) was investigated in the presence of pyridine, metal chloride catalysts, and phosphorus trichloride, respectively, which were expected to act as reaction promoters. The results obtained showed that the formation of *O*-aryl phosphorodichloridothioates from phenols and $PSCl_3$ in the presence of reaction promoters occurred in yields of less than 75% (*cf.* Table I).

B. Reactions of phosphorodichloridites with $PSCl_3$. Formation of phosphorothioates from certain phosphites and stoichiometric amounts of $PSCl_3$ has been reported.[4] The availability of a series of aromatic phosphorodichloridites[5] permitted investigation of their reaction with $PSCl_3$ according to reaction (c).

(1) R. Anschutz and W. O. Emery, *Ann.*, **253**, 105 (1889).
(2) W. Authenrieth and W. Meyer, *Ber.*, **58**, 840 (1925).
(3) W. Strecker and Ch. Grossmann, *Ber.*, **49**, 63 (1916).
(4) H. B. Gottlieb, *J. Am. Chem. Soc.*, **54**, 748 (1932).
(5) H. Tolkmith, *J. Org. Chem.*, **23**, 1682 (1958).

TABLE I

ArylCPSCl$_2$ FROM PHENOL AND $PSCl_3$ DIRECTLY

Reaction Promoter	ArylOPSCl$_2$ Obtained	Yield (% Theory)
Pyridine	4-NO_2—$C_6H_4OPSCl_2$	55
	2-Cl-4-NO_2—$C_6H_3OPSCl_2$	38.2
	3-Cl-4-NO_2—$C_6H_3OPSCl_2$	38.1
	2,4,6-Cl_3—$C_6H_2OPSCl_2$	55.6
$MgCl_2$	2,4,5-Cl_3—$C_6H_2OPSCl_2$	51
CuCl	2,4,5-Cl_3—$C_6H_2OPSCl_2$	65
$MgCl_2$ + CuCl	2,4,5-Cl_3—$C_6H_2OPSCl_2$	66.5
	2-Cl-4-*t*-C_4H_9—$C_6H_3OPSCl_2$	73.1
	$C_6H_5OPSCl_2$	62.1
$MgCl_2$ + PCl_3	2,4,5-Cl_3—$C_6H_2OPSCl_2$	67

It was found that phosphorodichloridothioates were formed with maximum yield when 100% excess of $PSCl_3$ was used and the phosphorus trichloride formed was removed by fractional distillation under atmospheric pressure during the reaction. On the basis of these findings a series of aryl phosphorodichloridothioates was prepared by sulfurating crude aryl phosphorodichloridites with excess $PSCl_3$ in the absence of metal chloride catalysts (*cf.* Table II). This method was found to be very convenient for laboratory preparation of various aromatic phosphorodichloridothioates in yields of 75–92% and purities of higher than 97%.

TABLE II

ArylOPSCl$_2$ FROM ArylOPCl$_2$ + $PSCl_3$

ArylOPSCl$_2$	Boiling Range (°C. at 10 mm.)	Yield (% Theory)
$C_6H_5OPSCl_2$	108–117	75.5
3-C_2H_5—$C_6H_4OPSCl_2$	130–138	92
2-Cl—$C_6H_4OPSCl_2$	127–136	76
2-Cl-4-*t*-C_4H_9—$C_6H_3OPSCl_2$	167–176	90.5
2-Br-4-*t*-C_4H_9—$C_6H_3OPSCl_2$	175–186	80
2,4-$Cl_2C_6H_3OPSCl_2$	151–158	81.5
2,5-$Cl_2C_6H_3OPSCl_2$	155–164	76.5
3,4-$Cl_2C_6H_3OPSCl_2$	152–162	84.5
2,4,5-$Cl_3C_6H_2OPSCl_2$	167–177	79.5

C. Noncatalytic reactions of phosphorodichloridites

with sulfur. A reinvestigation of the known reaction (b) with several aryl phosphorodichloridites showed that this reaction did not take place below 150° if catalysts were absent. At around 170° undiluted equimolar mixtures of reactants produced exothermic reactions causing a rapid rise of the reaction temperature to 230–250°. At such reaction end-temperatures partial decomposition took place causing unsatisfactory yields.

It was found that reaction temperatures of 160–180° were critical for obtaining high yields and that reaction times of 1.5–2 hours were sufficient to complete the reaction. The necessary range of reaction temperature was maintained by slow addition of one reactant to the other or by heating the mixture of the reactants under the same conditions in the presence of small amounts of a diluent which boiled at 125–160° under atmospheric pressure. Under these precautions stoichiometric mixtures of reactants gave consistently high yields of *O*-aryl phosphorodichloridothioates. It was found, however, that the reaction main products were regularly contaminated by unreacted starting products (*cf.* Table III). Removal of these impurities by repeated vacuum fractionation was not entirely successful. Therefore, this method was not suitable without modification for preparation of aromatic phosphorodichloridothioates in high purity.

dite caused a noticeable reduction of yield. Reactions in the presence of activated carbon and silica gave reaction temperatures which went through a characteristic minimum (*cf.* Experimental, Table VIII). This indicated that $PSCl_3$ was not merely a diluent but participated in the sulfuration reaction although it was finally recovered in high yields. Sulfur monochloride in place of $PSCl_3$ gave reduced yields.

Reaction (b), when carried out in the presence of $PSCl_3$ and catalytic amounts of activated carbon, gave phosphorodichloridothioate which contained less than 0.5% of elemental sulfur as the only impurity. However, the yields obtained were not better than those obtained from the nonmodified reaction (b).

E. Composite reaction of sulfur with phosphorodichloridite and PCl_3. The results described in Section *D* led to the conclusion that pure aryl phosphorodichloridothioates could be obtained by the reaction of phosphorodichloridites with an excess of sulfur, if coupled with removal of unreacted sulfur by a scavenger which would form a volatile sulfur derivative that could easily be separated from the main product by fractional distillation. Most suitable for this purpose appeared to be the use of phosphorus trichloride. Accordingly, the sulfuration was based upon the following composite reaction:

TABLE III

NONCATALYTIC ArylOPCl$_2$-SULFUR REACTIONS

Moles of Diluent/Mole ArylOPCl$_2$		ArylOPSCl$_2$ Obtained		
		Structure	Yield (% Theory)	Purity (%)
None		2,4,5-Cl_3—$C_6H_2OPSCl_2$	86	96.5
0.2	s-$C_2H_2Cl_4$	3-C_2H_5—$C_6H_4OPSCl_2$	86	96.0
0.37	C_6H_5Br	3,4-Cl_2—$C_6H_3OPSCl_2$	90.5	96.0
0.2	$PSCl_3$	2-Cl—$C_6H_4OPSCl_2$	90.0	98.8

D. Catalytic phosphorodichloridite-sulfur reactions. The observation that the reaction of phosphorodichloridites with sulfur gave phosphorodichloridothioates in high yield and fair purity, if carried out in the presence of $PSCl_3$ (*cf.* Table III), was apparently new though not entirely unexpected in view of the findings reported in the Sections *B* and *C*. This reaction was investigated more in detail in the presence of catalytic amounts of anhydrous aluminum chloride,[6] silica-powder and activated carbon.

It was found (*cf.* Table IV) that the reaction was most effectively catalyzed by highly activated carbon (Darco G60). The other catalysts investigated proved to be inferior. Presence of increasing quantities of $PSCl_3$ up to 2.5 moles per mole of phosphorodichloridite gave increasing yields. Chlorination of the aryl group of the phosphorodichlori-

$$m\ \text{ArylOPCl}_2 + n\ PCl_3 + (m + n)\ S \longrightarrow m\ \text{ArylOPSCl}_2 + n\ PSCl_3 \quad \text{(d)}$$

In practice, reaction (d) was carried with an excess of PCl_3 and studied with 2,4,5-$Cl_3C_6H_2OPCl_2$, because chlorinated aryl phosphorodichloridites were found to sulfurate less readily than nonhalogenated aryl phosphorodichloridites. It was found that reactions in the presence of an excess of sulfur and PCl_3 gave 2,4,5-$Cl_3C_6H_2POSCl_2$ with 99.3% purity and in a yield of about 85% (*cf.* Table V). From previous experiences it was known that sulfur would react somewhat better if dissolved prior to reaction. This suggested that reaction (d) could advantageously be carried out by employing as the sulfur solvent an aryl phosphorodichloridothioate of the same structure as the one to be prepared. Thus, it was possible to obtain the pure main product in yields of 93–98% by employing as the sulfur solvent 1.0–1.5 moles of 2,4,5-$Cl_3C_6H_2$-

(6) *Cf.* F. F. Knotz, U. S. Patent 2,715,561 (1955).

TABLE IV

ArylOPCl$_2$-Sulfur Reactions in the Presence of PSCl$_3$ and Various Catalysts

Catalyst	Moles of PSCl$_3$ per Mole of ArylOPCl$_2$	Structure	Yield (% Theory)	Impurities (% S)
$AlCl_3$	3.0	2,4,6-$Cl_3C_6H_2OPSCl_2$	41.5	0.4
SiO_2	2.0	3-C_2H_5—$C_6H_4OPSCl_2$	62.5	0.23
Act. Carbon	2.0	3-C_2H_5—$C_6H_4OPSCl_2$	95.0	0.23
	2.0	2-Cl—$C_6H_4OPSCl_2$	94.5	0.34
	2.0	4-Cl—$C_6H_4OPSCl_2$	88.0	0.35
	2.5		88.0	0.3
	0.74	2,4,5-$Cl_3C_6H_2OPSCl_2$	68.5	0.4
	None		59.5	0.5

TABLE V

Composite Reaction (d) in the Absence and in the Presence of ArylOPSCl$_2$

PCl$_3$[a]	S[a]	ArylOPSCl$_2$[a]	Structure	Yield (% Theory)	Impurities
0.4	1.0	—		78.7	10% 2,4,5-Cl_3—$C_6H_2OPCl_2$
0.5	1.16	—		84.5	0.6% S
0.5	1.16	0.1	2,4,5-$Cl_3C_6H_2OPSCl_2$	86.6	
0.5	1.16	0.5		88.0	
0.5	1.16	1.0		92.6	Less than 0.2% S
0.5	1.16	1.5		97.5	
0.5	1.10	1.0	2-Cl-4-*t*-$C_4H_9C_6H_3OPSCl_2$	95.8	

[a] In moles per mole of phosphorodichloridite.

TABLE VI

Aryl Phosphorodichloridothioates

Aryl	Sulfur Analysis (Calcd.)	Sulfur Analysis (Found)	d_4^{20}	n_D^{20}	B.P., °C/10 mm.
C_6H_5—	14.12	14.16	1.4091	1.5766	116
3-C_2H_5—C_6H_4—	12.57	12.70	1.3327	1.5683	136
2-Cl—C_6H_4—	12.26	12.31	1.5048	1.5861	134
4-Cl—C_6H_4—	12.26	12.10	1.5068	1.5869	141
2-Cl-4-*t*-C_4H_9—C_6H_3—	10.09	10.04	[a]		175
2-Br-4-*t*-C_4H_9—C_6H_3—	8.86	9.02	[b]		185
2,4-$Cl_2C_6H_3$—	10.83	10.72	1.5913	1.5960	158
2,5-$Cl_2C_6H_3$—		10.80	1.5943	1.5962	162
3,4-$Cl_2C_6H_3$—		10.66	1.5998	1.5985	160
2,4,5-$Cl_3C_6H_2$—	9.70	9.78	1.6728[c]	1.6072[c]	175
2,4,6-$Cl_3C_6H_2$—	9.70	9.72	[d]		178
4-NO_2—C_6H_4—	11.85	12.06	[e]		—
2-Cl-4-NO_2—C_6H_3—	10.46	10.32	1.6127[f]	1.6094[f]	—
3-Cl-4-NO_2—C_6H_3—	10.46	10.90	1.6219[f]	1.6063[f]	—

[a] M.p. 37–38°. [b] M.p. 41–42°. [c] M.p. +14°. [d] M.p. 47–48°. [e] M.p. 53–54°. [f] Data on crude product.

$OPSCl_2$ per mole of 2,4,5-$Cl_3C_6H_2OPCl_2$ (*cf.* Table V).

This method was found to produce pure aryl phosphorodichloridothioates in almost quantitative yields and to be the most economical of all methods investigated. It was not suitable for thermo-unstable compounds, like nitrophenyl phosphorodichloridites.

E. Physical properties. For the purpose of purification the *O*-aryl phosphorodichloridothioates prepared were vacuum fractionated twice through a 15 cm. Vigreux column. The highest thermal stability was shown by 2-halo-4-tert-butylphenyl phosphorodichloridothioates which did not decompose when heated at 190–200° for 10 hours. Polyhalophenyl compounds showed some decomposition under these conditions. Nitrophenyl phosphorodichloridothioates are much less stable and tend to decompose violently at such temperatures.

The pure phosphorodichloridothioates were isolated as viscous, almost colorless liquids. Some of them solidified after a few hours and were recrystallized from petrol ether (30–60°). All compounds prepared (*cf.* Table VI) were found to be soluble

without decomposition in those organic solvents which did not contain reactive hydrogen or carbonyl groups.

EXPERIMENTAL

Starting products. The phenols and aryl phosphorodichloridites used were of a purity as described in the preceding paper.[5] Thiophosphoryl chloride, pyridine, and phosphorus trichloride were employed as freshly redistilled commercial grade products.

Reaction (a) in the presence of pyridine. Pyridine, 565 g., was added to an agitated solution of 1385 g. of 2,4,6-$Cl_3C_6H_2OH$ and 5940 g. of $PSCl_3$ in 3.5 l. of benzene at 25–28°. The reaction mixture was agitated for 24 hr. at room temperature, filtered, the pyridine hydrochloride washed with ether, and the combined filtrates concentrated under atmospheric pressures up to a pot temperature of 130°. After cooling, the residue was filtered again and the filtrate concentrated up to a pot temperature of 110° at 13 mm. The residue was dissolved in 1 l. of petroleum ether (b.p. 30–60°) and set aside for crystallization. A total of 785 g. of white crystals of 2,4,6-$Cl_3C_6H_2OPSCl_2$ was obtained, m.p. 47–48°. Chemical analysis gave 53.7% Cl, 9.73% S. and 9.5% P. The mother liquor was evaporated and the residue vacuum fractionated. This gave 498 g. of 2,4,6-$Cl_3C_6H_2OPSCl_2$ which boiled sharply at 166° at 6 mm. Total yield of 2,4,6-$Cl_3C_6H_2$-$OPSCl_2$, 1283 g. (55.6% yield).

Anal. Calcd. for $C_6H_2Cl_5OPS$: Cl, 53.7; P, 9.4; S, 9.7. Found: Cl, 53.5; P, 9.3; S, 9.8.

Chloronitrophenol, 347 g., and *p*-nitrophenol, 278 g., respectively, were dissolved in 1 l. of ether. These solutions were added to agitated mixtures of 1700 g. of $PSCl_3$ plus 0.2 l. of methylene dichloride plus 165 g. of pyridine at +4 to +8° during 5 hr. (water cooling). The reaction mixtures were kept agitated for 6 hr. at 10–20°. After having stood overnight at room temperature, the mixtures were filtered and the filtrates evaporated to a pot temperature of 65°/12 mm. Methylcyclohexane (700 cc.) was added and again evaporated in the same manner. Each residue was extracted twice with a mixture of 500 cc. of cyclohexane and 500 cc. of petroleum ether (30/60°) and then with 500 cc. of cyclohexane alone. The hydrocarbon solution was evaporated to a pot temperature of 76° under 12 mm. and left the crude main products.

Recrystallization of crude 4-NO_2-$C_6H_4OPSCl_2$ from petroleum ether (30/60°) gave 299 g. (55% yield) of almost colorless crystals melting at 53–54°.

Anal. Calcd. for $C_6H_4Cl_2NO_3PS$: S, 11.85. Found: S, 12.06.

The crude *O*-chloronitrophenyl phosphorodichloridothioates could not be brought to crystallization and were analyzed without further purification. The data obtained are shown in Table VII.

hydrous CuCl, and 5.0 g. of a 1:1 mixture of anhydrous MgCl plus CuCl, respectively. After a reaction time of 15 hr. the mixtures were filtered and fractionated through a 15 cm. Vigreux column at 10 mm. pressure. While the first fraction consisted of excess $PSCl_3$, the second fraction of all three runs consisted of unreacted phenol, identified by freezing point and IR-analysis as described in the preceding paper. The runs were repeated with a total reflux time of 40 hr. and vacuum fractionated. The runs in the presence of $MgCl_2$ and CuCl again gave unreacted 2,4,5-$Cl_3C_6H_2OH$, in amounts of 68 g. and 25 g. respectively. Their third fraction consisted of 385 g. and 490 g. of 2,4,5-$Cl_3C_6H_2OPSCl_2$, boiling at 172–177° under 10 mm. pressure. The run in the presence of a $MgCl_2$-CuCl catalyst mixture gave no unreacted 2,4,5-$Cl_3C_6H_2OH$ and 501 g. (66.5% yield) of 2,4,5-Cl_3-C_6H_2OP-SCl_2, boiling at 170–177° at 10 mm. Redistillation of main product gave 2,4,5-Cl_3-$C_6H_2OPSCl_2$, boiling at 175° at 10 mm. and showing a freezing point of +14°.

Anal. Calcd. for $C_6H_2Cl_5OPS$: S, 9.7. Found: S, 9.78.

Solutions of C_6H_5OH, 94g., and 2-Cl-4-*t*-C_4H_9-C_6H_3OH, 185 g., respectively, in 850 g. of $PSCl_3$ were refluxed at atmospheric pressure with agitation in the presence of 1 g. of anhydrous $MgCl_2$ plus 1 g. of anhydrous CuCl. After a reaction time of 36 hr. the excess of $PSCl_3$ was removed by distillation under a pressure of 50 mm. The residues obtained were filtered and fractionated through a 15 cm. Vigreux column at a pressure of 10 mm. In either run, no unreacted phenol was recovered. The main cuts of these runs represented the desired phosphorodichloridothioates, *i.e.*, C_6H_5-$OPSCl_2$ [141 g. (62.1% yield) of a boiling range of 112–117° at 10 mm.] and 2-Cl-4-*t*-C_4H_9-$C_6H_3OPSCl_2$ [232 g. (73.1% yield) of a boiling range of 171–178° at 10 mm.]. Redistillation of them under the same pressure gave boiling points of 116° and 175°, respectively. The 2-chloro-4-*t*-butylphenyl derivative solidified upon standing and was recrystallized from petroleum ether (30/60°) to give white crystals melting at 37–38°.

Anal. Calcd. for $C_6H_5Cl_2OPS$: S, 14.12; Found: S, 14.16. Calcd. for $C_{10}H_{12}Cl_3OPS$: S, 10.09. Found: S, 10.04.

Reaction (a) in the presence of PCl_3 plus $MgCl_2$. A solution of 594 g. of 2,4,5-$Cl_3C_6H_2OH$ in a mixture of 3000 g. of $PSCl_3$ plus 1650 g. of phosphorus trichloride was refluxed with agitation under atmospheric pressure in the presence of 3 g. of anhydrous magnesium chloride. After 24 hr. of reaction time at 100–102° the reaction mixture was vacuum fractionated as described and gave 666 g. (67% yield) of 2,4,5-$Cl_3C_6H_2OPSCl_2$, boiling at 166–176° at 10 mm. and identified by infrared analysis.

Reaction (c). A mixture of one mole of an *O*-aryl phosphorodichloridite and two moles of $PSCl_3$ was heated with agitation under atmospheric pressure. At a pot temperature of 125°, phosphorus trichloride started to evolve and was immediately removed through a saddle-packed column of 50 cm. length. During a reaction time of 4 hr. the pot temperature rose steadily to 155° while the temperature at the

TABLE VII

O-CHLORONITROPHENYL PHOSPHORODICHLORIDOTHIOATES

Structure	2-Cl-4-NO_2—$C_6H_3OPSCl_2$	3-Cl-4-NO_2—$C_6H_3OPSCl_2$
Exterior appearance	Reddish-brown oil	Olive-colored o l
Crude yield	234 g. (38.2%)	233 g. (38.1%)
Found (Cl	34.3	34.6
Found (P	10.1	10.6
Found (S	10.32	10.9

Anal. Calcd. for $C_6H_3Cl_3NO_3PS$: Cl, 34.8; P, 10.22; S, 10.46.

Reaction (a) in the presence of metal chlorides. In three parallel runs a mixture of 453 g. of 2,4,5-$Cl_3C_6H_2OH$ and 1700 g. of $PSCl_3$ was refluxed with agitation under atmospheric pressure in the presence of 2.5 g. anhydrous $MgCl_2$, 2.5 g. of anhead of the column remained at the boiling point of PCl_3 (78–80°). Then the temperature at the head of the column rose rather rapidly to 124° and remained there (boiling temperature of $PSCl_3$). This indicated that the reaction was complete. The reaction mixture was fractionated first under a pressure of 50 mm. to remove all unreacted $PSCl_3$ and then

under a pressure of 10 mm. to obtain the phosphorodichloridothioate formed. The results obtained were as given in Table II. The compounds isolated were twice vacuum fractionated through a 15 cm. Vigreux column and the distillates analyzed for sulfur. The data obtained were those given in Table VI.

Reaction (b), noncatalytic. Sulfur, 21.5 g., was added in portions over a period of 1 hr. to an agitated quantity of 200 g. of 2,4,5-$Cl_3C_6H_2OPCl_2$, heated at 160° under atmospheric pressure. Agitation was continued for 2 hr. at 160–166°. Vacuum distillation of the reaction product gave 197 g. (86% yield) of 2,4,5-$Cl_3C_6H_2OPSCl_2$ of 96.5 purity according to IR analysis employing pure standards of 2,4,5-$Cl_3C_6H_2OPSCl_2$ and 2,4,5-$Cl_3C_6H_2OPCl_2$.

A mixture of 3-C_2H_5-$C_6H_4OPCl_2$, 112 g., with sulfur, 16 g., and s-$C_2H_2Cl_4$, 17 g., was heated to 160° over a period of 1 hr. with agitation under atmospheric pressure. The reaction mixture was kept agitated under the same conditions for 2 hr. and then fractionated through a 15 cm. Vigreux column under reduced pressure. After removal of diluent a main cut of 110 g. (86% yield) of 3-C_2H_5-C_6H_4-$OPSCl_2$, b.p. 129–138° at 10 mm., was obtained. Infrared analysis employing pure standards indicated a purity of 96.0%.

Sulfur, 39 g., was added in portions over a period of 1.5 hr. to an agitated solution of 3,4-Cl_2-$C_6H_3OPCl_2$, 320 g., in C_6H_5Br, 70 g., heated at 170–177° under atmospheric pressure. The reaction mixture was kept agitated under these conditions for another 0.5 hr. Workup of reaction mixture and analysis of main cut was as described in the preceding run. Obtained was 325 g. (90.5% yield) of 3,4-Cl_2-C_6H_4-$OPSCl_2$; boiling range, 157–162° at 10 mm.; purity, 96% by infrared analysis.

Sulfur, 48 g., was added in small portions over a period of 1 1/3 hr. to an agitated solution of 2-Cl-$C_6H_4OPSCl_2$, 345 g., in $PSCl_3$, 51 g., and heated at 175–180° under atmospheric pressure. Agitation was continued for another 0.5 hr. under the same conditions. Workup of reaction mixture, isolation, and analysis of main cut was as described in the preceding experiment. Obtained was 353 g. (90% yield) of 2-Cl-$C_6H_4OPSCl_2$, boiling at 128–138° at 10 mm. and showing 98.8% infrared purity.

Catalytic reaction (b) in the presence of $PSCl_3$. An agitated mixture of 10.5 g. of sulfur with 158 g. of $PSCl_3$ was warmed to 75° and then 2 g. of anhydrous aluminum chloride added. Over a period of 1 hr. 93 g. of 2,4,6-$Cl_3C_6H_2OPCl_2$ was added at 55–80°. The reaction mixture was refluxed for 1 hr. under atmospheric pressure, filtered, and vacuum fractionated through a 15 cm. Vigreux column. The first cut, boiling at 58–65° at 100 mm. weighed 135 g. and was found to consist of unreacted $PSCl_3$, by infrared analysis. The main cut, boiling at 177–181° at 11 mm., weighed 43 g. (41.5% yield) and represented 2,4,6-Cl_3-$C_6H_2OPSCl_2$ of 99% infrared purity.

Anal. Calcd. for $C_6H_2Cl_5OPS$: S, 9.7. Found: S, 10.1.

An agitated mixture of 67 g. of 3-C_2H_5-$C_6H_4OPCl_2$ with 102 g. of $PSCl_3$ and 10.0 g. of sulfur was heated at reflux under atmospheric pressure in the presence of 1.5 g. of anhydrous, powdered silica, and 1.5 g. of activated carbon (Darco G60), respectively. In the presence of silica the reaction temperature of the refluxing mixture changed from 137–114–132° over a period of 26 hr. In the presence of Darco G60 the reaction temperature changed from 132–115–140° within 19 hr. After these reaction times the mixtures were filtered and vacuum fractionated as described in the foregoing run. The run in the presence of silica gave 48 g. (62.5% yield) and the run in the presence of activated carbon gave 72.5 g. (95% yield) of main cut, boiling at 130–137° at 10 mm. and identified by infrared analysis.

Anal. Calcd. for $C_8H_9Cl_2OPS$: S, 12.57. Found: S, 12.8.

Mixtures of 115 g. of monochlorophenyl phosphorodichloridite with 170 g. of $PSCl_3$, 16.5 g. of sulfur and 3 g. of Darco G60 were refluxed with agitation under atmospheric pressure. The reaction temperature of the mixtures changed from 132–115–140° C. during 19 hr. The runs were filtered and vacuum fractionated as described above. Obtained 124 g. (94.5% yield) of 2-$ClC_6H_4OPSCl_2$, boiling at 130–136° under 10 mm., identified by infrared analysis. The other run gave 115 g. (88% yield) of a compound boiling at 135–142° under 10 mm.

Anal. Calcd. for $C_6H_4Cl_3OPS$: Cl, 40.68; P, 11.85; S, 12.26. Found: Cl, 40.8; P, 11.5; S, 12.6.

An agitated mixture of 149 g. of 2,4,5-$Cl_3C_6H_2OPCl_2$ with 16.5 g. of sulfur, 20 g. of S_2Cl_2, and 2.5 g. of activated carbon was refluxed under atmospheric pressure for 85 min. The reaction temperature rose from 135° to 148°. The run was filtered and vacuum fractionated. The main cut consisted of 86 g. (52% yield) of 2,4,5-$Cl_3C_6H_2OPSCl_2$, boiling at 155–179° at 11 mm. It showed 90 ± 2% purity by infrared analysis.

Anal. Calcd. for $C_6H_2Cl_5OPS$: S, 9.7. Found: S, 10.87.

Mixtures of 298 g. of 2,4,5-$Cl_3C_6H_2OPCl_2$ with 33 g. of sulfur and 5 g. of Darco G60 were heated with agitation under atmospheric pressure in the presence of varying quantities of $PSCl_3$. The runs were worked up as described in the previous experiments. The results obtained were as given in Table VIII.

TABLE VIII

REACTION OF 2,4,5-$Cl_3C_6H_2OPCl_2$ WITH SULFUR IN THE PRESENCE OF $PSCl_3$ AND ACTIVATED CARBON

$PSCl_3$ (g.)	Reaction Temp., °C.	Time (hrs.)	Main Product Yield (g.)	Main Product Sulfur found (%)
None	135–138	2	195	10.2
125	136–122–160	16	226	10.1
420	130–122–137	20	290	10.0

Composite Reaction (d). Sulfur, 32 g., was added in small portions over a period of 3.5 hr. to an agitated mixture of 298 g. of 2,4,5-$Cl_3H_6H_2OPCl_2$ and 55 g. of phosphorus trichloride at a temperature of 155–175° at atmospheric pressure. Vacuum fractionation of the reaction mixture gave 44 g. of a PCl_3-$PSCl_3$ mixture and 288 g. of an impure 2,4,5-$Cl_3C_6H_2OPSCl_2$. This product had a boiling range of 155–176° at 11 mm. and contained 10% of 2,4,5-$Cl_3C_6H_2OPCl_2$, by infrared analysis.

A mixture of 298 g. of 2,4,5-$Cl_3C_6H_2OPCl_2$ with 69 g. of phosphorus trichloride was added to 37 g. of sulfur over a period of 2 hr. at 160–175° with agitation under atmospheric pressure. The reaction mixture was kept agitated for an additional 2 hr. under the same reaction conditions and then vacuum fractionated. This gave 281 g. (84.5% yield) of a 2,4,5-$Cl_3C_6H_2OPSCl_2$ boiling at 171–176° at 10 mm.

Anal. Calcd. for $C_6H_2Cl_5OPS$: S, 9.7. Found: S, 10.3.

In order to carry out the composite reaction (d) in the presence of aryl phosphorodichloridothioate, mixtures of 298 g. of 2,4,5-$Cl_3C_6H_2OPCl_2$ with 69 g. of phosphorus trichloride were added dropwise over a period of 2 hr. at 160–175° to agitated mixtures of 37 g. of sulfur and 2,4,5-$Cl_3C_6H_2OPSCl_2$ in amounts of 33, 165, 330, and 495 g. respectively. After completed addition the mixtures were kept agitated under the same reaction conditions for another 2 hr. Vacuum fractionation of the runs gave 2,4,5-$Cl_3C_6H_2$-$OPSCl_2$ in amounts of 319, 455, 636, and 816 g. respectively. The main cuts showed a boiling range of 171–178° at 10 mm. The amounts of 2,4,5-$Cl_3C_6H_2OPSCl_2$ actually produced were 286, 290, 306, and 321 g., respectively. The products, isolated by vacuum fractionation, showed absence of unreacted 2,4,5-$Cl_3C_6H_2OPCl_2$ by infrared analysis. Sulfur analysis gave 9.7 to 9.72% of total sulfur in the products.

Sulfur, 32 g., was added portionwise over a period of 2 hr. to an agitated mixture of 286 g. of 2-Cl-4-*t*-C_4H_9-C_6H_3-

$OPCl_2$ plus 69 g. of phosphorus trichloride plus 318 g. of 2-Cl-4-*t*-C_4H_9-$C_6H_3OPSCl_2$ at 160–175° under atmospheric pressure. The reaction mixture was kept under the same conditions for an additional 2 hr. and then vacuum-fractionated. A total of 622 g. of desired product was obtained, boiling at 173–177°/10 mm. Actual yield, 304 g. = 95.8% theory.

Anal. Calcd. for $C_{10}H_{12}Cl_3OPS$: S, 10.09. Found: S, 10.2.

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[CONTRIBUTION FROM THE E. C. BRITTON RESEARCH LABORATORY OF THE DOW CHEMICAL COMPANY]

Aromatic Phosphorodichloridites and Phosphorodichloridothioates. III. Structure and Physical Properties

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The refractive and vapor pressure data of *O*-aryl phosphorodichloridites and *O*-aryl phosphorodichloridothioates were investigated.

The availability of a series of aryl phosphorodichloridites[1] and phosphorodichloridothioates[2] of sufficient purity made it possible to study some relationships between their structure and certain physical properties. The investigation described in the following concerned refractive and vapor pressure data.

Molecular refraction. Some extensive studies on refractivities of organic phosphorus compounds have been carried out.[3,4] Since then the *atomic refractions* determined by Kabachnik[4] were found to be the most accurate ones, they were employed in the calculation of the molecular refraction of phosphorodichloridites and phosphorodichloridothioates (*cf.* Table I).

Aryl phosphorodichloridites were found to show an average deviation of 0.25 cc./mole of the theoretical values from the experimental molecular refractions. The calculation of the theoretical refractions of aryl phosphorodichloridothioates was made on the basis of two different values[5,6] for the atomic refraction of sulfur in the P=S group. It was found that the experimental values of the molecular refraction were about 0.2 cc./mole lower than the theoretical values, based upon Vogel's sulfur value of 10.23 (*cf.* Table I) and about 0.33 cc./mole higher than those theoretical values as calculated from Kabachnik's value of 9.7.

It is well known that the atomic refraction of phosphorus is not constant but varies with the structure of its organic compounds. Even for a given type of compound, containing direct C—P bonds, the value for the atomic refraction of phosphorus is known to depend on the nature of the carbon atom (aliphatic or aromatic). Moreover, refraction is a property not of atoms but of bonds, fundamentally. It is desirable, therefore, to compute molecular refractions of phosphorus compounds from *P-bond refractions*. So far, three attempts at establishing systems of refractive values for phosphorus bonds have been reported.[7–9] They show considerable deviation in the values assigned to several P-bonds. An independent computation,

TABLE I

MOLECULAR REFRACTIONS

Type of Compound	Aryl	MR Found	MR Calculated from: Atomic refr.	MR Calculated from: Bond refr.
ArylOPCl$_2$	C_6H_5	46.49	46.57	46.67
	m-C_2H_5—C_6H_4	56.22	55.81	55.97
	2-Cl—C_6H_4	51.52	51.54	51.59
	4-Cl—C_6H_4	51.52	51.54	51.59
	2-Cl-4-*t*-C_4H_9—C_6H_3	70.78	70.01	70.19
	2-Br-4-*t*-C_4H_9—C_6H_3	73.55	72.81	72.98
	2,4-Cl_2—C_6H_3	56.59	56.51	56.52
	2,5-Cl_2—C_6H_3	56.58	56.51	56.52
	3,4-Cl_2—C_6H_3	56.55	56.51	56.52
	2,4,5-Cl_3—C_6H_2	61.70	61.47	61.44
	2,4,6-Cl_3—C_6H_2	61.72	61.47	61.44
S ‖ ArylOPCl$_2$	C_6H_5	53.14	53.51	53.12
	m-C_2H_5—C_6H_4	62.65	62.75	62.42
	2-Cl—C_6H_4	58.33	58.48	58.04
	4-Cl—C_6H_4	58.32	58.48	58.04
	2,4-Cl_2—C_6H_4	63.28	63.45	62.97
	2,5-Cl_2—C_6H_3	63.18	63.45	62.97
	3,4-Cl_2—C_6H_3	63.27	63.45	62.97
	2,4,5-Cl_2—C_6H_2	68.24	68.41	67.89
	2-Cl—4-NO_2—C_6H_3	65.84		65.94

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carried out in connection with investigations described in this paper, gave the following tentative values for refraction of phosphorus bonds: P—O (ester bond) 3.15, P-Cl 8.75 and P=S 6.45. These data in combination with the values for carbon bond refractions found by A. I. Vogel,[10] permitted calculation of theoretical molecular refractions of phosphorodichloridites and phosphorodichloridothioates on the basis of bond refractions. It was found (*cf.* Table I) that the data for experimental and theoretical molecular refractions of both groups of compounds showed an average deviation of 0.22 cc./mole.

Vapor pressure. The literature was found to contain very little on relationships of vapor pressure with structure of organic phosphorus compounds. Stull[11] had reported on the vapor pressure of some aryl phosphates and Kosolapoff[12] had investigated aliphatic phosphonates. For the purpose of the present investigation, the boiling points of five phenyl phosphorodichloridites and five phenyl phosphorodichloridothioates were measured under reduced pressure (*cf.* Table II).

The C-values thus obtained (*cf.* Table III) permitted calculation of the B-constants according to[13]

$$B = \frac{\log p_3 - \log p_1}{t_3 - t_1} \cdot (t_1 + C)(t_3 + C)$$

Finally, the A-values were calculated on the basis of the Antoine equation itself. It was found that the B-values of all compounds investigated actually were a constant; its value was 2336.25. All of the A-values also were found to be a constant whose figure was 7.5622.

To check the reliability of the values determined for A, B, and C, a series of boiling pionts at reduced pressure were calculated on the basis of the Antoine equation and compared with the experimental boiling point data published previously for some of the compounds investigated. The results of this comparison were those given in the Tables IV and V.

For interpretation of the data in the Tables IV and V, all data with a difference of not more than 2° between experimental theoretical boiling points were considered to be in agreement.

In a total of thirty-two comparisons a satisfactory agreement was found in twenty-five cases and a moderate agreement in four cases. A clear discrepancy between calculated boiling points and experimental data reported in the literature was found in only three cases. These cases concerned the boiling point reported by Strecker[17] for *p*-

TABLE II

BOILING POINTS OF PHOSPHORODICHLORIDITES AND PHOSPHORODICHLORIDOTHIOATES

[Pressure (p) in Mm. Hg; Temperature (t) in °C.]

	C_6H_5		2-Cl—C_6H_4—		4-Cl—C_6H_4—		2,4-$Cl_2C_6H_3$—		2,4,5-$Cl_3C_6H_2$—	
Aryl	*p*	*t*	*p*	*t*	*p*	*t*	*p*	*t*	*p*	*t*
$ArOPCl_2$	29.4	117.1	29.6	137.5	29.6	139.6	29.3	160.3	27.2	178.8
	33.1	122.3	32.9	142.0	33.0	144.2	33.2	164.0	32.2	184.1
	51.6	134.9	51.5	154.7	51.8	157.2	51.6	177.9	50.8	198.6
	92.3	151.9	92.1	172.3	92.3	174.6	91.9	195.7	90.2	216.2
	189.5	176.6	189.6	196.9	189.4	198.6	190.0	220.0	189.3	239.3
$ArOPSCl_2$	25.6	136.4	29.6	161.8	29.3	169.1	28.2	178.3	32.6	201.1
	33.9	144.3	32.9	166.0	33.0	174.2	33.6	184.9	33.4	205.0
	51.6	157.4	50.7	179.3	50.9	187.8	51.9	201.6	51.8	219.5
	90.2	174.6	91.7	196.8	91.9	205.9	91.9	218.7	92.1	239.0
	189.9	199.5	189.4	222.5	189.6	230.8	190.0	244.2	190.1	265.7

Thomson[13] had found that the Antoine equation, $\log_{10}p = A - B/(t + C)$, gives sufficiently accurate data for vapor pressure–temperature relationships and is less complicated in its application than the Henglein equation. Moreover, Antoine's equation was found to be useful over a wider pressure-temperature range than the commonly used equation, $\log p = A - B/T$. Antoine's equation requires a determination of three constants, A, B, and C, for each of the ten compounds investigated by us. Calculation of C was done on the basis of Thomson's relation by using the data of three experimentally determined boiling points of each compound.

$$\frac{t_3 - t_1}{t_3 + C} = 1 - \frac{\log p_3 - \log p_2}{\log p_2 - \log p_1} \cdot \frac{t_2 - t_1}{t_3 - t_2} \quad \begin{matrix} (t \text{ in °Cels.}) \\ (p \text{ in mm. Hg}) \end{matrix}$$

TABLE III

INDIVIDUAL C-VALUES

Aryl	Aryl-$OPCl_2$	Aryl-$OPSCl_2$
C_6H_5—	266	241
2-Cl—C_6H_4—	246	222
4-Cl—C_6H_4	244	214
2,4-Cl_2—C_6H_3	222	197
2,4,5-Cl_3—C_6H_2—	202	180

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TABLE IV

BOILING POINTS OF PHOSPHORODICHLORIDITES

Pressure		10 Mm., °C.	11 Mm., °C.	12 Mm., °C.	13 Mm., °C.	190 Mm., °C.
$C_6H_5OPCl_2$	Calcd.	90	92.3			176.2
	Obsd.	90[1]	90–92[14,15]			177[a]
2-Cl—$C_6H_4OPCl_2$	Calcd.	110			116.3	196.2
	Obsd.	111–112[1]			116–120[16]	197[a]
4-Cl—$C_6H_4OPCl_2$	Calcd.	112		116.4		198.2
	Obsd.	113–113.5[1]		118–120[15]		199[a]
				128–130[17]		
2,4-Cl_2—$C_6H_3OPCl_2$	Calcd.	134				220.2
	Obsd.	134[1]				220[a]
2,4,5-Cl_3—$C_6H_2OPCl_2$	Calcd.	154				240.2
	Obsd.	154–155[1]				240[a]

[a] Cf. Table II.

TABLE V

BOILING POINTS OF PHOSPHORODICHLORIDOTHIOATES

Pressure		2 Mm., °C.	4 Mm., °C.	10 Mm., °C.	11 Mm., °C.	15 Mm., °C.	16 Mm., °C.	22 Mm., °C.	190 Mm., °C.
S ‖ $C_6H_5OPCl_2$	Calcd.			115	117.3	124.8	126.5	134.6	201.2
	Obsd.			116[2]	119–120[18]	133–135[19]	132[19]	133[20,21]	199.8
S ‖ 2-Cl—$C_6H_4OPCl_2$	Calcd.			134					220.2
	Obsd.			134[2]					223.1[a]
S ‖ 4-Cl—$C_6H_4OPCl_2$	Calcd.		121.7	142	144.3				228.2
	Obsd.		125[22]	141[2]	143–145[17]				231.1[a]
S ‖ 2,4-$Cl_2C_6H_3OPCl_2$	Calcd.	124.7		159					245.2
	Obsd.	126–128[22]		158[2]					244.2[a]
S ‖ 2,4,5-$Cl_3C_6H_2OPCl_2$	Calcd.			176					263.2
	Obsd.			175[2]					265.4[a]

[a] *Cf.* Table II.

TABLE VI

C-VALUES OF PHOSPHORODICHLORIDATES

2-Cl—$C_6H_4OPOCl_2$	4-Cl—$C_6H_4OPOCl_2$	2,4-Cl_2—$C_6H_3OPOCl_2$	2,4,5-Cl_3—$C_6H_2OPOCl_2$
225	221	208	188

chlorophenyl phosphorodichloridite (Table IV) and the boiling points reported by Autenrieth[19] for phenyl phosphorodichloridothioate (Table V). In view of the agreement found in the high majority of comparisons, it appeared possible that these three boiling points were actually inaccurate.

It was concluded that boiling points at pressures of 5 to 200 mm. of chlorinated phenyl phosphorodichloridites and phosphorodichloridothioates could be calculated with practically acceptable accuracy from the following simplified Antoine equation (by using the C-values given in Table III):

$$t(°C.) = \frac{2336.25}{7.5622 - \log_{10} P} - C$$

An application of this finding to a series of aryl phosphorodichloridates showed that it was not possible to calculate the correct boiling points of *p-tert*-butylphenyl phosphorodichloridate and biphenylyl phosphorodichloridate from the same equation. It was found, however, that fairly correct boiling points of some chlorinated phenyl phosphorodichloridates could be calculated if the following individual C-values were used (*cf.* Table VI).

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[CONTRIBUTION FROM RESEARCH AND DEVELOPMENT DEPARTMENT, WESTVACO CHLOR-ALKALI DIVISION, FOOD MACHINERY AND CHEMICAL CORP.]

Preparation of Trichloromethylphosphonous Dichloride. Reduction of Tetrachlorophosphoranes with Methyl Phosphorodichloridite[1]

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Methylphosphonous dichloride was chlorinated in the cold to form tetrachloromethylphosphorane and then at higher temperatures to form tetrachloro(trichloromethyl)phosphorane. This compound was reduced by the action of methyl phosphorodichloridite to trichloromethylphosphonous dichloride.

A synthesis of trichloromethylphosphonous dichloride, heretofore unknown, has been accomplished. The method may be useful in obtaining other halomethyl phosphonous dichlorides.

In this synthesis, the unsubstituted phosphonous dichloride, CH_3PCl_2,[4] in an inert solvent is treated in the cold with chlorine. A quantitative yield of tetrachloromethylphosphorane, CH_3PCl_4, results. This compound, without isolation, is then chlorinated at 60–70° to produce tetrachloro(trichloromethyl)phosphorane. An earlier example of the smooth substitution of hydrogen in an alkyl tetrachlorophosphorane is the synthesis of this same trichloromethyl derivative by the chlorination of tetrachloro(chloromethyl)phosphorane[5]; the latter substance was formed from chlorine and chloromethylphosphonous dichloride, in turn obtained from diazomethane and phosphorus trichloride.[6]

The synthesis is completed by the reduction of the above tetrachlorophosphorane, again without isolation, to trichloromethylphosphonous dichloride in 85% over-all yield. We have introduced the use of methyl phosphorodichloridite, prepared from methanol and phosphorus trichloride,[7] for this type of reduction. Phosphorus[8,9] and certain metals[9] have previously been used for removal of chlorine from chlorophosphoranes and in fact we have used the former successfully in this reduction. The new reagent, however, is attractive because of the smoothness and simplicity of the reduction and ease of removal of its oxidation products, methyl chloride and phosphorus oxychloride, as well as any excess of the reagent. The reduction is postulated to proceed as follows:

$$CCl_3PCl_4 + CH_3OPCl_2 \longrightarrow CCl_3PCl_2 + CH_3OPCl_4 \quad (1)$$

$$CH_3OPCl_4 \longrightarrow CH_3Cl + POCl_3 \quad (2)$$

The exchange of chlorine in Equation 1 is facilitated by the decomposition of one of the products as shown in Equation 2. The literature[10] suggests such instability for CH_3OPCl_4, and this was established when an attempted preparation of this compound from chlorine and methyl phosphorodichloridite resulted in only the formation of methyl chloride and phosphorus oxychloride.

Tetrachloromethylphosphorane was also reduced smoothly by methyl phosphorodichloridite to the phosphonous dichloride in about 80% yield, and it is believed the reagent may be widely applicable for this type of reduction. The occurrence of a likely side-reaction (3) was not noted in the case where R

$$CH_3OPCl_2 + RPCl_4 \longrightarrow CH_3Cl + PCl_3 + RPOCl_2 \quad (3)$$

is $-CCl_3$ but may have occurred to a slight extent where R is $-CH_3$. Phosphites other than methyl phosphorodichloridite may also prove to be useful in the reduction of chlorophosphoranes.

The chlorination of methylphosphonous dichloride in concentrated solution or at temperatures above 30–40° is accompanied by some cleavage of the carbon-phosphorus bond. It is therefore an essential feature of the synthesis of trichloromethylphosphonous dichloride, and probably in any application of the synthetic method to the preparation of other substituted alkyl phosphonous dichlorides, that the starting material be stabilized in the form of the tetrachlorophosphorane. This derivative is chlorinated smoothly without bond cleavage, and the product is readily converted to the phosphonous dichloride. A variation of the classical principle of the protection of a sensitive functional group and its subsequent regeneration has thus been employed in this synthesis.

As is true of other phosphorus halides containing the strongly electronegative trichloromethyl group, trichloromethylphosphonous dichloride is resistant

(1) Portions of this paper report work done under contract with the Chemical Corps, U. S. Army, Washington 25, D. C.

(2) Chemistry Department, Duke University, Durham, N. C.

(3) Explosives Department, E. I. du Pont de Nemours & Co., Gibbstown, N. J.

(4) F. W. Hoffmann and T. R. Moore, *J. Am. Chem. Soc.*, **80**, 1150 (1958).

(5) A. Y. Yakubovich and V. A. Ginsburg, *Zhur. Obshch. Khim.*, **24**, 1465 (1954).

(6) A. Y. Yakubovich, V. A. Ginsburg, and S. P. Makarov, *Doklady Akad. Nauk S.S.S.R.*, **71**, 303 (1950).

(7) D. R. Martin and P. J. Pizzolato, *J. Am. Chem. Soc.*, **72**, 4584 (1950).

(8) E. N. Walsh, T. M. Beck, and W. H. Woodstock, *J. Am. Chem. Soc.*, **77**, 929 (1955).

(9) W. A. Higgins, U. S. Patent **2,779,787**, Jan. 29, 1957.

(10) G. M. Kosolapoff, *Organophosphorus Compounds*, John Wiley and Sons, Inc., New York, N. Y., 1950, p. 325.

to hydrolysis. In oxidation reactions, however, it reacts with vigor. It is oxidized rapidly on exposure to the atmosphere, and although much heat is generated, it does not inflame as has been reported for trifluoromethylphosphonous dichloride.[11]

EXPERIMENTAL

Preparation of tetrachloro(trichloromethyl)phosphorane. A solution of 234 g. (2.0 moles) methylphosphonous dichloride[4] in 600 g. phenylphosphonic dichloride as solvent[12] was stirred at 0° while 149 g. (2.1 moles) chlorine was added. The slurry of tetrachloromethylphosphorane was warmed to 60° and held there by cooling while 490 g. (6.9 moles) chlorine was added over a period of 3 hr. Chlorine consumption was complete until shortly before the stoichiometric amount (6.0 moles) had been added. The slurry was stirred at 55–60° under 100–150 mm. pressure to remove hydrogen chloride and excess chlorine. The product was not isolated but was used directly in the next step.

Preparation of trichloromethylphosphonous dichloride. The above reaction mixture was protected with nitrogen while 266 g. (2.0 moles) methyl phosphorodichloridite was added in 1.5 hr. The use of a small excess of this reagent causes no difficulty, but a large excess appears to reduce the yield. The mild exotherm was controlled to give a reaction temperature of 35°; higher temperatures cause slight yield reduction. Evolution of methyl chloride occurred near the end of the reaction as its solubility in the mixture was exceeded. The resulting clear solution was rectified *in vacuo* with a 0.75 in. by 15 in. column of Hastelloy B Heli-Pak. After a cut of phosphorus oxychloride, a 39-g. fraction, possibly a mixture of the chlorinated methylphosphonous dichlorides, was obtained over the range 63° at 30 mm. to 70° at 26 mm. Trichloromethylphosphonous dichloride was then collected at 69–70° at 23 mm. There was obtained 375 g. (1.70 moles), a yield of 85% on methylphosphonous dichloride charged. The still bottoms of phenylphosphonic dichloride were recovered for further use by simple distillation.

Trichloromethylphosphonous dichloride freezes at 47°[13] and boils at 171–172°[13] at 750 mm. It must be protected from the atmosphere, as oxidation occurs with great ease. It is insoluble in, and reacts only slowly with, water. It reacts quantitatively with chlorine to form tetrachloro(trichloromethyl)phosphorane.

Anal. Calcd. for CCl_5P: C, 5.45; Cl, 80.48; P, 14.07. Found: C, 5.23; Cl, 80.30; P, 14.33.

Reduction of tetrachloromethylphosphorane with methyl phosphorodichloridite. To a solution of 35.1 g. (0.30 mole) methylphosphonous dichloride in 300 g. chlorobenzene was added 22.0 g. (0.31 mole) chlorine. The temperature was held at 10° during this formation of tetrachloromethylphosphorane. The slurry was then warmed to 50° and treated over a period of 30 min. with 39.5 g. (0.30 mole) methyl phosphorodichloridite. The resulting clear solution was rectified. A 26.9-g. fraction of methylphosphonous dichloride (77% recovery) boiling at 81–82° was collected. In addition, a small forerun (5 g.) boiling from 77–81° was obtained; this probably contained more of the product along with phosphorus trichloride, formed as shown in Equation 3.

Attempted preparation of tetrachloromethoxyphosphorane. A solution of 40 g. (0.30 mole) methyl phosphorodichloridite in 265 ml. chlorobenzene was held below 10° while 22 g. (0.31 mole) chlorine was added. The exothermic reaction was completed in 45 min. Distillation was then conducted at reduced pressure (15–20 mm.) so as to maintain a pot temperature of 30°. Methyl chloride was evolved and collected in a Dry Ice trap. The distillate consisted of phosphorus oxychloride and the solvent. No residue remained after distillation. Tetrachloromethoxyphosphorane was thus shown to be unstable near room temperatures, decomposing cleanly according to Equation 2.

South Charleston, W. Va.

(11) F. W. Bennett, H. J. Emeléus, and R. N. Haszeldine, *J. Chem. Soc.*, 1565 (1953).

(12) Available from Victor Chemical Works. This compound is inert in the reactions discussed and is used as solvent throughout; its high boiling point (258°) permits its use as a "chaser" in the distillation to isolate trichloromethylphosphonous dichloride. Other inert solvents are also useful.

(13) Uncorrected.

[Contribution from the Department of Chemistry, University of Southern California and the Research Department, Stauffer Chemical Co.]

Derivatives of Sulfenic Acids. XXXIII. Studies of Thioperoxides. Part 4. Reactions of Trichloromethanesulfenyl Chloride with 1,2-Epoxides and Alcohols

ROBERT B. LANGFORD and NORMAN KHARASCH

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Trichloromethanesulfenyl chloride (I) reacts with 1,2-epoxides and with *meso*-1,2,3,4-diepoxybutane to form *beta*-chloroalkyl trichloromethanesulfenates. The reaction is catalyzed by tertiary amines, and identical products are obtained by substituting appropriate *beta*-chloro alcohols for the epoxides. The results agree with the mechanism which postulates *trans* opening of the epoxide rings, as previously suggested for the similar reactions of 2,4-dinitrobenzenesulfenyl chloride. The new products from reaction of I with epoxides and certain alcohols are reported.

Trichloromethanesulfenyl chloride (I) holds a unique position among aliphatic sulfenyl halides. Historically, it was the first of this group of substances to be reported,[1] its precise structure has been carefully investigated by infrared spectra,[2] and both the sulfenyl chloride and its derivatives have intrigued many industrial investigators.[3]

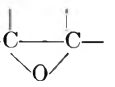
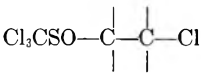
(1) B. Rathke, *Ann.*, **167**, 204 (1873); *Cf.* also N. Kharasch, S. J. Potempa, and H. L. Wehrmeister, *Chem. Revs.*, **39**, 269 (1946).

(2) J. A. A. Ketelaar and W. Vedder, *Rec. trav. chim.*, **74**, 1482 (1955).

(3) *Cf. e.g.* (a) A. R. Kittleson and H. L. Yowell, U. S. Patent 2,553,771 (1951); (b) G. H. Birum and R. J. Kern, U. S. Patent 2,769,777 (1956); and (c) E. M. Nygaard and J. H. McCracken, U. S. Patent 2,326,102 (1943).

In the present study, the reactions of I with certain 1,2-epoxides and alcohols were examined, for comparison with the similar reactions of 2,4-dinitrobenzenesulfenyl chloride.[4] The reactions involved were (*a*) and (*b*):

(*a*) $Cl_3CSCl + ROH + C_5H_5N \longrightarrow Cl_3CSOR + C_5H_5N{:}HCl$

(*b*) $Cl_3CSCl +$  $\xrightarrow[C_5H_5N]{\text{Trace}}$ 

The products obtained are listed in Table I.

If *trans* opening of the epoxide ring is involved in reaction *b*, the product from 1,2-epoxycyclohexane should be *trans*-2-chlorocyclohexyl trichloromethanesulfenate (II). This was verified by finding that the alcohol obtained by acid hydrolysis of II was *trans*-2-chlorocyclohexanol,[8] and, as expected, the product from reaction of I with 2-chloroethanol was the same as formed with epoxyethane. Since ring opening of the epoxide should follow predictions for acidic openings of such rings (attack by the anion on the protonated epoxide taking place preferentially at a primary carbon rather than at a secondary or tertiary one), the major product from reaction of I and 3-chloro-1,2-epoxypropane should be 1,3-dichloro-2-propyl trichloromethanesulfenate, which should also result by reaction of I and 1,3-dichloro-2-propanol. These predictions were verified, since the major product obtained from both routes was identical, as shown by boiling points, refractive indices, and infrared spectra.

TABLE I

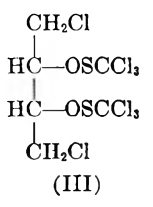
SYNTHESIS OF TRICHLOROMETHANESULFENATES FROM TRICHLOROMETHANESULFENYL CHLORIDE AND EPOXIDES OR ALCOHOLS

Epoxide or Alcohol	Yield, %	B.P./Mm.[a]	n_D^{20}	Analyses							
				Calcd.				Found			
				C	H	S	Cl	C	H	S	Cl
Epoxyethane	85	45–46°/0.1	1.5230	15.67	1.75	13.94	61.68	15.72	1.72	13.91	61.59
2-Chloroethanol	59	52–53°/0.2	1.5223	[b]							
1,2-Epoxypropane	83	43–44°/0.1	1.5124	19.69	2.48	13.14	58.13	19.83	1.56	13.10	57.98
1-Chloro-2-propanol	54	53–54°/0.2	1.5106	[b]							
3-Chloro-1,2-epoxypropane	76	75–76°/0.2	1.5321	17.25	1.81	11.51	63.67	17.02	1.50	11.65	63.72
1,3-Dichloro-2-propanol	57	79–80°/0.1	1.5320	[b]							
1,2-Epoxycyclohexane[e]	74	89–90°/0.1	1.5334	29.60	3.55	11.29	49.93	29.53	3.56	11.38	50.09
Phenylepoxyethane[f]	74	119–121°/0.1	1.5270	35.32	2.63	10.48	46.34	35.55	2.57	10.18	46.02
meso-1,2,3,4-Diepoxybutane[g]	24	(m.p. 96–97°)	-	15.74	1.32	-	61.95	15.88	1.33	—	62.10
Methanol[c]	77	53–54°/14	1.5050	13.24	1.66	17.67	58.61	12.93	1.58	18.09	58.45
1-Propanol[c]	52	31–32°/0.3	1.4800	[d]							
2-Propanol[c]	41	32–33°/0.4	1.4820	[d]							
Allyl alcohol[c]	55	52–53°/0.1	1.5413	[d]							
Tetrahydrofurfuryl alcohol[c]	48	74–75°/0.2	1.5180	[d]							

[a] Read from a tilting McLeod gauge. [b] These alcohol derivatives were not analyzed for elementary composition, as they were shown to be identical with the epoxide derivatives by comparison of infrared spectra. [c] Previously reported by Sosnovsky. [d] Not analyzed. Identity verified by infrared spectra. [e] Product is *trans*-2-chlorocyclohexyl trichloromethanesulfenate. [f] Product is 1-phenyl-2-chloroethyl trichloromethanesulfenate. [g] Product is *meso*-1,4-dichloro-2,3-bis(trichloromethanesulfenoxy)butane, III.

Certain of the esters of trichloromethanesulfenic acid are recorded in the literature, having been prepared by the reaction of I with the metallic salt of an alcohol or phenol.[5] The use of pyridine and other tertiary amines as catalytic condensing agents has been reported earlier in this series,[4] and recently, also, for the reaction of I with primary and secondary alcohols.[6] Brintzinger *et al.*,[7] found that the reaction of monochloromethanesulfenyl chloride with two equivalents of epoxyethane took place without the necessity of an added catalyst.

The product from *meso*-1,2,3,4-diepoxybutane with I would be expected to be III, *i.e.* *meso*-1,4-dichloro-2,3-bis(trichloromethanesulfenoxy)-butane. The product isolated from the reaction of the



(III)

(4) (a) N. Kharasch, D. P. McQuarrie, and C. M. Buess, *J. Am. Chem. Soc.*, **75**, 2658 (1953); (b) L. Goodman and N. Kharasch, *J. Am. Chem. Soc.*, **77**, 6541 (1955); and (c) D. Peters and N. Kharasch, *J. Org. Chem.*, **21**, 590 (1956).

(5) J. M. Connolly and G. M. Dyson, *J. Chem. Soc.*, 822 (1934); *J. Chem. Soc.*, 679 (1935); and *J. Chem. Soc.*, 827 (1937).

(6) G. Sosnovsky, *J. Chem. Soc.*, 3139 (1956).

(7) H. Brintzinger, H. Schmahl, and H. Witte, *Ber.*, **85**, 338 (1952).

(8) H. C. Stevens and O. Grummit, *J. Am. Chem. Soc.*, **74**, 4877 (1952).

epoxide[9] and I, mixed in 1:2 molar ratios, gave a glycol, on hydrolysis, which melted at 127°, and was identical with *meso*-1,4-dichloro-2,3-butanediol, prepared from *trans*-1,4-dichloro-2-butene by oxidation with peracetic acid[10,11] Permanganate oxidation[12] of the same olefin gave *dl*-1,4-dichloro-2,3-butanediol, m.p. 62°. Infrared spectra of the glycol obtained from the sulfenyl ester and the *meso*-1,4-dichloro-2,3-butanediol were identical, but the spectrum of the racemic diol was quite different.

Except for the *meso*-1,2,3,4-diepoxybutane derivative, which is a white crystalline solid, the esters of Table I, when pure, are water-white liquids which may be distilled at low pressure with very little decomposition. Samples have been kept for over a year in well stoppered containers without noticeable change. Sunlight and heat, however, appear to induce decomposition, although a systematic study of this behavior has not yet been made. Hydrolysis has also been noted on storing poorly stoppered samples, with some of the alcohol being found on redistillation.

It is to be noted that these compounds are related to both disulfides and peroxides, and have been designated also as *thioperoxides*. The use of some of these substances as agents for inducing the photopolymerization of olefins[3b] undoubtedly shows that they can undergo free-radical decomposition. Certain of these esters also show oxidizing ability toward iodide ion.[13]

Some difficulty was encountered in obtaining good analytical results for the products in Table I, as Barltrop, Hayes, and Calvin have noted.[13] It was found, however, that good analyses were obtained with samples purified by rigorous redistillations through a suitable column.

Triethylamine, and presumably other tertiary amines, may be used in place of pyridine in the reactions of trichloromethanesulfenyl chloride with alcohols and epoxides. The necessity of such a catalyst for the epoxide reaction was demonstrated in the reaction of I with epoxyethane. Although the reaction normally goes to completion within a few hours when a small amount of a tertiary amine is present, no apparent reaction occurred in eight days without a catalyst. On distillation of the reaction mixture, over 95% of the initial amount of I was recovered and no distillate was obtained in the boiling range of the sulfenyl ester.

The infrared spectra of these compounds were obtained in the region from 650 to 10,000 cm.$^{-1}$, and were found to agree with the assigned structure of the products in Table I. The region from 710 to 810 cm.$^{-1}$, in particular, showed the typical curve associated with the trichloromethylthio group in trichloromethanesulfenyl chloride.[2]

In the course of this investigation several of the trichloromethanesulfenates reported by Sosnovsky[6] were prepared. Their identity was confirmed by infrared spectra and by their boiling points which agree quite well with the literature. Although incidental to the primary topic discussed here, they are included in Table I to increase the available information on this series of compounds.

EXPERIMENTAL

Trichloromethanesulfenyl chloride was prepared by redistilling technical grade "perchloromethyl mercaptan," obtained from the Stauffer Chemical Co. Cyclohexene oxide was obtained from Arapahoe Chemicals, Inc., and the other epoxides and alcohols were the product of Distillation Products Industries. With the exception of practical grade 1-chloro-2-propanol, which was carefully fractionated, these were all reagent grade, and were used as supplied. Reagent pyridine, dried over sodium hydroxide, and 1,2-dichloroethane, dried by distillation, were used in these reactions. The infrared spectra were made in carbon disulfide solutions or on the neat liquids, using a Perkin-Elmer double-beam spectrophotometer, Model 21.

General procedure for the reaction of trichloromethanesulfenyl chloride with epoxides. To a solution of 0.10 mole of I in 100 ml. of dry 1,2-dichloroethane was added 0.11 mole of the epoxide. To this mixture 0.5 ml. of dry pyridine was added. Completion of this reaction, which may require several hours, was determined by the disappearance of the odor of I and by a negative starch-iodide test for the presence of I. The mixture was washed with water to remove the amine and amine hydrochloride and dried over anhydrous sodium sulfate. The dried solution was aspirated to remove the solvent and the residue distilled under reduced pressure to obtain the product.

Procedure for the reaction of trichloromethanesulfenyl chloride with 1,2,3,4-diepoxybutane. To a solution of 0.20 mole of I in 100 ml. of dry ethylene chloride was added 0.10 mole of 1,2,3,4-diepoxybutane.[9] To this mixture was added 1.0 ml. of dry pyridine. Although the last trace of I remained after two days, the mixture was water-washed, dried, and aspirated, as in the general procedure above. The residual viscous oil readily dissolved in 200 ml. of methanol, at room temperature. Within a minute, a precipitate of white crystals began to form. After cooling to 0°, the crystals were collected and air-dried (11 g.; 24%); m.p. after recrystallization from methanol, 96–97°.

General procedure for the reaction of trichloromethanesulfenyl chloride with alcohols. To a solution of 0.10 mole of I in 100 ml. of dry 1,2-dichloroethane was added 0.11 mole of the dry alcohol. To this was gradually added, with stirring, 0.11 mole of dry pyridine. Completion of the reaction, which may require several hours, was determined as above, and the product was isolated by fractional distillation.

(9) The 1,2,3,4-diepoxybutane was kindly supplied by Union Carbide Chemicals Co., and was reported to be over 90% *meso* isomer. This material causes painful blistering on contact with the skin and was also reported possibly carcinogenic.

(10) The identity of the *trans*-1,4-dichloro-2-butene was verified by comparing its infrared spectrum with that recorded by K. Mislow and H. M. Hellman, *J. Am. Chem. Soc.*, **73**, 246 (1951).

(11) D. Swern, G. N. Billen, T. W. Findley, and J. T. Scanlan, *J. Am. Chem. Soc.*, **67**, 1787 (1945).

(12) R. M. Evans and L. N. Owen, *J. Chem. Soc.*, 239 (1943).

(13) J. A. Barltrop, P. M. Hayes, and M. Calvin, *J. Am. Chem. Soc.*, **76**, 4348 (1954).

Acknowledgment. We wish to express our appreciation to Mr. D. M. Frankel, of the Stauffer Chemical Co., for his assistance in the preparation and evaluation of the infrared spectra of the compounds in Table I and to Dr. Adalbert Elek for microanalyses.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE VIRGINIA POLYTECHNIC INSTITUTE]

Unsaturated Cyclic Sulfones. IV. Isomeric 2-Methyldihydrothiophene 1,1-Dioxides

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Received June 12, 1958

2-Methyl-2,5-dihydrothiophene 1,1-dioxide (I) has been carefully characterized, and from this sulfone the remaining two isomeric sulfones have been obtained. Isomerization of I in basic medium gives 2-methyl-4,5-dihydrothiophene 1,1-dioxide and the pyrolysis of the acetate from the alcohol from I gives 2-methyl-2,3-dihydrothiophene 1,1-dioxide.

The characterization of 2-methyl-2,5-dihydrothiophene 1,1-dioxide (I) and the development of reasonably simple methods of preparation of the remaining isomeric sulfones and their subsequent characterization are necessary to the study of the chemistry of the sulfones[2] of the 2-methyl series.

In 1943 Craig[3] reported the preparation of I from the reaction of 1,3-pentadiene and sulfur dioxide, and although he reported that he was able to distill the sulfone no physical constants were given for this product. In 1945 Morris and Finch[4] reported the density and refractive index of this sulfone. Although studies concerning this sulfone have been reported by Frank,[5] Drake,[6] and Grummitt and co-workers[7] no characterization of the compound was reported. Thus, the first objective of the present work is the purification and characterization of I. The sulfone was prepared by the reaction of sulfur dioxide and 1,3-pentadiene in the presence of hydroquinone, to give a colorless oil in 55% yield. Purification of I was effected by distillation at reduced pressure in an atmosphere of sulfur dioxide or more simply by the method described in detail in the Experimental section of this paper. The latter method was found to give as good a product and one which exhibits practically no absorption in the ultraviolet between 220 and 320 mμ at concentrations up to 1 g./liter in ethanol. The crude sulfone, as it moved through the purification scheme, showed a steady decrease in absorption at 220–230 and 280–300 mμ. The loss of absorptivity in these regions was found to be due to removal of traces of 1,3-pentadiene and sulfur dioxide, respectively. The infrared spectra of the distilled sulfone and the extracted sulfone are in excellent agreement.

Under refrigeration at 0° the decomposition of the purified sulfone becomes perceptible through the odor of sulfur dioxide after 11 days, and the sulfone undergoes complete dissociation at 100°. Previous studies in this laboratory demonstrated the utility of bromine adducts as aids in the characterization of certain unsaturated sulfones, hence, the dibromide from I was prepared. Actually, two dibromides from I appear to have been obtained, and it is suggested that these two dibromides are two racemic mixtures. The higher melting dibromide will be referred to as IIa and the lower melting substance as IIb. Sulfone I as well as adducts IIa and IIb are optically inactive; however, if one assumes the trans addition of bromine (see reaction conditions) to sulfone I four stereoisomers are indeed possible (two racemic mixtures). Quantitative analysis supports the formula $C_5H_8Br_2O_2S$ for IIa and IIb. While the infrared spectra of IIa and IIb are similar, the spectra are definitely not identical. Sulfone I was converted to the tetrahydro derivative, 2-methyltetrahydrothiophene 1,1-dioxide (III) in 91% The physical constants for III are in good agreement with those reported by Grishkevich-Trokhimovskii[8] who prepared this compound by the reaction of 1,4-dibromopentane and sodium sulfide, and the subsequent oxidation of the cyclic sulfide of the sulfone. The infrared spectrum of III appears in good agreement with the spectra of 3-methyltetrahydrothiophene 1,1-dioxide and with

(1) American Chemical Society Graduate Fellow. This research was supported by a grant from The Petroleum Research Fund administered by the American Chemical Society. Grateful acknowledgment is hereby made to the donors of said fund.

(2) For the previous paper see R. C. Krug, G. R. Tichelaar, and F. E. Didot, *J. Org. Chem.*, **23**, 212 (1958).

(3) D. Craig, *J. Am. Chem. Soc.*, **65**, 1006 (1943).

(4) R. C. Morris and H. deV. Finch (to Shell Development Co.), U. S. Patent 2,373,329, April 10, 1945.

(5) E. J. Frank, *J. Am. Chem. Soc.*, **69**, 2313 (1947).

(6) S. P. Drake, *J. Am. Chem. Soc.*, **68**, 2521 (1946).

(7) O. Grummitt, A. E. Ardis, and J. Fick, *J. Am. Chem. Soc.*, **72**, 5167 (1950).

(8) E. Grishkevich-Trokhimovskii, *J. Russ. Phys. Chem. Soc.*, **48**, 901 (1916).

tetrahydrothiophene 1,1-dioxide with respect to the presence of the saturated ring system.

In view of previous studies[2] it seemed reasonable to expect that sulfone I in the presence of a strong base should undergo isomerization. Indeed, such was found to be the case and the reaction product was identified as 2-methyl-4,5-dihydrothiophene 1,1-dioxide (IV). The melting point of this sulfone and of its bromine adduct are in good agreement with the values given by Birch and McAllan.[9] These authors obtained a compound which they tentatively identified as sulfone IV by the oxidation of a minor reduction product from 2-methylthiophene. In 1953 Bacchetti and Fiecchi[10] prepared a compound having a melting point similar to that reported by Birch and McAllan for IV by the cyclization of 5-mercapto-2-pentanone to give the cyclic sulfide which was oxidized to the sulfone. In the present work, sulfone IV was converted to III in 81% with hydrogen in the presence of a catalyst. The infrared spectrum of IV supports the presence of the $-CH=\overset{|}{C}-$ type of double bond.

There remained of course the synthesis of the third isomer, 2-methyl-2,3-dihydrothiophene 1,1-dioxide. One of the most direct methods of synthesis appeared to be the hydration of sulfone I (depending on the location of the hydroxy group), conversion of the alcohol to the acetate, and the pyrolysis of the acetate. The alcohol was obtained in 18% yield by the action of aqueous potassium hydroxide on sulfone I. The position of the hydroxy group is assigned in agreement with the formula 4-hydroxy-2-methyltetrahydrothiophene 1,1-dioxide (V), as will be subsequently established. Sulfone V, a colorless oil, gave a 3,5-dinitrobenzoate and an acetate. The infrared spectrum of V was prepared; however, no information regarding the location of the hydroxy group was obtained. The alcohol was converted to its corresponding acetate (VI) in 81% yield. By means of the infrared spectra the relationship between V and VI was established. Thus, VI was assigned the formula in agreement with 4-acetoxy-2-methyltetrahydrothiophene 1,1-dioxide. Vapor phase pyrolysis of the acetate at 440–452° gave, after purification, a colorless oil (VII). Analytical data clearly support the formula $C_5H_8O_2S$, and the infrared spectrum of VII gave evidence of the presence of a symmetrical —CH=CH— ethylenic unit. Sulfone I and the pyrolysis product absorb strongly near 690 cm.$^{-1}$, while sulfone IV does not absorb in this region of the spectrum. Sulfone VII was converted to a dibromide, and catalytic reduction of VII gave II in 74% yield. Parenthetically, the trans addition of bromine to VII should give four stereoisomeric dibromides (two racemic mixtures); however, one dibromide m.p. 84–85° has thus far been identified. Thus, the formula of sulfone VII is established as 2-methyl-2,3-dihydrothiophene 1,1-dioxide, and the structures of sulfones V and VI are as indicated by their respective names.

(9) F. F. Birch and D. T. McAllan, *J. Chem. Soc.*, 3411 (1951).

(10) T. Bacchetti and A. Fiecchi, *Gazz. chim. ital.*, **83**, 1037 (1953).

EXPERIMENTAL[11]

2-Methyl-2,5-dihydrothiophene 1,1-dioxide (I). Commercial 1,3-pentadiene (90% pentadiene, Phillips Petroleum Co.) was enriched in the trans-1,3-pentadiene component by the method of Frank.[5] The crude diene showed a change in refractive index during enrichment from n_D^{20} 1.4326 to n_D^{20} 1.4290 (lit.[12]; cis, n_D^{20} 1.4359; trans n_D^{20} 1.4299). In a steel reaction vessel were placed 250 ml. (3.88 moles) of liquid sulfur dioxide 90.0 g. (1.32 moles) of the enriched 1,3-pentadiene (peroxide free), and 5.0 g. of hydroquinone. The vessel was sealed, and heated to 95° for 3 hr. The vessel was cooled, and the volatile components were vented to give 150 g. of a red colored oil. Of this oil 60.0 g. was added to 600 ml. of water, and the mixture was shaken thoroughly and refrigerated overnight. The supernatant liquid was decanted, filtered, and the filtrate was extracted with four portions of chloroform. The chloroform was evaporated from the combined extracts to give 48.0 g. of a yellow oil which was dissolved in 250 ml. of distilled water and refrigerated overnight. The aqueous phase was separated from the gum and extracted with four portions of chloroform under refrigerated (0°) conditions. Removal of chloroform from the combined extracts gave 38.1 g. of colorless oil, n_D^{20} 1.4942, d_4^{20} 1.2433. A sample of this oil, distilled under reduced pressure in an atmosphere of sulfur dioxide, gave the following: b.p. 85°/7 mm., n_D^{20} 1.4929, and d_4^{20} 1.2539. The yield of purified I based on the trans content of the diene as 86%[5] was 55%. Infrared spectra of the distilled product and the extracted product were entirely similar, and the principal frequencies are: 3040, 2970, 2930, 1615, 1450, 1409, 1380, 1348, 1305, 1250, 1223, 1128, 1077, 1008, 960, 916, 896, 830, 726, 704, and 657 cm.$^{-1}$

2-Methyl-3,4-dibromotetrahydrothiophene 1,1-dioxide (II). To a flask containing 16.0 g. (0.100 mole) of bromine and 0.146 g. of aluminum chloride was added 12.4 g. (0.094 mole) of I. After four days a slight sediment was filtered, and the chloroform was evaporated. The residue was continuously extracted with water for 33 hr. The solid which did not dissolve was recrystallized from ethanol to give 4.6 g. (17%) of IIa, m.p. 145.0–145.5°. The aqueous extract was chilled and the solid was recrystallized from methanol to give white crystals weighing 2.3 g. (8%), m.p. 89–90° (IIb).

Anal. Calcd. for $C_5H_8Br_2O_2S$: C, 20.56; H, 2.76; Br, 54.74; S, 10.98. Found (IIa): C, 20.26; H, 3.20; Br, 54.75; S, 11.12. Found (IIb): C, 20.49; H, 2.99; Br, 54.60; S, 10.94.

The infrared spectrum of IIa showed the following principal frequencies: 3000, 2930, 1448, 1399, 1380, 1318, 1300, 1280, 1230, 1221, 1190, 1175, 1133, 1109, 1083, 1071, 1043, 994, 936, 891, 881, 801, and 701 cm.$^{-1}$

(11) All melting and boiling points are uncorrected. Analyses performed by Galbraith Microanalytical Laboratories, Knoxville, Tenn. Infrared spectra prepared by Kendall Infrared Laboratories, Plainfield, N. J. Ultraviolet spectra were obtained with a Perkin-Elmer Spectracord. Anhydrous sulfur dioxide was supplied through the courtesy of the Virginia Smelting Co., West Norfolk, Va.

(12) F. D. Rossini *et al.*, Selected Values of Properties of Hydrocarbons, Nat. Bur. Stds. Circular C461, U. S. Gov't. Printing Office, Washington, D. C., 1947, p. 55.

The infrared spectrum of IIb showed the following principal frequencies: 3000, 2930, 1453, 1409, 1383, 1311, 1278, 1250, 1221, 1192, 1179, 1132, 1122, 1082, 1071, 1043, 1024, 981, 911, 887, 818, and 718 cm.$^{-1}$

2-Methyl-4,5-dihydrothiophene 1,1-dioxide (IV). To 500 ml. of 0.5*N* potassium hydroxide was added 25.0 g. (0.189 mole) of I, and the mixture was stirred at 30° for 30 hr. after which time it was chilled and filtered. The residue was recrystallized from ethanol to give 11.1 g. (45%) white needles, m.p. 128.0–128.5° (lit.,[9,10] 128°, and 128–129°).

The bromine adduct from IV was prepared by the procedure described from the preparation of II. The crude product was extracted with hot water and the residue was recrystallized from ethanol, m.p. 69.5–70.0° (lit.,[9] 68–69°).

4-Hydroxy-2-methyltetrahydrothiophene 1,1-dioxide (V). An emulsion of 26.4 g. (0.199 mole) of I in 100 ml. of water was added very slowly to 300 ml. of 9.3*N* potassium hydroxide. The mixture was allowed to stir for 14 hr. after which time it was chilled and filtered. The solid, weighing 13.6 g. was recrystallized from ethanol, m.p. 128–129°. The filtrate was neutralized with hydrochloric acid, and the water was evaporated. The residue was extracted with four portions of acetone and the acetone was evaporated. The residual oil was dissolved in 30 ml. of water and extracted with five portions of chloroform. The water raffinate was concentrated and the residue was distilled *in vacuo* to yield 5.5 g. (18%) of a colorless oil, b.p. 128–130°/1 mm., n_D^{25} 1.4951, d_4^{25} 1.317.

Anal. Calcd. for $C_5H_{10}O_3S$: C, 39.98; H, 6.17; S, 21.35. Found: C, 39.54; H, 6.75; S, 22.43.

The 3,5-dinitrobenzoate from V was prepared by the method of Shriner and Fuson,[13] utilizing pyridine. After recrystallization from ethanol, the product melted 190–191°.

Anal. Calcd. for $C_{12}H_{12}N_2O_8S$: C, 41.86; H, 3.51; N, 8.14; S, 9.31. Found: C, 41.98; H, 3.29; N, 8.13; S, 9.19.

The infrared spectrum of V showed the following principal frequencies: 3460, 2930, 1453, 1400, 1340, 1300, 1258, 1207, 1193, 1135, 1111, 1070, 1030, 1015, 982, 935, 913, and 794 cm.$^{-1}$

4-Acetoxy-2-methyltetrahydrothiophene 1,1-dioxide (VI). Twenty-five grams (0.32 mole) of acetyl chloride was slowly added to a flask containing 16.0 g. (0.107 mole) of V. The reaction mixture was cooled externally and stirred for 30 min. The mixture was then poured into 140 ml. of distilled water, and the water was extracted with four portions of chloroform. Upon evaporation of the chloroform there remained an oil which was distilled under reduced pressure to give 18.0 g. (81%) of VI, b.p. 100°/1 mm.

Anal. Calcd. for $C_7H_{12}O_4S$: C, 43.73; H, 6.29; S, 16.68. Found: C, 43.72; H, 6.09; S, 16.78.

The infrared spectrum of VI showed the following principal frequencies: 2940, 1738, 1640, 1500, 1450, 1404, 1372, 1309, 1235, 1181, 1137, 1120, 1072, 1042, 1022, 983, 947, 931, 893, 855, and 779 cm.$^{-1}$

2-Methyl-2,3-dihydrothiophene 1,1-dioxide (VII). The apparatus involved in this experiment consisted of a separatory funnel (with necessary gas lines) attached to a vertically mounted glass tube which passed through a furnace 12 inches in length. The tube was packed with glass wool for a length of 6 inches in the furnace zone. The tube was connected in series to a water-cooled condenser and a receiver cooled in an ice salt bath. Before each run the system was swept with nitrogen, and a very low flow of nitrogen was maintained during the run. The portion of the tube containing the glass wool was maintained at 440–452° during the pyrolysis. A solution of 15.0 g. (0.078 mole) of VI in 35 ml. of benzene was introduced into the reaction tube at a rate of 25 drops per min. After the addition of the solution was complete, the reaction tube was flushed by the introduction of benzene followed by a small amount of acetone. The liquid in the receiver was warmed to remove solvents. The residue was distilled and a fraction was collected $b._1$ 87–95°. The residue was recycled through the furnace. Distillation and the recycling of the residue was continued until the conversion of the residue was complete. The pyrolysis products were collectively distilled through a 5-inch Vigreux column at 82–87° at 1 mm. This latter fraction (8.5 g.) was redistilled to give a colorless liquid, b.p. 75–77.5°/1 mm., m.p. 25–26°, n_D^{20} 1.4949, d_4^{20} 1.2504. The yield of crude product ($b._1$ 82–87°) was 83%.

Anal. Calcd. for $C_5H_8O_2S$: C, 45.43; H, 6.10; S, 24.21. Found: C, 45.44; H, 6.02; S, 24.08.

The infrared spectrum of VII showed the following principal frequencies: 3050, 2950, 2900, 1600, 1500, 1450, 1433, 1380, 1311, 1290, 1236, 1176, 1132, 1077, 1073, 1011, 950, 910, 895, 829, and 704 cm.$^{-1}$

2-Methyl-4,5-dibromotetrahydrothiophene 1,1-dioxide (VIII). The procedure described for the preparation of the bromine adduct from I was employed. The oil was crystallized from ethanol and subsequently recrystallized from ethanol to give VIII in 27%, m.p. 85–86°.

Anal. Calcd. for $C_5H_8Br_2O_2S$: C, 20.56; H, 2.76; Br, 54.74; S, 10.98. Found: C, 20.66; H, 3.37; Br, 54.49; S, 10.84.

The infrared spectrum of VIII showed the following principal frequencies: 2970, 2920, 2890, 1450, 1320, 1307, 1290, 1257, 1207, 1180, 1150, 1144, 1111, 1105, 1090, 1032, 1000, 942, 913, 877, 816, 790, and 708 cm.$^{-1}$

The ethanolic liquors from the above mentioned recrystallizations were combined, and the ethanol was evaporated at reduced pressure. The residue was washed with a small amount of ethanol and filtered. This residue was dissolved in the minimum amount of ethanol and allowed to stand overnight at room temperature. The mixture was then filtered (crystals m.p. 78–83°) and the filtrate was refrigerated. The resulting precipitate was filtered and vacuum dried, m.p. 56–58°. This solid was not further characterized.

2-Methyltetrahydrothiophene 1,1-dioxide (III). In a Parr hydrogenation apparatus 13.2 g. (0.100 mole) of I in 220 ml. of chloroform was reduced with hydrogen (42 p.s.i.) in the presence of 0.5 g. of 10% palladium on charcoal. After the reaction mixture was filtered, the chloroform was evaporated The residue was heated to 130° for 1 hr. to remove unreacted I, and subsequent distillation of the residue gave 12.0 g. (91%) of III, b.p. 70°/1 mm., 273–274°/701 mm., n_D^{20} 1.4801, d_4^{20} 1.2055 (lit.,[8] b.p. 279–280°/758 mm., n_D^{20} 1.4801, d_4^{20} 1.207). Under similar conditions IV gave 81% of III, $b._1$ 70°, n_D^{20} 1.4817. The reduction of VII resulted in a 74% yield of III, b.p. 58–60°/1 mm., n_D^{20} 1.4809, d^{20} 1.2027.

The principal frequencies observed for III are: 2940, 2870, 1640, 1452, 1419, 1380, 1300, 1252, 1208, 1139, 1111, 1072, 1065, 1021, 1000, 967, 949, 886, 833, and 723 cm.$^{-1}$

BLACKSBURG, VA.

(13) R. L. Shriner and R. C. Fuson, *The Systematic Identification of Organic Compounds*, John Wiley and Sons, Inc., New York, New York, 1948, p. 164.

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

Competitive Reductive *o*-Debenzylation of Ethers and Esters[1]

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A comparison has been made of the susceptibility to Pd-catalyzed hydrogenolysis of different benzyl type groups in ether and ester linkage.

Benzyl type groups could be valuable as protective groups in complex syntheses. One of their advantages is that, once their protective function is accomplished, they can easily be removed by catalytic hydrogenation under mild conditions. For example, $C_6H_5CH_2$—O—R on hydrogenation in the presence of palladium on charcoal gives toluene plus an alcohol.

It would be advantageous in some syntheses to have two benzyl type protective groups which could be removed one at a time. In competitive reductions of tertiary amines containing two different benzyl groups attached to the nitrogen, it was found that the unsubstituted benzyl group was removed by hydrogenolysis in preference to the benzyl groups which contained methyl, chloro, or amino groups in the para positions.[4] In other studies, it was found that the α-naphthylmethyl group was removed in preference to the *p*-phenylbenzyl group, and that the latter is removed in preference to the benzyl group.[5] Thus in an amine containing the four groups, α-naphthylmethyl, *p*-phenylbenzyl, benzyl, and *p*-methylbenzyl, attached to nitrogen, it is to be expected that the four could be removed stepwise by catalytic hydrogenation in the order in which they are listed above.

It was the object of this work to determine whether comparable selectivity could be obtained in the ether and ester series. Accordingly, the cyclohexyl ethers of the above four groups were prepared and competitively hydrogenolyzed. Also benzyl acetate and α-naphthylmethyl acetate were competitively hydrogenolyzed with each other and with these ethers.

In the competitive reductive debenzylation of ethers, summarized in Table I, it was found that the order of ease of cleavage of benzyl groups which was established for tertiary amines holds in the case of the ethers also, except that the α-naphthylmethyl group could not be cleaved from its ether linkage under the conditions used. In the presence of α-naphthylmethyl cyclohexyl ether, even the benzyl cyclohexyl ether could not be reduced. The possibility that the α-naphthylmethyl cyclohexyl ether used in these experiments contained some poison was eliminated when it was found that benzyl acetate or α-naphthylmethyl acetate mixed with this ether were hydrogenated easily with cleavage of the ester group.

Although the order of ease of cleavage of the benzyl type groups in ether linkage was the same as that established for amines, 100% selectivity was not obtained in any case. Thus when benzyl cyclohexyl ether and *p*-phenylbenzyl cyclohexyl ether were simultaneously hydrogenated (No. 1 in Table I), *p*-methylbiphenyl was isolated in greater yield than toluene, but both were obtained in significant quantities. These results offer little encouragement for the use under these conditions of selective debenzylation of benzyl type protective groups in ether linkage.

The result with the two esters studied was more encouraging. When benzyl acetate was reduced competitively with α-naphthylmethyl acetate (No. 4), it was found that the α-naphthylmethyl group was cleaved with almost complete selectivity However, benzyl benzoate and benzyl acetate showed no selectivity of reduction between themselves (No. 5), indicating that the acid portion of the ester does not exert much effect on selectivity.

A comparison of the ease of cleavage of benzyl type groups in ester linkage with those in ether linkage showed that the esters are preferentially cleaved. Thus when benzyl benzoate and benzyl cyclohexyl ether were simultaneously hydrogenated (No. 6), the ester was practically completely cleaved, while the ether was apparently not attacked at all, since no cyclohexanol could be detected among the reduction products. Also, as is to be expected, when a mixture of α-naphthylmethyl acetate and benzyl cyclohexyl ether was hydrogenated (No. 7), the ester was completely cleaved, while the ether was not attacked, since no toluene or cyclohexanol could be detected among the reduction products. When benzyl benzoate was simultaneously hydrogenated with α-naphthylmethyl cyclohexyl ether (No. 8), again

(1) We wish to thank the Research Corp. for partial support of this work. Taken from a portion of a thesis submitted by Stanley M. Dec in partial fulfillment of requirements for the M.S. degree, 1955.

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(4) R. Baltzly and J. S. Buck, *J. Am. Chem. Soc.*, **65**, 1984 (1943). R. Baltzly and P. B. Russell, *J. Am. Chem. Soc.*, **72**, 3410 (1950); *J. Am. Chem. Soc.*, **75**, 5598 (1953).

(5) H. Dahn, U. Solms, and P. Zoller, *Helv. Chim. Acta*, **35**, 2117 (1952).

TABLE I

COMPETITIVE REDUCTION OF BENZYL ETHERS AND ESTERS

Expt. No.	Starting Materials	Moles	H_2 Absorbed, Moles	Time, Min.	Products Isolated	Yield, Mole %
1.	Ph benz-O-Cx[a] plus	0.05	0.05	2.5	p-C_6H_5-C_6H_4-CH_3	51.2
	Benzyl cyclohexyl ether	0.05			Toluene	30.3
					Cyclohexanol	68
2.	Me benz-O-Cx[b] plus	0.1	0.1	3.0	p-Xylene	29.1
	Benzyl cyclohexyl ether	0.1			Toluene	41.3
3.	Ph benz-O-Cx[a] plus	0.05	0.05	8	p-C_6H_5-C_6H_4-CH_3	50.5
	Me benz-O-Cx[b]	0.05			p-Xylene	29.1
4.	Men-O-Ac[c] plus Benzyl acetate	0.1	0.1	154[e]	α-Methylnaphthalene	84.5
		0.1			Toluene	2.2
5.	Benzyl benzoate plus	0.1	0.1	111[f]	Benzoic acid	41.0[h]
	Benzyl acetate	0.1			Total acid	88.5[i]
6.	Benzyl benzoate plus	0.1	0.1	30[f]	Benzoic acid	85.5[i]
	Benzyl cyclohexyl ether	0.1			Cyclohexanol	0.0
7.	Men-O-Ac[a] plus	0.05	0.05	1	α-Methylnaphthalene	76.0
	Benzyl cyclohexyl ether	0.05			Toluene	0.0
8.	Men-O-Cx[d] plus	0.05	0.05	105[g]	Cyclohexanol	0.0
	Benzyl benzoate	0.05			Toluene	56.5
					Benzoic acid	63.8[h]
9.	Ph benz-O-Cx[a] plus	0.05	0.05	3	p-C_6H_5-C_6H_4-CH_3	34.5
	Benzyl acetate	0.05			Cyclohexanol	26
					Toluene	45.6

[a] Ph benz-O-Cx is p-phenylbenzyl cyclohexyl ether. [b] Me benz-O-Cx is p-methylbenzyl cyclohexyl ether. [c] Men-O-Ac is α-naphthylmethyl acetate. [d] Men-O-Cx is α-naphthylmethyl cyclohexyl ether. [e] Four g. of catalyst used. [f] One g. of catalyst used. [g] Three g. of catalyst used. [h] By isolation. [i] By titration.

the ester was completely cleaved, and the ether was untouched, in accordance with expectations, since the ether could not be reduced alone under these conditions.

However, when the most easily cleaved ether, p-phenylbenzyl cyclohexyl ether, and the less easily cleaved ester, benzyl acetate, were hydrogenated together (No. 9), it was found that the selectivity of reduction was not complete. To be sure, the ester was cleaved to a greater extent, but a 35% yield of p-methylbiphenyl was also isolated, indicating at least this much ether cleavage.

At first glance it may appear anomalous that the α-naphthylmethyl group, which is considered to be the "most easily cleaved" of all benzyl type groups in hydrogenolysis of tertiary amines and quaternary ammonium bases, is not cleaved at all in its ether linkage. The explanation of this fact rests on the observation of Dahn *et al.*,[6] that although the naphthylmethyl group in a competitive reduction is preferentially cleaved, it gives the slowest reactions of all the benzyl type groups with which they worked. This is explained by assuming that the selectivity of reduction is governed by the degree of adsorption of the compound on the palladium catalyst, and not by the speed of hydrogenation. Thus, apparently α-naphthylmethyl cyclohexyl ether is adsorbed very strongly on the catalyst, but its rate of hydrogenation is impracticably slow.

The ability of the α-naphthylmethyl cyclohexyl ether to prevent the reduction of benzyl cyclohexyl ether is explained on the same basis: the menaphthyl ether is adsorbed so much more strongly that it occupies all the available catalytic sites on the catalyst, leaving none available for the benzyl ether.

EXPERIMENTAL

Reductions. The Parr Adams Pressure Reaction Apparatus was used throughout this work. Reductions were carried out with an overpressure of three atmospheres of hydrogen. A drop of 7 pounds was equivalent to 0.1 mole of hydrogen absorbed. In all cases either 0.05 or 0.1 mole of compound dissolved in 100 ml. of ether was taken for hydrogenation. The hydrogenation catalyst used was 10% Palladium on Darco (made by The American Platinum Works, Newark, N.J.).

For each 0.1 mole of compound taken for hydrogenation, six grams of catalyst were used, except that with the esters, smaller quantities were used, as noted in Table I.

When the desired amount of hydrogen had been absorbed, the catalyst was filtered off and washed with ether. In some cases where acetic and/or benzoic acid had been produced during hydrogenation, a titration was performed to determine the amount of acid, after which the acid was extracted with sodium hydroxide. Then the non-acidic products were separated by distillation in a micro apparatus fitted with a small Vigreux column.

Benzyl benzoate and *benzyl acetate* were obtained commercially.

Benzyl cyclohexyl ether was prepared by the method of

Jarrousse,[6] from cyclohexanol and benzyl chloride in the presence of 55% sodium hydroxide and triethylamine at 50–55°. Yield of benzyl cyclohexyl ether, b.p. 164° (37 mm.), 141° (18 mm.), 132° (12 mm.), was 70%.

p-Xylyl bromide, b.p. 85–95° (4 mm.), m.p. 34–35° (needles from ethanol), was prepared in 44% yield by sunlight initiated bromination of *p*-xylene in carbon tetrachloride solution.

p-Xylyl cyclohexyl ether. Cyclohexanol (10.0 g., 0.1 mole) was added to a stirred mixture of 25 ml. of absolute ether and 3.9 g. (0.1 mole) of sodamide. Then 18.5 g. (0.1 mole) of *p*-xylyl bromide was added dropwise. The reaction was stirred in an oil bath at 70° for 21 hr. Then water was added to dissolve the sodium salt and the organic layer was extracted with ether. The ether layer was washed with water, dried with magnesium sulfate, and distilled. *p*-Xylyl cyclohexyl ether, b.p. 114° (4 mm.), was obtained in 44% yield.

Anal. Calcd. for $C_{14}H_{20}O$: C, 82.28; H, 9.87. Found: C, 79.92; H, 9.60.

4-Phenyl benzyl alcohol was made from 4-bromodiphenyl by the Grignard reaction.[7]

4-Chloromethyl diphenyl was made from the alcohol and thionyl chloride.[7]

p-Phenylbenzyl cyclohexyl ether, b.p. 160–167° (5 mm.), m.p. 84–86° (colorless plates from ethanol), was made by two methods. It was made from cyclohexanol and 4-chloromethyl diphenyl in 41% yield by the method described above for *p*-xylyl cyclohexyl ether; and it was made in 47% yield by the method of Jarrousse[6] described above for benzyl cyclohexyl ether.

1-Chloromethyl naphthalene was made by the method of Coles and Dodds.[8] *α-Naphthylmethanol* was made in 75% yield by hydrolysis of 1-chloromethylnaphthalene and in 45% yield by the Grignard reaction *via* alpha-bromonaphthalene according to Bourquelot and Bridel.[9] *α-Naphthylmethyl acetate*, b.p. 142–143° (4 mm.), 172–173° (13 mm.), was made in 24% yield by direct reaction of acetyl chloride with the alcohol. Acetic anhydride would not react with α-naphthylmethanol in the absence of a catalyst; and in the presence of sulfuric acid only polymeric products could be obtained.

Anal. Calcd. for $C_{13}H_{12}O_2$: C, 77.92; H, 6.04. Found: C, 76.94; H, 6.13.

α-Naphthylmethyl cyclohexyl ether was made in 27% yield from the chloride and cyclohexanol by the method of Jarrousse[4] described above for benzyl cyclohexyl ether. The compound is described in the literature[10] as a liquid, b.p. 165–166° (0.8 mm.). It was found in this work to be a solid, m.p. 40–41.5° (needles from ethanol), b.p. 176–177° (6 mm.).

Anal. Calcd. for $C_{17}H_{20}O$: C, 84.89; H, 8.39; M. W. 240.2. Found: C, 84.64; H, 8.21; M. W. 244.0.

(6) J. Jarrousse, *Compt. rend.*, **232**, 1424 (1951).

(7) S. Goldschmidt, P. Modderman, and G. A. Overbeek, *Rec. trav. chim.*, **69**, 1109 (1950).

(8) H. W. Coles and M. L. Dodds, *J. Am. Chem. Soc.*, **60**, 853 (1938).

(9) E. Bourquelot and M. Bridel, *Compt. rend.*, **168**, 323 (1919).

(10) W. Kruyt and H. Veldstra, *Landbouwk. Tijdschr.*, **63**, 398 (1951); *Chem. Abstr.*, **55**, 7287 (1951).

AMHERST, MASS.

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

Heterocyclic Vinyl Ethers. XIII. The Reaction of 2,5-Diphenyl-1,4-dithiadiene with *n*-Butyllithium and Dimethyl Sulfate[1]

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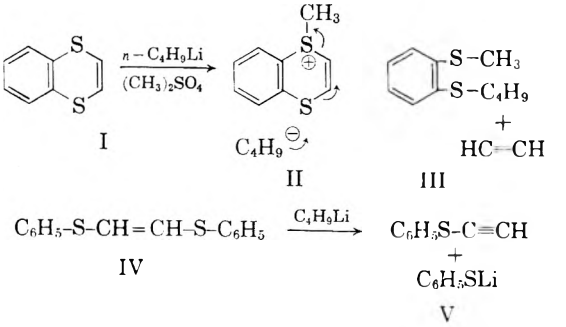
2,5-Diphenyl-1,4-dithiadiene (VI) does not react appreciably with *n*-butyllithium in ether at 0°; however, when dimethyl sulfate is present a substitution-elimination reaction occurs leading to phenylacetylene and the sulfides VIII and IX. VIII was shown to be a major component of the mixed sulfides, by alkaline hydrolysis of the corresponding crude sulfone to benzyl *n*-butyl sulfone (XII). It appears that the cleavage of the dithiadiene ring to acetylenes and alicyclic ethylenic sulfides is a general reaction, for both VI and benzo-1,4-dithiadiene (I) react similarly, and in a manner different from their open chain analogs.

The reaction of the ethylenic sulfides VIII and IX with phenyllithium was studied, and cleavage of the expected acetylenic sulfides to phenylacetylene was observed.

It has been previously shown that benzo-1,4-dithiadiene (I) does not undergo appreciable metalation by reaction with butyllithium in ether at 0°. However, when such reaction mixtures are treated with alkylating agents, a substitution-elimination reaction occurs (II), leading to the formation of acetylene and sulfides such as III. The open chain analogs of I, *cis* or *trans* bis-(phenylmercapto)-ethylene (IV), on the other hand, react rapidly with butyllithium in ether at 0° to give high yields of phenylmercaptoacetylene and lithium thiophenolate. The presence of dimethyl sulfate



(1) This work was supported by the office of Ordnance Research, U. S. Army, Contract No. DA-11-022-Ord-2616.

(2) From the M.S. Thesis of M. T. Kneller, University of Minnesota, 1958.

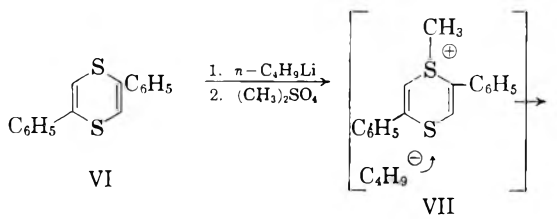
(3) W. E. Parham and Paul L. Stright, *J. Am. Chem. Soc.*, **78**, 4783 (1956).

does not alter the course of this reaction, but does lead to methylated derivatives of phenylacetylene and thiophenol.

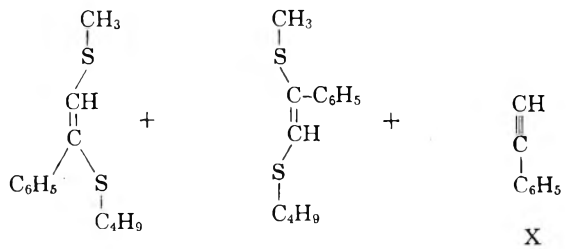
We were interested in extending our knowledge of the cleavage of dithiadienes, and their open chain analogs, and have accordingly completed a study of the reaction of 2,5-diphenyl-1,4-dithiadiene (VI), and products derived from VI, with organolithium derivatives. These reactions were studied both in the presence and absence of alkylating agents, and the results are described in this report.

The initial study concerned the reaction of 2,5-diphenyl-1,4-dithiadiene (VI) with *n*-butyllithium. The conditions employed were essentially identical to those previously reported for the conversion of IV to V. Only a small evolution of gas, presumably butane, was observed over a 2.5-hr. period. Water was then added to decompose the organometallic reagents, and the organic products were processed by chromatography and distillation. There was obtained an 87% recovery of 2,5-diphenyl-1,4-dithiadiene. The relatively small amount of butane liberated, together with the high recovery of 2,5-diphenyl-1,4-dithiadiene, suggested that very little reaction had occurred. Thus, under these conditions VI behaves in a manner analogous to I, but not to IV.

The reaction of 2,5-diphenyl-1,4-dithiadiene with butyllithium was then carried out in the presence of dimethyl sulfate. The procedure used was similar to that previously described for I. As judged by spectral data, boiling points, and refractive index a number of products were formed in



VI VII



VIII IX X

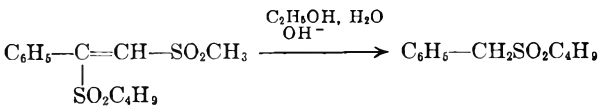
the reaction; however, two principal products were characterized.

The infrared spectrum of the lower boiling liquids showed strong absorption at 3315 cm.$^{-1}$ and 2105 cm.$^{-1}$, typical of the terminal acetylenic group. The presence of phenylacetylene in these products was positively established by their conversion into mercury phenylacetylide. The product was identified by comparison of melting points, mixed melting points, and infrared spectrum of the derivative with authentic mercury phenylacetylide. The amount of derivative obtained corresponded to a 33% yield of phenylacetylene (X). In addition, small fractions with intermediate boiling points showed absorption at 2160 cm.$^{-1}$ typical of non-terminal acetylene. Although these products were not identified, they were most probably methylphenylacetylene and/or sulfides such as XIII.

The principal organic product, obtained in consistent yields of 60–71%, was a high boiling yellow oil (b.p. 114–115°/0.3 mm., n_D^{25} 1.6042). This material had the empirical formula $C_{13}H_{18}S_2$, which was consistent with the two probable sulfides VIII and IX.

The formation of VIII and/or IX, together with phenylacetylene, from 2,5-diphenyl-1,4-dithiadiene, established the general course of reaction to be that shown in the above equation. Thus, diaryldithiadienes react with *n*-butyllithium and dimethyl sulfate in a manner analogous to that previously observed for benzo-1,4-dithiadeine (I).

There remained the problem of determining the structure of the sulfide VIII and/or IX. It can be seen that the elimination of phenylacetylene from VII can occur in either of two ways, leading to VIII or IX. Distillation of various samples of this material gave relatively narrow ranges of boiling point and refractive index (n_D^{25} 1.6029–1.6059), and the infrared spectra of these samples were essentially identical. These results suggested that the product was homogeneous. However, the product failed to give a solid sulfone, or sulfilimine, and vapor phase chromatography suggested the possibility of four components. Assuming that no decomposition occurred during the chromatography, then the four components are considered to be the *cis* and *trans* isomers of VIII and IX.[4] That the crude sulfide was composed principally of VIII, (*cis* and/or *trans*) was shown by alkaline hydrolysis of the crude sulfone. *n*-Butyl benzyl sulfone (XII) was obtained in 51% yield. The yield of crude XII was 84%; there was no evidence for the presence of

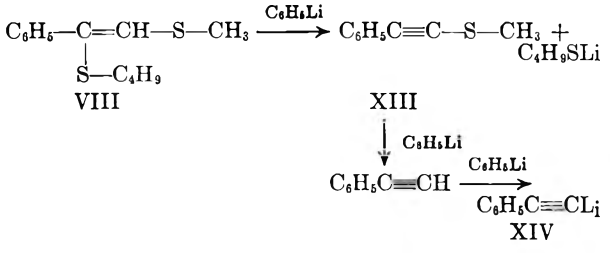


XI XII

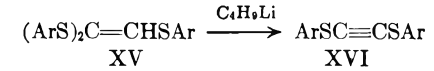
appreciable quantities of benzylmethyl sulfone, which would result from hydrolysis of the sulfone of IX.

(4) The *cis* isomers of VIII and/or IX should be formed in the reaction; however, the oils were processed by distillation. We have shown that partial or complete isomerization of related bis-sulfides occurs upon vacuum distillation [unpublished work, see also W. E. Truce and R. J. McManimie, *J. Am. Chem. Soc.*, **76**, 5745 (1954); W. E. Parham and I. Heberling, *J. Am. Chem. Soc.*, **77**, 1175 (1955)].

The reaction of VIII[5] with one equivalent of phenyllithium was also investigated. It was hoped that the principal acetylenic sulfide that resulted



would establish whether the elimination reaction (IV–V or VIII–XIII) was occurring by: metalation with subsequent *beta* elimination of mercaptide, or metalation with subsequent α-elimination and rearrangement,[6] of the resulting carbene. There was obtained instead a 31% recovery of starting sulfide, a 35% yield of phenylacetylene, and only relatively small amounts of material boiling in an intermediate range. Some non-terminal acetylenes (infrared absorption at 2160 cm.$^{-1}$), presumably XIII and the corresponding butyl derivative, were present in the latter materials; however, they were present in such small amounts that their identification was considered to be of no significance. A 35% yield of phenylacetylene could account for 70% of the starting phenyllithium (VIII→XIV). It is probable, therefore, that the intermediate mercaptoacetylene (XIII) reacts at a comparable, or even faster, rate with phenyllithuim than does the starting sulfide VIII. These results suggest that the synthesis of substituted mercaptoacetylenes, by elimination of mercaptan from bis-substituted mercaptoethylenes, may prove generally unsatisfactory unless terminal acetylenes, such as V, result. The recent report by Truce, and his coworkers, of the cleavage of XV to XVI,[7] by re-



action with *n*-butyllithium, suggest that there may be a considerable difference between butyllithium and phenyllithium in these reactions. This possibility will be the subject of further study.

EXPERIMENTAL

The reaction of butyllithium with 2,5-diphenyl-1,4-dithiadiene in the absence of alkylating agent. 2,5-Diphenyl-1,4-dithiadiene[8] (5.36 g., 0.02 mole), in benzene (35 ml.), was added to a cold (−5°) solution of butyllithium[9] (from 1.07 g., 0.15 g.-atom of lithium) in ether (41 ml.). The mixture was stirred for 2.5 hr.; however, only a small evolution of gas was noted. Water (30 ml.) was added, and 7.8 g. of oil was isolated from the dry ($MgSO_4$) ethereal solution. This oil was chromatographed on a column of Alcoa alumina (300 g.), using petroleum ether and petroleum ether–benzene as eluant. There was recovered 4.68 g. of VI (m.p. 114–118°, 87% recovery); mixture melting point with authentic VI (m.p. 116–117°) was 114–117°.

The reaction of 2,5-diphenyl-1,4-dithiadiene (VI) *with butyllithium and dimethyl sulfate.* A solution of VI (13.8 g., 0.0052 mole), in dry benzene (120 ml.), was added dropwise to a solution of butyllithium[9] (from 35.4 g., 0.258 mole, of butyl bromide) in ether (155 ml.). An atmosphere of nitrogen was maintained, and the reaction temperature was maintained at −10°, with stirring, for 2 hr. Dimethyl sulfate (39 g., 0.31 mole), in ether (39 ml.), was added over a 23-min. period; the reaction temperature rose to 0°, even with external cooling. The resulting mixture was allowed to warm to room temperature (3.5 hr.), then water (210 ml.) was added. The ethereal solution was dried ($MgSO_4$), and concentrated and the resulting yellow-brown oil (19.2 g.) was distilled. The principal product 8.80 g. (71.5% yield) was collected at 117–121°/0.45 mm.; n_D^{26} 1.6059.

Anal. Calcd. for $C_{13}H_{18}S_2$: C, 65.49; H, 7.61; S, 26.90; M.W., 238.4. Found: C, 65.73; H, 7.56; S, 27.29; M.W. (freezing point, benzene), 223.

This procedure was repeated several times with minor variations; the yield of high boiling product varied between 64 and 71%.

Lower boiling fractions, collected between 25°/135 mm. and 77°/0.3 mm., contained terminal acetylene (infrared absorption at 3315 cm.$^{-1}$ and 2105 cm.$^{-1}$) and non-terminal acetylene (infrared absorption at 2180 cm.$^{-1}$).

The amount of phenylacetylene present was estimated by the conversion of X, in the lower boiling fractions with boiling point close to that of phenylacetylene, to mercury phenylacetylide. The procedure used was that previously reported[10] by J. R. Johnson and W. L. McEwen; the yield of derivative (m.p. 126–127°) was 90% when authentic phenylacetylene was employed. The amount of mercury phenylacetylide (m.p. 125–126°, mixture m.p. 125–126°) obtained from the lower boiling fractions corresponded to 33% of the theoretical yield of phenylacetylene.

Oxidation of VIII *and/or* IX *with hydrogen peroxide. Alkaline hydrolysis of the product.* Hydrogen peroxide (30%, 13 ml.) was added in three portions, at 20-min. intervals, to a solution of VIII and/or IX (1.02 g., 0.0043 mole) in glacial acetic acid (16 ml.). The mixture was heated at the reflux temperature for 1 hr., and was then cooled and diluted with water (20 ml.). The *p*H of the solution was adjusted to 8 by the addition of solid sodium bicarbonate; the resulting solution was saturated with sodium chloride, extracted with ether (150 ml.), and then with methylene chloride (150 ml.). The combined organic extract was dried and concentrated, affording 0.95 g. of viscous oil.

The crude sulfone (0.95 g., 0.003 mole calcd. as XI) was dissolved in a solution prepared from ethanol (10 ml.) and 3*N* potassium hydroxide (10 ml.). The resulting mixture was heated for 5 hr. at the reflux temperature under a nitrogen atmosphere. The resulting mixture was cooled, and the resulting solid (0.47 g., 84% calcd. as XII) was collected and recrystallized from petroleum ether. There was obtained 0.34 g. (51% yield) of benzyl *n*-butyl sulfone melting at 96–

(5) VIII was obviously contaminated with IX; however, this fact does not obviate the ensuing argument.

(6) *Cf.* D. Y. Curtin, E. E. Harris, *J. Am. Chem. Soc.*, **73**, 2716, 4519 (1951); S. J. Cristol, R. F. Helmreich, *J. Am. Chem. Soc.*, **77**, 5034 (1955); A. Bothner-By, *J. Am. Chem. Soc.*, **77**, 3293 (1955), for discussion of related elimination reactions.

(7) W. E. Truce and R. Kassinger (paper presented before the Organic Division of the American Chemical Society, San Francisco, April 1958.

(8) R. H. Barker and C. Barkenbus, *J. Am. Chem. Soc.*, 58, 262 (1936).

(9) H. Gilman and J. W. Morton, Jr., *Org. Reactions*, *VI*, 295 (1954).

(10) J. R. Johnson and W. L. McEwen, *J. Am. Chem. Soc.*, **48**, 474 (1926).

98° (mixture melting point with authentic[11] benzyl *n*-butyl sulfone, m.p. 94°, was 96–97°).

The reaction of VIII *and* IX *with phenyl lithium.* The apparatus employed was a 100-ml. three-necked flask, fitted with a condenser, nitrogen inlet, stirrer, and dropping funnel. The sulfide VIII and IX (5.04 g., 0.0211 mole) was added dropwise (15 min.) to a solution of phenyllithium, prepared[12] from bromobenzene (3.65 g., 0.0232 mole, and lithium, 0.34 g., 0.049 g.-atom) in ether (20 ml.). The mixture was stirred in a nitrogen atmosphere for 3 hr. at room temperature. The precipitated salts (containing the lithium salt of methyl and *n*-butyl mercaptans) were removed by filtration and discarded. The ether layer was acidified with dilute hydrochloric acid, washed with water, and dried over $MgSO_4$, and concentrated. The residual oil was distilled, and there was obtained a low boiling fraction (1.24 g.) and a high boiling fraction (1.60 g., b.p. 99–108°/0.06 mm., n_D^{25} 1.603). The higher boiling fraction was identified by physical properties, and by infrared spectra, as nearly pure starting sulfide (31.7% recovery).

The lower boiling fraction was a mixture containing phenylacetylene (infrared absorption at 3315 cm.$^{-1}$ and 2100 cm.$^{-1}$), non-terminal acetylene (infrared absorption at 2160 cm.$^{-1}$), and other products. An attempt to resolve this material by distillation was not successful since the quantities of each component present, other than phenylacetylene, was relatively small.

The amount of phenylacetylene present was estimated by its conversion into mercury phenylacetylide. The amount of derivative isolated (m.p. 125–126°, mixture m.p. 125–126°) corresponded to a 35.3% yield of phenylacetylene. This is a minimum quantity since some phenylacetylene was undoubtedly lost during the distillation.

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(11) J. Buchi, M. Prost, H. Eichenberger, and R. Liberherr, *Helv. Chim. Acta*, **35**, 1527 (1952).

(12) G. Wittig, *Newer Methods of Preparative Organic Chemistry*, Interscience Publishers, Inc., New York, N. Y., 1948, p. 576.

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

Formation of Carbenes from α-Haloesters[1]

WILLIAM E. PARHAM AND FREDERIC C. LOEW[2]

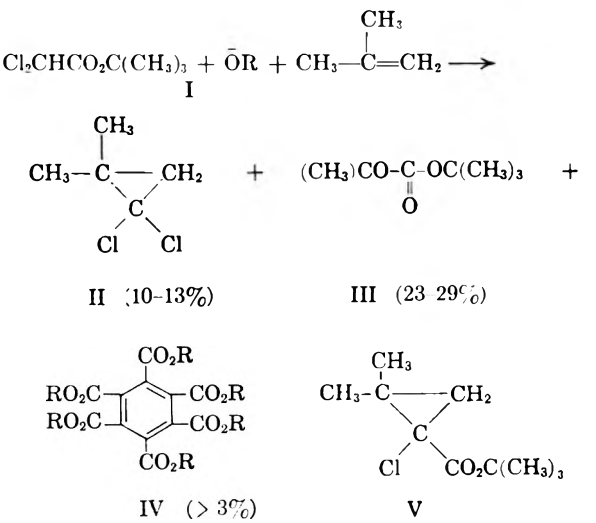
Received May 19, 1958

The reaction of butylate ion with the *t*-butyl esters of chloroacetic, dichloroacetic and trichloroacetic acid has been studied, and it has been shown that carbene intermediates result from the di- and tri-chloro esters. The reaction of *t*-butyl dichloroacetate with butylate ion, in the presence of isobutylene, results in the formation of 1,1-dichloro-2,2-dimethylcyclopropane (II), di-*t*-butyl carbonate (III) and hexa-*t*-butyl mellitate (IVa). The reaction of the trichloro ester, under similar conditions, affords di-*t*-butyl carbonate (III) and the cyclopropane II. Thus, under the conditions employed, both of these esters are converted into dichlorocarbene.

In a previous communication[3] we suggested that the reaction between esters of dichloroacetic acid and base might lead to carbenes. However, when indene was used as the carbene acceptor no products were obtained which could have been derived from chlorocarbalkoxy carbene. We have now made a study of the action of the *t*-butylate ion upon the *t*-butyl esters of chloroacetic, dichloroacetic, and trichloroacetic acid and have found that carbenes result from the last two.

The reaction of *t*-butyl dichloroacetate with *t*-butylate ion in the presence of isobutylene was first studied, and the products isolated were 1,1-dichloro-2,2-dimethylcyclopropane (II), *t*-butyl carbonate (III) and a neutral ester which has been shown to be hexa-*t*-butyl mellitate (IVa).

The isolation of 1,1-dichloro-2,2-dimethylcyclopropane (II) from the above reaction is convincing evidence for the formation of dichlorocarbene (VII) as an intermediate.[3-6] The formation of this car-



(1) This work was supported by a grant (NSF-G2163) from the National Science Foundation.

(2) Sinclair Refining Company Fellow, 1956–1957.

(3) W. E. Parham and R. R. Twelves, *J. Org. Chem.*, **22**, 730 (1957).

(4) (a) J. Hine, *J. Am. Chem. Soc.*, **72**, 2438 (1950); (b) J. Hine and A. M. Dowell, Jr., *J. Am. Chem. Soc.*, **76**, 2688 (1954); (c) J. Hine, P. C. Peek, Jr., and B. D. Oakes, *J. Am. Chem. Soc.*, **76**, 6162 (1954); (d) J. Hine, A. M. Dowell, Jr., and J. E. Singley, Jr., *J. Am. Chem. Soc.*, **78**, 479 (1956).

(5) (a) W. von E. Doering and A. K. Hoffmann, *J. Am. Chem. Soc.*, **76**, 6162 (1954); (b) W. von E. Doering and P. LaFlamme, *J. Am. Chem. Soc.*, **78**, 5448 (1956).

bene is rationalized by equation (a) below; carbon monoxide was identified[7] as a reaction product.[8]

$$Cl_2CHCO_2R + RO^- \longrightarrow$$

$$Cl_3C^-—CO_2R \quad \text{(VI)} \quad \begin{cases} \text{(a)} \longrightarrow Cl_2C + CO + RO^- \quad \text{(VII)} \\ \text{(b)} \longrightarrow ClCCO_2R + Cl^- \quad \text{(VIII)} \end{cases}$$

It is interesting to note that the cyclopropyl ester V was not found as a reaction product; consequently it was concluded that either: (a) the carbene VIII was not formed (reaction b) in appreciable quantity, or (b) the carbene VIII does not add appreciably to isobutylene. The former explanation is preferred in view of the electrophilic nature of carbene centers[6b] and the probable relative instability[6a] of carbene VIII with respect to the carbanion VI and carbene VII.

The formation of hexa-*t*-butyl mellitate (IVa) was unexpected; the assignment of structure was made on the basis of the following data: (1) the neutral ester had the composition (C and H) and molecular weight commensurate with IVa, and the infrared spectrum showed carbonyl absorption at 1730 cm.$^{-1}$, (2) the ester was hydrolyzed by action of 20% hydrochloric acid to mellitic acid (IVb), and the latter was converted by conventional methods into the acid chloride (IVc), and methyl ester (IVd). The properties of IVc and IVd were in agreement with those previously reported for these derivatives, and the methyl ester (IVd) was shown to be identical with a sample of hexamethyl mellitate prepared from hexamethyl benzene. Whether hexa-*t*-butyl mellitate (IVa) was formed by trimerization of the possible intermediate di-*t*-butyl acetylenedicarboxylate,[9] or by some other mechanism is the subject of a study to be reported at a later date.

In view of the steric requirements imposed by the bulky *t*-butoxide groups, the formation of *t*-butyl carbonate (III), in relatively large amounts, was unexpected. The formation of this ester is thought to occur[10] as illustrated below. The fate of the

$$Cl_2CH—\underset{\underset{O}{\|}}{C}—O—R + \bar{O}R \longrightarrow$$

I

$$[Cl_2CH—\underset{\underset{O^-}{|}}{\overset{\overset{OR}{|}}{C}}—OR] \longrightarrow Cl_2CH^- + ROC(=O)—OR$$

III

Cl_2CH^- ion was not determined; however, there was no evidence for the formation of appreciable quantities of 1-chloro-2,2-dimethylcyclopropane, which could result if Cl_2CH^- lost chloride ion to give HCCl, or methylene chloride.

The carbonate cleavage observed for I, suggested that α-haloesters which do not contain α-hydrogen atoms may serve as convenient sources for carbenes. This apparently is the case, since a 55% yield of pure 1,1-dichloro-2,2-dimethylcyclopropane (II), together with a 91% yield of di-*t*-butyl carbonate (III), resulted from the reaction of *t*-butyl trichloroacetate[11] and potassium *t*-butylate in the presence of isobutylene.

$$Cl_3C—\underset{\underset{O}{\|}}{C}—O—R + R\bar{O} \longrightarrow [Cl_3C—\overset{\overset{O}{|}}{\underset{\underset{OR}{|}}{C}}—\bar{O}R] \longrightarrow$$

$$\text{III} + CCl_2 + Cl^-$$

The reaction of *t*-butyl chloroacetate and potassium *t*-butylate, in the presence of 2-methylbutene-2, was investigated. Tars resulted, and no *t*-butyl carbonate or volatile halogen containing products were noted.

EXPERIMENTAL

The reaction of t-butyl dichloroacetate (I) with potassium t-butylate in the presence of isobutylene. t-Butyl dichloroacetate[3] (185 g., 1.0 mole) was added over a 90 minute period to a cold (−6 to −10°) mixture of powdered potassium *t*-butoxide[5a] (1.28 mole), isobutylene (300 ml. at −80°, *ca.* 4 mole), and olefin-free pentane (300 ml.). The resulting deep red mixture was stirred for an additional 90 min., the dry ice condenser and cooling bath were removed, and the isobutylene was allowed to evaporate (overnight). Water (300 ml.) was added to the reaction mixture to dissolve solids, and the organic layer was separated and dried ($MgSO_4$). After several days, a solid precipitated from this solution. The mixture was filtered and processed as described below.

Hexa-t-butyl mellitate (IVa). The solid, containing magnesium sulfate, was treated with water, and the organic component was collected by filtration. This material was triturated with methanol and recrystallized from benzene-petroleum ether. There was obtained 3.2 g. (2.8% yield) of IVa (dec. upon heating, does not melt below 360°).

(6) (a) P. S. Skell and A. Y. Garner, *J. Am. Chem. Soc.*, **78**, 3409 (1956); (b) P. S. Skell and A. Y. Garner, *J. Am. Chem. Soc.*, **78**, 5430 (1956); (c) P. S. Skell and R. C. Woodworth, *J. Am. Chem. Soc.*, **78**, 4496 (1956); (d) P. S. Skell and R. M. Etter, *Chem. and Ind. (London)*, 624 (1958).

(7) E. G. Voiret and A. L. Bonaimé, *Ann. chim. anal.* **26**, 11 (1944).

(8) Hine and coworkers [J. Hine, E. L. Pollitzer, and H. Wagner, *J. Am. Chem. Soc.*, **75**, 5607 (1953)] have found that alcohols are dehydrated in the presence of haloforms and alkali with the formation of CO. Therefore, the detection of CO as a product in this reaction is not positive evidence for reaction path a. However, the dehydration of alcohols under these conditions can best be explained by assuming the intermediate formation of dichlorocarbene. Thus, although the CO may be formed primarily by dehydration of *t*-butyl alcohol, reaction path a appears to be the only plausible route to dichlorocarbene.

(9) O. Diels, *Ber.*, **75B**, 1452–67 (1942) has shown that hexamethyl mellitate is formed from dimethyl acetylenedicarboxylate by the action of pyridine acetate.

(10) See M. L. Bender, *J. Am. Chem. Soc.*, **75**, 5986 (1953).

(11) This observation supports the suggestion that difluorocarbene may result from the reaction of ethyl trifluoroacetate and ethoxide ion [E. Bergman, *J. Org. Chem.*, **23**, 476 (1958)]. Bergman also reports that the reaction of higher perfluoroesters with alkoxide leads to the formation of diethyl carbonate.

Anal. Calcd. for $C_{36}H_{54}O_{12}$: C, 63.68; H, 8.02; mol. wt., 678. Found: C, 63.56; H, 7.76; mol. wt. (cryoscopic in benzene), 700.

The infrared spectrum in Nujol showed peaks at 2940 (s), 2860 (s), 1730 (s), 1465 (m), 1425 (w), 1395 (w), 1370 (m), 1335 (m), 1260 (s), 1238 (s), 1150 (s), 1113 (m), 1035 (w), 985 (m), 905 (w), 883 (m), 853 (m), 838 (m), 785 (w), 735 (m), 717 (w), 685 (w), and 658 cm.$^{-1}$ (m).

The organic solution, described above, was distilled through a 12 inch glass-helices packed column. After removal of pentane, four fractions were collected: (1) b.p. 50–55°/135 mm., consisting mainly of *t*-butyl alcohol, (2) 14.34 g., b.p. 60–63°/115 mm., n_D^{25} 1.4320–1.4430, (3) 39 g., b.p. 88°/65 mm., m.p. 35–40°, and (4) residue, dark in color, 59 g.

1,1-Dichloro-2,2-dimethylcyclopropane (II). Fraction 1 was dissolved in petroleum ether, washed with 5 portions of water, dried ($MgSO_4$), and distilled at atmospheric pressure. There was obtained, in addition to *t*-butyl alcohol, 8.2 g. of II, b.p. 118–120°, n_D^{25} 1.4410–1.4462. This material was combined with fraction 2, above, and redistilled through a Piros-Glover spinning band column. There was obtained 18.2 g. (13.1%) of II, b.p. 118–120°, n_D^{25} 1.4466 (reported[5a] b.p. 118–120°, n_D^{25} 1.4454).

Anal. Calcd. for $C_5H_8Cl_2$: C, 43.19; H, 5.80. Found: C, 43.38; H, 5.80.

The infrared spectrum of the product showed bands at 1735, 1290, and 1140 cm.$^{-1}$, attributed to small contamination by di-*t*-butyl carbonate (III). This impurity was easily removed by treating a pentane solution of the cyclopropane with several portions of concentrated sulfuric acid. The spectrum of the resulting material (n_D^{25} 1.4468) was identical with that of an authentic sample of II prepared, as previously described,[5a] from chloroform.

Di-t-butyl carbonate (III). Fraction 3 (m.p. 35–40°), described above, was principally di-*t*-butyl carbonate (III, 23–29% yield in several runs). The product was recrystallized from methanol, and the resulting product (m.p. 39.5–40.5°, yield range 16–20%) was identical (mixture m.p. and I.R. spectra) with an authentic sample of III.[12]

Infrared bands at 3000 cm.$^{-1}$ (s), 2960 (m), 1735 (v.s.), 1475 (w), 1460 (w), 1395 (m), 1370 (s), 1290 (v.s.), 1250 (w), 1140 (v.s.), 895 (w), 845 (m), 790 (w), and 715 (w). 5% in CCl_4—CS_2 using a 37 μ cell.

Residue. The residue (59 g.), described above, was chromatographed on a column of Alcoa alumina (600 g.), using petroleum ether and mixtures of petroleum ether and benzene, as eluant. A pale yellow resinous material (15 g.) was isolated. This material showed unsaturation (I.R. absorption at 1620 cm.$^{-1}$), ester carbonyl (I.R. absorption at 1725 cm.$^{-1}$, shoulder at 1740 cm.$^{-1}$), and chlorine (sodium fusion). The material decomposed upon attempted distillation (short path) at 0.1 mm. This product was not identified, but was considered to be higher condensation products of *t*-butyl dichloroacetate.

Attempts to isolate 1-chloro-2,2-dimethylcyclopropane in the above reaction were unsuccessful.

The reaction of *t*-butyl dichloroacetate, potassium *t*-butylate and isobutylene, was repeated in the absence of the solvent pentane. No evidence for the formation of either methylene chloride or 1-chloro-2,2-dimethylcyclopropane was noted.

Proof of structure of hexa-t-butyl mellitate (IVa). *Hydrolysis of* IVa *to mellitic acid* (IVb). A mixture of hexa-*t*-butyl mellitate (3.4 g.) and 20% hydrochloric acid (25 ml.) was heated at the reflux temperature until all the solid material had dissolved (5–6 hr.). The resulting solution was evaporated to dryness, and the residue (1.7 g.) was recrystallized three times from 20% HCl. The acid did not have a sharp melting point (285–299°, uncorrected). Mellitic acid is reported[13] to melt at 285–287°.

Anal. Calcd. for $C_{12}H_6O_{12}$: C, 42.11; H, 1.77; Neut. eq., 57.0. Found: C, 42.46; H, 2.00; Neut. eq., 57.0.

Conversion of mellitic acid to the acid chloride (IVc). The acid IVb (0.1 g.) was converted to the acid chloride (IVc) by reaction with phosphorous pentachloride (0.7 g.) at 150° for 2 hr. The resulting solid was recrystallized from benzene, and sublimed (flame) at 1 mm. The product sublimed at 240–245° (reported m.p. 240°).[14]

Anal. Calcd. for $C_{12}O_6Cl_6$: C, 31.84; H, 0.00. Found: C, 31.97; H, 0.24.

Conversion of mellitic acid (IVb) *to hexamethyl mellitate* (IVd). Mellitic acid (0.9 g.) was esterified by reaction with excess diazomethane in ether. The crude product (1.3 g.) was recrystallized from benzene-petroleum ether which afforded 1.15 g. of colorless hair-like needles, m.p. 192–193°. Analysis of this material gave values consistent with the formula $C_{18}H_{18}O_{12} \cdot {}^1/_3\ C_6H_6$. The sample was redried (100°/0.1 mm. for 3 hr.) and the resulting product melted at 188–188.5° (reported[15] m.p. 187–188°).

Anal. Calcd. for $C_{18}H_{18}O_{12}$: C, 50.72; H, 4.23; mol. wt. 426. Found: C, 50.98; H, 4.08; mol. wt. (cryoscopic in benzene), 430, 437.

This material proved identical (m.p., mixture m.p., infrared spectrum) with authentic IVd.

Authentic hexamethyl mellitate (IVd). Mellitic acid was prepared[13] by oxidation of hexamethyl benzene (2 g.) with a mixture of fuming nitric acid (7 ml., d. 1.52) and water (2 ml.). The Carius tube employed had a volume of 100 ml. and a wall thickness of 3 mm. Attempts to carry out this reaction on a larger scale, or in smaller tubes, resulted in failure of the tube. Recrystallization of the product from 65% HNO_3 afforded 1.18 g. (28%) of mellitic acid.

This material was methylated with diazomethane as described above. The product was recrystallized twice from benzene-petroleum ether B and dried at 100° (0.1 mm.), m.p. 187–189° (reported[15] 187–188°).

Authentic 1,1-dichloro-2,2-dimethylcyclopropane (II). This compound was prepared from potassium *t*-butylate (0.40 mole), isobutylene (160 ml. at −80°), and chloroform (90 g.) according to the procedure of Doering and Hoffmann,[5a] except that pentane (150 ml.) was used as the solvent rather than *t*-butyl alcohol (obviating extensive washings of the reaction mixture and foreruns). The reaction mixture was washed with two portions of water, separated, dried ($MgSO_4$), and distilled to afford 33.5 g. (60%) of product, b.p. 118–120/738 mm., n_D^{25} 1.4468.

Authentic di-t-butyl carbonate. The procedure of Choppin and Rogers[12] was used except that potassium *t*-butylate in hexane was substituted for sodium *t*-butylate in dioxane-*t*-butyl alcohol. Phosgene (13.8 g., 0.139 mole) was bubbled into the warm (60°) suspension of potassium *t*-butylate (0.255 mole) in hexane (200 ml.) in a stream of nitrogen. After the addition was completed (1 hr.), the reaction mixture was poured into 200 ml. of ice and water. The organic layer was separated, dried ($MgSO_4$), and distilled. The distillate (16.7 g. (75%), b.p. 88/65 mm., m.p. 33–38) was recrystallized twice from methanol-water to yield 9.8 g. (44%) of di-*t*-butyl carbonate, m.p. 39.5–40.5° (reported m.p., 39.5–40.5°).

The reaction of t-butyl trichloroacetate with potassium t-butoxide in the presence of isobutylene. The reaction of *t*-butyl trichloro acetate[16] (205 g., 0.94 mole), potassium *t*-butylate (1.25 mole), and isobutylene (300 ml. at −80°, *ca.* 4 moles)

(12) A. R. Choppin and J. W. Rogers, *J. Am. Chem. Soc.*, **70**, 2967 (1948).

(13) J. P. Wibaut, J. Overhoff, E. W. Jonker, and K. Gratama, *Rec. trav. chim.* **60**, 742 (1941).

(14) A. Claus, *Ber.*, **10**, 561 (1877).

(15) H. v. Pechmann, *Ber.* **31**, 502 (1898).

(16) W. E. Scovill, R. E. Burk, and H. P. Lankelma, *J. Am. Chem. Soc.*, **66**, 1039 (1944).

in pentane (300 ml.) solvent was carried out according to the procedure described for the dichloro ester. The final organic solution was distilled. The material boiling at 62–67°/115 mm. (92 g., n_D^{25} 1.4372) was redistilled to give 72 g. (b.p. 67°/115 mm., n_D^{25} 1.4468, 55.5% yield) of pure 1,1-dichloro-2,2-dimethylcyclopropane (II). The yield of di-*t*-butyl carbonate (148 g., b.p. 89°/65–70 mm., m.p. 38–40°) was 91%.

MINNEAPOLIS, MINN.

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

Synthesis of Medium- and Large-Ring Ketones *via* the Dieckmann Condensation

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The Dieckmann cyclization of a series of α,ω-diesters, diethyl suberate through diethyl thapsate, has been carried out with potassium *t*-butoxide in xylene under high dilution conditions with high speed stirring in a nitrogen atmosphere, and some medium- and large-ring monoketones and large-ring diketones, with carbonyl groups diametric, have been obtained. The relative yields have been compared with those of the corresponding carbocyclic ketones and diketones obtained by other methods.

The concept has been generally held that the Dieckmann cyclization of diesters is applicable only to the formation of the classical rings of five, six, and seven members, as originally employed.[1] With the conviction that suitable conditions could extend the usefulness of this reaction and in the interest of providing an additional route to larger cyclic ketones, we have examined the relative proportions of monoketones and diketones obtainable following the cyclization of a series of α,ω-diesters with potassium *t*-butoxide in xylene under high dilution conditions in a nitrogen atmosphere.

These cyclization conditions were employed originally for the synthesis of an eight-membered ring aminoketone by Sentz[2] in this laboratory, who also suggested their application to the formation of cycloakanones of greater ring size than seven members. Potassium *t*-butoxide has been used successfully for the cyclization of various aminodiesters to eight-[3–7] and ten-membered[6] ring aminoketones and sixteen-[6] and twenty-membered[6] ring diaminodiketones. Sodium hydride, which Blicke and his co-workers[8] employed for the synthesis of cyclooctanone *via* a Dieckmann condensation, has also been used for the preparation of eight-membered[6,9,10] ring aminoketones and sixteen-membered[9] ring diaminodiketones.

In the present investigation we have carried out the Dieckmann cyclization of the esters (I), diethyl suberate through diethyl thapsate, under identical conditions, employing potassium *t*-butoxide in xylene, under high dilution conditions with high speed stirring in a nitrogen atmosphere. A uniform isolation procedure was used and the monoketones (II) and diketones (III) were collected and identified, while no attempt was made to characterize any triketones or polymeric products. The yields of mono- and diketones are given in Table I. It will be observed that the conditions employed are useful for obtaining the cyclic 14- and 15-membered monoketones and the 18-, 20-, 22-, and

TABLE I

YIELDS OF KETONES PRODUCED BY THE DIECKMANN CYCLIZATION

	Actual Yield, %	
Diester (I)	Monoketone (II)	Diketone (III)
$(CH_2)_{n-1}(COOEt)_2$	$(CH_2)_{n-1}CO$	$(CH_2)_{n-1}(CO)_2(CH_2)_{n-1}$
n = 7	47	0
8	15	11
9	0	28
10	0	12
11	0.53	23
12	0.47	16
13	24	19
14	32	2.2
15	48	0.94

(1) (a) W. Dieckmann, *Ber.*, **27**, 102 (1894); (b) W. Dieckmann, *Ann.*, **317**, 27 (1901).

(2) R. C. Sentz, Ph.D. thesis, University of Illinois, 1952.

(3) N. J. Leonard and R. C. Sentz, *J. Am. Chem. Soc.*, **74**, 1704 (1952).

(4) N. J. Leonard, S. Swann, Jr., and E. H. Mottus, *J. Am. Chem. Soc.*, **74**, 6251 (1952).

(5) N. J. Leonard, S. Swann, Jr., and Glenn Fuller, *J. Am. Chem. Soc.*, **76**, 3193 (1954).

(6) N. J. Leonard, M. Ōki, and S. Chiavarelli, *J. Am. Chem. Soc.*, **77**, 6234 (1955).

(7) N. J. Leonard, D. F. Morrow, and M. T. Rogers, *J. Am. Chem. Soc.*, **79**, 5476 (1957).

(8) F. F. Blicke, J. Azuara, N. J. Doorenbos, and E. B. Hotelling, *J. Am. Chem. Soc.*, **75**, 5418 (1953).

(9) N. J. Leonard and M. Ōki, *J. Am. Chem. Soc.*, **77**, 6241 (1955).

(10) N. J. Leonard and M. Ōki, *J. Am. Chem. Soc.*, **77**, 6245 (1955).

TABLE II

HIGHEST YIELD METHODS FOR THE SYNTHESIS OF KETONES

Compound II	Method	Yield,[a] %
Cycloheptanone	Ziegler's cyclization of dinitrile	96[11]
Cyclooctanone	Ziegler's cyclization of dinitrile	89[11]
Cyclononanone	Diazomethane on cyclooctanone or	61[12]
	Acyloin condensation; reduction	27[13]
Cyclodecanone	Acyloin condensation; reduction	*ca.* 50,[14] 54[13]
Cyclohendecanone	Acyloin condensation; reduction	53[13]
Cyclododecanone	Acyloin condensation; reduction	68[13]
Cyclotridecanone	Acyloin condensation; reduction	59[13]
Cyclotetradecanone	Acyloin condensation; reduction	75[13]
Cyclopentadecanone	Ziegler's cyclization of dinitrile	60[11]
III		
1,8-Cyclotetradecanedione	Blomquist's diketene reaction	10[15]
1,9-Cyclohexadecanedione	Blomquist's diketene reaction	*ca.* 33[16]
1,10-Cyclooctadecanedione	Dieckmann reaction or	28[17]
	Ziegler's cyclization of dinitrile	28[11]
1,11-Cycloeicosanedione	Blomquist's diketene reaction or	26[18]
	Ziegler's cyclization of dinitrile	25[11]
1,12-Cyclodocosanedione	Ziegler's cyclization of dinitrile	60[11]
1,13-Cyclotetracosanedione	Dieckmann reaction	16[17]
1,14-Cyclohexacosanedione	Dieckmann reaction	19[17]
1,15-Cyclooctaeosanedione	Dieckmann reaction	2.2[17]
1,16-Cyclotriacontanedione	Ziegler's cyclization of dinitrile	18[19]

[a] From precursor specified or obviously assumed from the steps mentioned.

24-membered diketones. Diethyl azelate and diethyl tetradecanedioate provided approximately equimolar quantities of the corresponding mono- and diketones. In the range of lowest (or negligible) monoketone yield (II—9, 10, 11, 12), where the steric repulsion of the alkylene chains suppresses the closure of the medium-size rings, intermolecular condensation followed by intramolecular cyclization of the longer chains resulted in diketone formation (III—9, 10, 11, 12). In selected cases where the yield of monoketone was appreciable, it was improved in ratio to diketone by operating under higher dilution conditions, that is, by extending the addition time for the diester from 24 hr., which was taken as the standard, to a longer period.

While the Dieckmann reaction, even as here modified, has uneven utility in synthesizing carbocyclic ketones from straight-chain diesters, its addition to the storehouse of synthetic tools for preparing many-membered rings is significant. The steps from ester to carbalkoxyketone involve the use of a strong base, a base which acts practically irreversibly for best results, but since the hydrolysis and decarboxylation steps may not require strong acid treatment, the latter feature may direct the use of the Dieckmann condensation for the closure of a ring containing a labile group. The intermediate carbalkoxyketone may also provide the means of bringing about the attachment of other substituents on the large ring.

Finally, a comparison of yields of carbocyclic ketones obtained by various methods leads to the conclusion that there is no one reaction which is perfect for the synthesis of the entire spectrum of cyclic ketones. The methods which give the highest yield of ketone in each case, irrespective of ease or expense of synthesis and ease of purification of product, are summarized in Table II. It will, of course, be recognized that not all of the possible methods may have been applied to the synthesis of each compound; nevertheless, this table is intended as a useful guide and as an indication of our present state of experience based on published, detailed methods.

Blomquist, Prager, and Wolinsky[16] have provided a method for the reduction of diametric diketones to monoketones, so that compounds of type III may be considered to be precursors of large-ring carbocyclics of type II.

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(11) K. Ziegler and R. Aurnhammer, *Ann.*, **513**, 43 (1934).

(12) E. P. Kohler, M. Tischler, H. Potter, and H. T. Thompson, *J. Am. Chem. Soc.*, **61**, 1057 (1939).

(13) F. H. Owens, Ph.D. thesis, University of Illinois, 1958, based on the following: V. L. Hansley, *J. Am. Chem. Soc.*, **57**, 2303 (1935); V. L. Hansley, U.S. Patent 2,228,268 [*Chem. Abstr.*, **35**, 2534 (1941)]; V. Prelog, L. Frenkiel, M. Kobelt, and P. Barman, *Helv. Chim. Acta*, **30**, 1741 (1947); M. Stoll and J. Hulstkamp, *Helv. Chim. Acta*, **30**, 1815 (1947); M. Stoll and A. Rouvé, *Helv. Chim. Acta*, **30**, 1822 (1947).

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(16) A. T. Blomquist, J. Prager, and J. Wolinsky, *J. Am. Chem. Soc.*, **77**, 1804 (1955).

(17) Present work.

(18) A. T. Blomquist and R. D. Spencer, U.S. Patent 2,584,664 (Feb. 5, 1952).

(19) K. Ziegler, H. Eberle, and H. Ohlinger, *Ann.*, **504**, 94 (1933).

EXPERIMENTAL[20]

General procedure for the Dieckmann cyclizations. The Dieckmann cyclizations were all run using the special apparatus previously described.[3-6,9] A 2-l. Morton flask was equipped with a Morton high speed stirrer[21] and a cyclic high dilution apparatus[3,22,23] which carried a dropping funnel and a reflux condenser with stopcock attached.[3] Nitrogen was admitted through the lower end of the stirrer shaft and passed out through a drying tube which protected the top of the reflux condenser. A third joint of the flask was used for the admission of reactants to the flask. The dry apparatus was flushed with nitrogen, and 1.2 l. of dry xylene was added to the flask. Two hundred milliliters of xylene were distilled from the flask at the stopcock on the reflux condenser. This insured removal of any moisture which might have resisted preliminary drying. Refluxing was discontinued and nitrogen passage was accelerated. Twelve molar equivalents of distilled *t*-butyl alcohol and 4.8 atomic equivalents of potassium were added to the flask. After the potassium *t*-butoxide had been formed, the excess *t*-butyl alcohol and about 100 ml. of xylene were distilled from the flask. One molar equivalent of diethyl ester (I) dissolved in 250 ml. of xylene was then introduced dropwise over a period of approximately 24 hr. During this period a nitrogen atmosphere was retained, stirring and refluxing were continued, and an ethanol-xylene mixture was removed by distillation at approximately the same rate as liquid was being added. After all of the ester had been added stirring and refluxing were continued for an hour; then the reaction mixture was allowed to cool to room temperature.

The reaction mixture was made acidic by adding glacial acetic acid in excess. The reaction mixture was washed three times with 50 ml. of water. The xylene solution was filtered to remove insoluble polymeric ketones, and the filtrate was concentrated to a small volume by distillation at reduced pressure. To the residue was added a dilute solution of hydrochloric acid (*ca.* 3*N*); hydrolysis and decarboxylation were effected by refluxing overnight. In several cases ethanol was added to the decarboxylation medium to promote solubility of the ketoesters. In these cases the unreacted starting material was recovered as diester instead of as acid. The reaction mixture was extracted with ether, and the combined ether extracts were extracted with a 10% aqueous solution of sodium bicarbonate. The bicarbonate extracts, when acidified, yielded unreacted starting material as dicarboxylic acid.

The ethereal solution was distilled and the ketones and ester were collected. The ketones were characterized by the close similarity of their physical properties with those previously reported: boiling point or melting point, n_D, and melting point of a suitable derivative. The infrared carbonyl maxima (5% solutions in carbon tetrachloride) for the diketones are given for the first time. The yields appear in Table I.

Cycloheptanone.[24]

Cycloöctanone,[24] and 1,9-cyclohexadecanedione, m.p. 83–85°,[25] ν_{max} 1713 cm.$^{-1}$

1,10-Cycloöctadecanedione, m.p. 95–97°,[25] ν_{max} 1716 cm.$^{-1}$

1,11-Cycloeicosanedione, m.p. 49–51°,[25] ν_{max} 1715 cm.$^{-1}$

Cyclohendecanone; semicarbazone, m.p. 202–204°,[26] and 1,12-cyclodocosanedione, m.p. 54–55.5°,[25] ν_{max} 1715 cm.$^{-1}$

Cyclododecanone, m.p. 58–61°,[25] and 1,13-cyclotetracosanedione, m.p. 62–63.5°,[25] ν_{max} 1716 cm.$^{-1}$

Cyclotridecanone, m.p. 26–29°;[25] semicarbazone, m.p. 205–206° (dec.),[26] and 1,14-cyclohexacosanedione, m.p. 65–68°,[25] ν_{max} 1715 cm.$^{-1}$

Cyclotetradecanone, m.p. 55.5–56°,[25] and 1,15-cycloöctacosanedione, m.p. 72–73.5°,[25] ν_{max} 1716 cm.$^{-1}$

Cyclopentadecanone, m.p. 64–66°,[26] and 1,16-cyclotriacontanedione, m.p. 76–78°,[15] ν_{max} 1716 cm.$^{-1}$

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(20) Melting points are corrected. Infrared spectra were recorded by Mr. James Brader and his associates in this laboratory.

(21) A. A. Morton, B. Darling, and J. Davidson, *Ind. Eng. Chem., Anal. Ed.*, **14**, 734 (1942).

(22) A. C. Cope and E. C. Herrick, *J. Am. Chem. Soc.*, **72**, 983 (1950).

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(26) L. Ruzicka, M. Stoll, and H. Schinz, *Helv. Chim. Acta*, **9**, 249 (1926). Reported melting points are close or identical.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STANFORD RESEARCH INSTITUTE, AND THE ETHYL CORP.]

Uncatalyzed Addition of Bromotrichloromethane to Ethylene and Substituted Ethylenes. I. Nature and Scope of the Reaction[1]

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The uncatalyzed addition of bromotrichloromethane to ethylene and various substituted ethylenes has been found to give good yields of the 1:1 adducts. The adducts are the same as those obtained from the peroxide-, light-, or gamma radiation-induced additions. The reaction is believed to be a thermally initiated free radical chain reaction.

Numerous workers[3-15] have studied the catalytic addition of bromotrichloromethane to ethylene and substituted ethylenes. These reactions have been initiated by the use of peroxides, gamma radiation,

(1) The work reported herein was supported in part by the Ethyl Corp., Baton Rouge, La., and by Stanford Research Institute, Menlo Park, Calif.

(2) Stanford Research Institute, Menlo Park, Calif.

(3) R. L. Huang, *J. Chem. Soc.*, 1749 (1956).

(4) M. S Kharasch, U. S. Patent 2,464,869 (March 22, 1949).

(5) M. S. Kharasch, U. S. Patent 2,525,912 (Oct. 17, 1950).

(6) M. S. Kharasch, U. S. Patent 2,485,099 (Oct. 18, 1949).

(7) M. S. Kharasch, O. Reinmuth, and W. H. Urry, *J. Am. Chem. Soc.*, 69, 1105 (1947).

or actinic light. We have now found that none of the previously used initiators is necessary. This paper reports some results of this uncatalyzed addition.

Bromotrichloromethane was found to add to ethylene at 120° in the absence of any catalyst or light to yield 1,1,1-trichloro-3-bromopropane.

This uncatalyzed addition of bromotrichloromethane to ethylene was extended to substituted ethylenes. Octene-1 and bromotrichloromethane were found to react in the dark and in the absence of air or peroxides to yield the 1:1 adduct (3-bromo-1,1,1-trichlorononane).

The free radical nature of the reaction was shown by its inhibition by Ionol (2,6-di-*t*-butyl-4-methylphenol), air, and nitromethane. Freshly distilled bromotrichloromethane and octene-1 were used to avoid traces of peroxides. Attempts to form peroxides by bubbling air through the bromotrichloromethane prior to its use resulted in a slight decrease in product yield rather than an increase. Indications are that the initiation of the addition reaction is the easy thermal dissociation of bromotrichloromethane into bromine atoms and trichloromethyl radicals.

The uncatalyzed addition of bromotrichloromethane to vinyl acetate yielded 1-bromo-3,3,3-trichloropropylacetate; to styrene, 1-bromo-3,3,3-trichloropropyl benzene; to 3,9-divinylspirobimetadioxane (3,9-divinyl-2,4,8,10-tetroxaspiro[5.5]undecane), the adduct formed by the addition of two moles of bromotrichloromethane to one of the divinyl compound; to butene-1, 3-bromo-1,1,1-trichlorobutane, to butene-2, 2-bromo-3-methyl-4,4,4-trichlorobutane; to allyl chloride, 2-bromo-1,4,-4,4-tetrachlorobutane; and to butadiene, 1-bromo-5,5,5-trichloropentene-2 and 3-bromo-5,5,5-trichloropentene-1.

In the butadiene addition, the major product was identified as the 1,4-adduct by infrared and halide analyses. A low yield of this butadiene adduct was obtained when butadiene was passed through refluxing bromotrichloromethane for 24 hr.

In all cases, the yields were not as high as those previously reported by Kharasch[7] when acetyl peroxide was used as initiator. With styrene, a 78% yield of the 1:1 adduct was obtained in 4 hr. at 70° using 2.3 wt. % of diacetyl peroxide as initiator. The same proportions of reagents in an uncatalyzed reaction gave a 40% yield in 5.5 hr. at 100°. With octene-1, a 71% yield of the 1:1 adduct was obtained in 4 hr. at 70° using 1.4 wt. % of diacetyl peroxide as initiator. Using comparable amounts of starting materials, a 50 % yield was obtained at 100° in 3 hr. without catalyst. With vinyl acetate, Kharasch[7] reports an 89% yield of the adduct in 3 hr. at 60° with 1.5 g. of acetyl peroxide. The uncatalyzed addition to vinyl acetate gave a 63% yield in 5.5 hr. at 100°.

The uncatalyzed addition of bromotrichloromethane to diethylmaleate, maleic anhydride, allylidene diacetate, isopropenyl acetate, 1-methoxy-1,3-butadiene, methyl methacrylate, divinylcarbitol, and ethyl crotonate failed to yield any appreciable amounts of the 1:1 adducts at 100°.

Polymers were obtained when the uncatalyzed addition of bromotrichloromethane to methyl isopropenyl ketone, bischloroethylvinylphosphonate, vinyl crotonate, diallyl cyanamide, diethylaminoethylacrylate, or diallylphthalate was attempted.

EXPERIMENTAL

Uncatalyzed addition of bromotrichloromethane to ethylene. Bromotrichloromethane (780 g., 3.9 moles, freshly distilled) was added to a 1.4-liter stainless steel rocking bomb, purged with ethylene to remove air, pressurized with ethylene to 700 p.s.i.g., and heated at 120° for 4 hr. The products were removed from the bomb and distilled. The 1:1 adduct, 1,1,1-trichloro-3-bromopropane (174 g., b.p. 82° at 34 mm.), was isolated by distillation (weight of silver halide from 0.3358 g. sample: calcd., 0.9060; found, 0.9056). In addition to the 1:1 adduct, 11.2 g. of 1,1,1-trichloro-5-bromopentane was formed (b.p. 110° at 2 mm., weight of silver halide from 0.2476 g. sample: calcd. 0.4830; found, 0.4881).

When bromotrichloromethane (200 ml.) was dissolved in heptane (200 ml.), pressured to 1200 p.s.i.g. with ethylene, and heated at 120° for 4 hr., 129 g. of 1,1,1-trichloro-3-bromopropane and 24 g. of 1,1,1-trichloro-5-bromopentane were produced.

Uncatalyzed addition of bromotrichloromethane to vinyl acetate. Bromotrichloromethane (198 g., 1.0 mole, freshly distilled) was refluxed under nitrogen and vinyl acetate (25 ml., 0.25 mole) was added over a 4.5-hr. period and heated 1 hr. longer under reflux. 1-Bromo-3,3,3-trichloropropylacetate (45 g., 63% yield, n_D^{24} 1.4920, b.p. 65° at 0.5 mm., weight of silver halide for 0.2348 g. sample: calcd., 0.5060; found, 0.5033) was produced. When 2,4-dinitrophenylhydrazine in alcohol was added to the adduct and the solution acidified with sulfuric acid, the orange-red hydrazone of 3,3-dichloroacrolein precipitated (m.p. 162–164°). Kharasch[7] reported m.p. 164–165° for this hydrazone formed from the peroxide-catalyzed reaction.

Uncatalyzed addition of bromotrichloromethane to styrene. Bromotrichloromethane (136 g., 0.69 mole, freshly distilled) was refluxed under nitrogen, and styrene (20.7 g., 0.19 mole, freshly distilled) was added over a 2.5-hr. period and heated 0.5 hr. longer. The major product was 1-bromo-2,2,2-trichloropropyl-benzene (4.8 g., b.p. 98°, m.p. 53–55°, weight of silver halide for 0.1519 g. sample: calcd. 0.3096; found, 0.2854). Kharasch[15] reports a melting point of 54–55°. When styrene (13 g., 0.12 mole) and bromotrichloromethane (100 g., 0.50 mole) were heated under nitrogen on a steam bath for 5.5 hr., 14.5 g., 40% yield, of the 1:1 adduct was

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(11) P. S. Skell and R. C. Woodworth, *J. Am. Chem. Soc.*, **77**, 4638 (1955).

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(13) H. W. Melville, J. C. Robb, R. C. Tutton, *Discussions Faraday Soc.*, **19**, 150 (1953).

(14) A. M. Lovelace and D. A. Rausch, W.A.D.C. Tech. Report No. 55461, April (1956).

(15) M. S. Kharasch, U. S. Patent **2,468,208** (April 26, 1949).

formed. Kharasch[15] reported a yield of 18.6 g. of crude addition product under identical conditions when magnesium and iodine was used as a "catalyst".

Study of the effect of Ionol, nitromethane, air, and light on the uncatalyzed addition of bromotrichloromethane to octene-1. Bromotrichloromethane (98 g., 0.44 mole, freshly distilled) and octene-1 (24 g., 0.22 mole, Phillips, 99 mole %, freshly distilled) were refluxed under nitrogen for 3 hr. The major product was 3-bromo-1,1,1-trichlorononane (31.5 g., 50% yield, b.p. 85° at 0.6 mm.).

When the above reaction was repeated with 10 g. of Ionol (2,6-di-*t*-butyl-4-methylphenol) added, only 11.0 g. of 3-bromo-1,1,1-trichlorononane was produced.

When the reaction was repeated without Ionol but with air bubbling through the solution for the 3-hr. period, only 18.5 g. of 3-bromo-1,1,1-trichlorononane was produced.

Blowing air through the bromotrichloromethane for 4 hr. prior to use resulted in a lower yield of adduct.

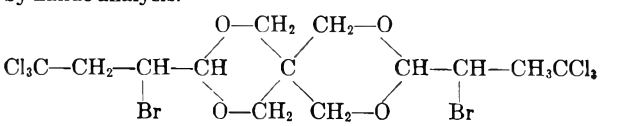
No change in the yield of 3-bromo-1,1,1-trichlorononane was obtained when the bromotrichloromethane used was refluxed under nitrogen for 17 hr. to destroy any peroxides present prior to reacting with octene-1. Kharasch[15] claimed that peroxides build up in bromotrichloromethane.

When the uncatalyzed reaction between bromotrichloromethane and octene-1 was carried out in the dark, no change in the product yield from that obtained under normal laboratory lighting conditions was noticed.

The use of nitromethane (125 ml.) as a solvent for the uncatalyzed addition of bromotrichloromethane (146 g., 0.74 mole) to octene-1 (32 g., 0.28 mole) resulted in only 16.8 g. of 3-bromo-1,1,1-trichlorononane after 5 hr. of refluxing.

When bromotrichloromethane (146 g., 0.74 mole), *n*-heptane (125 ml., Phillips 95 mole %, freshly distilled), and octene-1 (28 g., 0.25 mole) was refluxed under nitrogen for 5 hr., 73 g., 94% yield, of 3-bromo-1,1,1-trichlorononane was produced.

Uncatalyzed addition of bromotrichloromethane to 3,9-divinylspirobimetadioxane. 3,9-Divinylspirobimetadioxane (15 g., 0.07 mole, m.p. 42°, Union Carbide Chemicals Co.) was slowly added to refluxing bromotrichloromethane (97.5 g., 0.49 mole) under nitrogen. The solution was refluxed for 6 hr., and upon cooling a crystalline solid crystallized was obtained. The yield of solid product was 25.6 g. (0.04 mole, 57% yield). Unlike 3,9-divinylspirobimetadioxane, the product was very insoluble in water and melted at 184–186°. The product was identified as having the following formula by halide analysis.



Weight of silver halide for 0.2500 g. sample: calcd., 0.5140; found, 0.4926.

Uncatalyzed addition of bromotrichloromethane to butene-1 and butene-2. Bromotrichloromethane (390 g., 1.97 moles, freshly distilled) and butene-1 (21 g., 0.38 mole, freshly distilled, Phillips 95 mole %) were added to a 1.4-liter rocking bomb and heated at 100° for 4 hr. in the absence of air. The product was 3-bromo-1,1,1-trichloropentane (41.2 g., 0.163 mole, 43% yield, b.p. 66–68° at 3 mm., weight of silver halide for 0.1765 g. sample: calcd., 0.427; found, 0.422).

Bromotrichloromethane (390 g., 1.97 moles, freshly distilled) and butene-2 (36 g., 0.64 mole, freshly distilled, Phillips 95 mole %) were heated in a 1.4-liter rocking bomb in the absence of air for 4 hr. at 100°. The product formed was 2-bromo-4,4,4-trichloro-3-methylbutane (18.5 g., 0.079 mole, 13% yield, b.p. 95° at 10 mm., weight of silver halide for 0.1546 g. sample: calcd., 0.3711; found, 0.3760).

Uncatalyzed addition of bromotrichloromethane to allyl chloride. When allyl chloride (23 g., 0.302 mole) was added slowly over a period of an hour to refluxing bromotrichloromethane (97.5 g., 0.49 mole) and the solution refluxed for 20 hr., only 6.3 g. of a product, b.p. 60° at 0.5 mm., was obtained.

When allyl chloride (46.8 g., 0.61 mole, freshly distilled) was heated with bromotrichloromethane (390 g., 1.97 moles) at 110° for 4 hr. and in a stainless steel rocking bomb, 2-bromo-1,4,4,4-tetrachlorobutane (63 g., 0.23 mole, 38% yield, b.p. 86–89° at 2.8 mm., weight of silver halide for 0.2144 g. sample: calcd., 0.5910; found, 0.5903) was formed.

Uncatalyzed addition of bromotrichloromethane to butadiene. Butadiene (130 g., 2.4 moles, Phillips 99 mole %) was distilled into an evacuated 1.4-liter stainless steel bomb containing bromotrichloromethane (390 g., 1.97 moles, freshly distilled). The bomb was heated and rocked at 100° for 4 hr. The major product was 1-bromo-5,5,5-trichloropentene-2 (62 g., 0.25 mole, 10% yield, b.p. 69° at 1.6 mm., n_D^{20} 1.5328, weight of silver halide for 0.2113 g. sample: calcd., 0.5170; found, 0.5120 for 1:1 adduct). A small amount of higher boiling material was also produced. Two possible 1:1 adducts exist: 1-bromo-5,5,5-trichloropentene-2 and 4-bromo-3-trichloromethylbutene-1. The infrared spectra of the product shows the presence of trans internal double bonds, but no terminal double bonds are present. The product is 1-bromo-5,5,5-trichloropentene-2 formed by 1,4-addition of bromotrichloromethane to butadiene.

When butadiene was bubbled through refluxing bromotrichloromethane (458 g., 2.3 moles) for 24 hr., 3-bromo-5,5,5-trichloropentene-1 (6.2 g., n_D^{20} = 0.5350) was formed.

Acknowledgments. The authors wish to express appreciation to Mr. Oliver I. Smith, who carried out the halide analyses, and to Mr. Wiley Crawford for the infrared analysis.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Alkylations of Certain Carbanions with 1-Chloro-1,2-diphenylethane. β-Eliminations with Other Bases.[1]

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1-Chloro-1,2-diphenylethane underwent the substitution type of reaction with sodium diphenylmethide and sodio- or potassiophenylacetonitrile in liquid ammonia to form the corresponding alkylation products in high yields. However, this halide exhibited β-elimination with disodiophenylacetic acid and sodium ethoxide under similar conditions.

1-Chloro-1,2-diphenylethane (I) has recently[2] been prepared in good yield through the self-alkylation of benzyl chloride by means of lithium amide or sodium amide in liquid ammonia (Equation 1).

$$2C_6H_5CH_2Cl \xrightarrow[\text{inverse addition}]{LiNH_2\ (liq.\ NH_3)} \underset{I}{C_6H_5CH_2\overset{C_6H_5}{\overset{|}{C}}HCl} \quad (1)$$

The success of this preparation is dependent on the use of the inverse addition procedure, since halide I readily undergoes dehydrohalogenation (β-elimination) in the presence of excess of the amide ion to form stilbene.[2]

In spite of its tendency to undergo β-elimination,[3] halide I has now been found to enter into the substitution type of reaction with certain carbanions in liquid ammonia. Thus, sodium diphenylmethide underwent alkylation with halide I to form hydrocarbon II in 93% yield (Equation 2).

$$(C_6H_5)_2CH_2 \xrightarrow[liq.\ NH_3]{NaNH_2} (C_6H_5)_2CHNa \xrightarrow{I} \underset{II}{(C_6H_5)_2CH\overset{C_6H_5}{\overset{|}{C}}HCH_2C_6H_5} \quad (2)$$

Analogous alkylations of sodium diphenylmethide with various halides including β-phenylethyl chloride have previously been described.[4]

Similarly sodio- or potassiophenylacetonitrile underwent alkylation with halide I to form nitrile III in 80–81% yield (Equation 3).

$$C_6H_5CH_2CN \xrightarrow[liq.\ NH_3]{NaNH_2} C_6H_5\overset{Na}{\overset{|}{C}}HCN \xrightarrow{I} \underset{III}{C_6H_5CH\overset{C_6H_5CH_2C_6H_5}{\overset{|}{C}}HCN} \quad (3)$$

The product from this reaction consisted of only one of the two possible diastereoisomers of nitrile III. The analogous alkylation of sodio- or potassiophenylacetonitrile with α-phenylethyl chloride[5] has been shown[6] to produce the erythro isomer of 2,3-diphenylbutyronitrile in 99% yield.

The reaction represented by Equation 3 has furnished a convenient starting point for a subsequent study[7] of the influence of stereochemistry on the acid-catalyzed five- versus six-carbon ring cyclizations of the corresponding carboxylic acid.

However, disodiophenylacetic acid failed to undergo appreciable alkylation with halide I. Instead, β-elimination occurred to form stilbene (75%) and monosodiophenylacetic acid which was isolated as the free acid (73%) (Equation 4).

$$C_6H_5CH_2COOH \xrightarrow[liq.\ NH_3]{2NaNH_2} C_6H_5\overset{Na}{\overset{|}{C}}HCOONa \xrightarrow{I} C_6H_5CH{=}CHC_6H_5 + C_6H_5CH_2COONa \quad (4)$$

This result might suggest that the dianion of phenylacetic acid functions more like an oxygen base as in resonance structure IV than a carbanion, although this carbanion has been alkylated with certain other halides.[8]

$$\underset{(IV)}{C_6H_5C(H){=}C(O^-)(O^-)}$$

Also halide I underwent β-elimination with sodium ethoxide to form stilbene (92%); none of the corresponding substitution product was found.

In Table I are summarized the types of reaction exhibited by halide I with the anions of these sodio

(1) Supported by the Office of Ordnance Research, U.S. Army.

(2) C. R. Hauser, W. R. Brasen, P. S. Skell, S. W. Kantor, and A. E. Brodhag, *J. Am. Chem. Soc.*, **78**, 1653 (1956).

(3) It should be mentioned that halide I was kept in the refrigerator for several months without apparent decomposition.

(4) C. R. Hauser and P. J. Hamrick, Jr., *J. Am. Chem. Soc.*, **79**, 3142 (1957).

(5) C. R. Hauser and W. R. Brasen, *J. Am. Chem. Soc.*, **78**, 494 (1956).

(6) W. R. Brasen and C. R. Hauser, *J. Am. Chem. Soc.*, **79**, 395 (1957).

(7) D. Lednicer and C. R. Hauser, *J. Am. Chem. Soc.*, **80**, 3409 (1958).

(8) C. R. Hauser and W. J. Chambers, *J. Am. Chem. Soc.* **78**, 4942 (1956).

bases or, in certain cases, potassio bases[9] in liquid ammonia at −33°.

TABLE I

TYPES OF REACTION OF HALIDE I WITH ANIONS IN LIQ. NH_3 AT −33°

Substitution	β-Elimination
$(C_6H_5)_2\bar{C}H$	$\bar{N}H_2$
$C_6H_5\bar{C}HCN$	$C_6H_5\bar{C}HCO\bar{O}$
	$O\bar{C}_2H_5$

Since halide I undergoes β-elimination with ethoxide ion but the substitution type of reaction with the more strongly basic diphenylmethide ion, the well known generalization[10] that the former reaction is favored by an increase in basic strength is not applicable to these two anions. The generalization was based mostly on studies of a series of oxygen bases such as the acetate, phenoxide, and hydroxide ions[10]; it might possibly be applicable also to a series of carbanions when considered alone.

EXPERIMENTAL[11]

Alkylation of sodium diphenylmethide with halide I to form hydrocarbon II. To a stirred suspension of 0.05 mole of sodium amide in 200 ml. of liquid ammonia[12] there was added a solution of 8.80 g. (0.05 mole) of diphenylmethane in 200 ml. of anhydrous ether, followed after 5 min. by a solution of 10.8 g. (0.05 mole) of 1-chloro-1,2-diphenylethane (I)[2] in 50 ml. of anhydrous ether. The red color of the diphenylmethide ion was discharged within a few minutes to produce a yellow mixture. After stirring for 0.5 hr., the liquid ammonia was evaporated on the steam bath as an equal volume of ether was added. The resulting ethereal suspension was shaken with water, and the two layers were separated. The ethereal layer was dried over Drierite, and, after filtering, the solvent was removed. The residue was recrystallized twice from methanol to give 16.2 g. (93%) of 1,1,2,3-tetraphenylpropane (II), m.p. 82–83°.

Anal. Calcd. for $C_{27}H_{24}$: C, 93.05; H, 6.94. Found: C, 93.31; H, 6.77.

Alkylation of alkali phenylacetonitriles with halide I to form nitrile III. To a stirred suspension of 0.05 mole of sodium amide in 200 ml. of liquid ammonia[12] there was added a solution of 5.85 g. (0.05 mole) of phenylacetonitrile in 50 ml. of anhydrous ether, followed after 5 minutes by a solution of 10.8 g. (0.05 mole) of 1-chloro-1,2-diphenylethane (I) in 50 ml. of anhydrous ether. The mixture was stirred for several hours (Dry Ice-acetone condenser), and the liquid ammonia was then replaced by ether. The resulting suspension was shaken with water, and the layers were separated. The ethereal layer was washed with water, dilute hydrochloric acid, and sodium bicarbonate solution. After drying over Drierite, the solvent was removed, and the residue was recrystallized from petroleum ether (b.p. 30–60°) to give several crops of crystals of 2,3,4-triphenylbutyronitrile (III). The total yield was 11.8 g. (80%), m.p. 131–132°; reported m.p. 129–131°.[13]

Anal. Calcd. for $C_{22}H_{19}N$: C, 88.85; H, 6.44; N, 4.71. Found: C, 88.71; H, 6.55; N, 4.63.

Similarly a solution of 0.10 mole of potassium amide in 200 ml. of liquid ammonia was treated with a solution of 12.87 g. (0.11 mole) of phenylacetonitrile in 50 ml. of ether. The resulting green solution of potassiophenylacetonitrile was stirred for 15 min., and then treated during 5 min. with a solution of 21.65 g. (0.10 mole) of halide I in 50 ml. of ether. The color was discharged within 45 min. A little ammonium chloride was added, and the suspension was taken to dryness on the steam bath. The residue was washed well with water, and recrystallized from ethanol to give 23.2 g. (81%, needles) of nitrile III, m.p. 131–132°.

Reaction of disodiophenylacetic acid with halide I (β-Elimination). To a stirred suspension of 0.1 mole of sodium amide in 200 ml. of liquid ammonia[12] was added a solution of 6.80 g. (0.05 mole) of phenylacetic acid in 50 ml. of dry ether, followed after 5 min. by a solution of 10.80 g. (0.05 mole) of 1-chloro-1,2-diphenylethane (I) in 50 ml. of ether. A purple color appeared immediately. After 25 min., the liquid ammonia was replaced by ether (steam bath), and the resulting ethereal suspension was extracted with two 50 ml. portions of water. The combined aqueous solution (after heating to remove dissolved ether) was cooled and acidified to precipitate 5.0 (73%) of phenylacetic acid, m.p. and mixed m.p. 75–76°. The ethereal solution was dried over Drierite, and the solvent was removed. The yellow residue (9.0 g.) melted at 119–125°. Recrystallization from methanol-chloroform solution (ratio 4:1) gave 6.7 g. (75%) of stilbene, m.p. and mixed m.p. 126–127°.

Reaction of sodium ethoxide with halide I (β-elimination). To a solution of 1.6 g. (0.07 mole) of sodium metal in 300 ml. of liquid ammonia there was added 3.5 g. (0.0701 mole) of absolute ethanol (blue color discharged). The resulting solution of sodium ethoxide (0.07 mole) was stirred, and a solution of 15 g. (0.069 mole) of 1-chloro-1,2-diphenylethane (I) in 50 ml. of ether was added. After 5 hr. (Dry Ice–acetone condenser), solid ammonium chloride (10 g.) was added, and the liquid ammonia was replaced by ether (200 ml.). Water was added, and the two layers separated. The ethereal layer was evaporated (steam bath) to leave a solid residue which was taken up in 25 ml. of hot benzene. Petroleum ether (b.p. 30–60°) was added to precipitate 10.2 g. (82%) of stilbene, m.p. and mixed m.p. 124–125°. More (1.3 g.) of stilbene was isolated from the mother liquor; total yield 92%. No other product was found.

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(9) Although the metallic cation appears to have no significant influence on the ratio of the substitution and elimination products from a halide with ethoxide ion in ethanol (see M. S. Newman and F. J. Evans, *J. Am. Chem. Soc.*, **76**, 4187 (1954)), such an influence has been observed with certain stronger bases. Thus, β-phenylethyl chloride reacts with sodium diphenylmethide in liquid ammonia to form almost exclusively the substitution product, whereas this halide undergoes appreciable (18%) β-elimination with potassium diphenylmethide, which effectively functions as the stronger base; see ref. 4.

(10) See C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, Cornell University Press, Ithaca, N. Y., 1953, p. 451–2; E. E. Royals, *Advanced Organic Chemistry*, Prentice–Hall, Inc., New York, N. Y., 1954, p. 299.

(11) Melting points were taken on a Fisher-Johns melting point apparatus. Analyses are by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

(12) See C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. Reactions*, *VIII*, 122 (1954).

(13) Y. De Schuttenbach, *Ann. chim.* (11), **6**, 90 (1936).

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

Chemistry of Spiropentane. I. An Improved Synthesis of Spiropentane

DOUGLAS E. APPLEQUIST, GEORGE F. FANTA, AND BERTEL W. HENRIKSON

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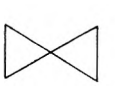
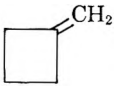
It has been found that nearly pure spiropentane can be obtained from the reaction of pentaerythrityl tetrabromide with zinc by inclusion of ethylenediaminetetraacetate in the reaction mixture. It is concluded that the rearranged product, methylenecyclobutane, which normally predominates in the product, is probably formed by a carbonium ion rearrangement of an intermediate dibromide.

The extensive literature[1] on the synthesis of spiropentane (I) by the reaction of pentaerythrityl



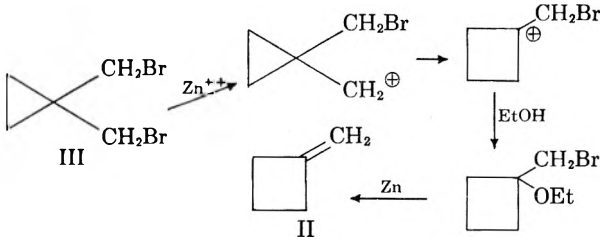
I



II

tetrabromide with zinc has failed to reveal a satisfactory method for the prevention of extensive simultaneous formation of methylenecyclobutane (II). There is suggestive evidence that II is formed by way of an electrophilically induced rearrangement of the intermediate 1,1-bis(bromomethyl)-cyclopropane (III), perhaps as shown in Chart I.

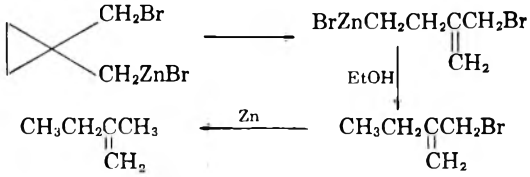
CHART I



In support of this hypothesis are the absence of spiropentane in the product when zinc bromide is present initially,[2] the improvement in spiropentane yield when sodium in dioxane is used in place of zinc in ethanol,[3] and the known tendency of III to undergo zinc bromide catalyzed rearrangement to 1-bromo-1-bromomethylcyclobutane.[4] An alternative mechanism which has been suggested by Schubert and Leahy[5] for the formation of II is a "base-induced" rearrangement of III with zinc metal acting as the base. Strong confirmation of the former hypothesis and a much improved synthesis of spiropentane have now been obtained by the discovery that the formation of methylenecyclobutane as a product of the reaction of pentaerythrityl tetrabromide with zinc in aqueous ethanol may under optimum conditions be reduced to less than one per cent of the hydrocarbon product by inclusion of tetrasodium ethylenediaminetetraacetate in the reaction mixture to remove free zinc ion. Under the conditions specified in the Experimental section, an 81% yield of hydrocarbon, consisting of 94% spiropentane, 4.2% 2-methyl-1-butene, 0.7% 1,1-dimethylcyclopropane, and 0.6% methylenecyclobutane, was obtained.

The persistence of 2-methyl-1-butene as an important impurity in the spiropentane in spite of the sequestering agent suggests that this olefin is not entirely, if at all, a product of an anionotropic rearrangement of III, as had been suggested.[1h] A reasonable alternative explanation for its formation is a rearrangement of an intermediate organozinc compound (Chart II), analogous to the rearrangement which would account for the allylcarbinyl derivatives obtained from Grignard reactions of cyclopropylcarbinyl chloride.[6]

CHART II



EXPERIMENTAL

Pentaerythrityl tetrabromide was prepared from phosphorus tribromide and pentaerythritol (Heyden Chemical, technical grade) according to Murray and Stevenson's modification[1d] of the *Organic Syntheses* preparation.[7] The melting point was approximately 158–160° in three separate runs.

(1) (a) Gustavson, *J. Prakt. Chem.*, **54**, 97 (1896); (b) N. D. Zelinskii and V. P. Kraevich, *J. Russ. Phys. Chem. Soc.*, **44**, 1870, 1873 (1912); *Chem. Abstr.*, **7**, 1175 (1913); (c) F. Rogowski, *Ber.*, **72B**, 2021 (1939); (d) M. J. Murray and E. H. Stevenson, *J. Am. Chem. Soc.*, 66, 314, 812 (1944); (e) V. A. Slabey, *J. Am. Chem. Soc.*, **68**, 1335 (1946); (f) V. A. Slabey, *Natl. Advisory Comm. Aeronautics Tech. Note No.* 1023 (1946); *Chem. Abstr.*, **40**, 3729 (1946); (g) Y. M. Slobodin and I. N. Shokhor, *Zhur. Obshchei Khim.*, **21**, 2005 (1951); *Chem. Abstr.*, **46**, 6598 (1952); (h) Y. M. Slobodin and I. N. Shokhor, *Zhur. Obshchei Khim.*, **23**, 42 (1953); *Chem. Abstr.*, **48**, 543 (1954).

(2) J. D. Roberts and C. W. Sauer, *J. Am. Chem. Soc.*, **71**, 3925 (1949).

(3) H. O. House, R. C. Lord, and H. S. Rao, *J. Org. Chem.*, **21**, 1487 (1956).

(4) D. E. Applequist and J. D. Roberts, *J. Am. Chem. Soc.*, **78**, 874 (1956).

(5) W. M. Schubert and S. M. Leahy, *J. Am. Chem. Soc.*, **79**, 381 (1957).

(6) (a) J. D. Roberts and R. H. Mazur, *J. Am. Chem. Soc.*, **73**, 2509 (1951); (b) H. C. Brown and M. Borkowski, *J. Am. Chem. Soc.*, **74**, 1894 (1952).

(7) H. B. Schurink, *Org. Syntheses*, Coll. Vol. II, 476 (1943).

Spiropentane (I). In a 5-l. three-necked creased flask fitted with a high-speed stirrer, a solids-addition apparatus, and a water-cooled reflux condenser in series with a spiral condenser (arranged for distillation) and two Dry Ice traps, was placed 852 g. (2.57 moles) of disodium dihydrogen ethylene diaminetetraacetate, 297 g. (7.43 moles) of sodium hydroxide dissolved in 510 ml. of water, 1470 ml. of 95% ethanol, and 20.7 g. (0.138 mole) of sodium iodide. The mixture was heated to reflux, and 214.5 g. (3.28 g.-atoms) of zinc dust was then added. A slow stream of nitrogen was passed through the system to carry volatile products to the cold traps, and 321 g. (0.828 mole) of pentaerythrityl tetrabromide was added slowly to the stirred, refluxing mixture. After the addition was complete, the mixture was stirred at reflux temperature for 1 hr. The condensate in the cold traps was washed with two 150-ml. portions of a cold, saturated solution of sodium chloride in water and then dried over Drierite to give 45.5 g. (81%) of crude spiropentane.

Vapor chromatography (Perkin-Elmer Model 154B; column B, di-2-ethylhexyl sebacate as stationary phase) of a sample of crude spiropentane showed five other components to be present besides spiropentane. Collection of three of these in pure form by vapor chromatography of a sample of crude hydrocarbon, which had been enriched in the low-boiling impurities by fractional distillation, and comparison of their infrared spectra with those of known compounds permitted identification of 2-methyl-1-butene,[8] 1,1-dimethylcyclopropane,[9] and ethanol. Methylenecyclobutane was identified by comparison of its retention time on the column with that of a known sample. The major component was identified as spiropentane by comparison of the infrared spectrum of the crude hydrocarbon with the published spectrum.[9] The crude hydrocarbon from one run was found to be 94% spiropentane, 4.2% 2-methyl-1-butene, 0.7% 1,1-dimethylcyclopropane, 0.6% methylenecyclobutane, 0.2% ethanol, and 0.3% of an unidentified low-boiling material (possibly neopentane).

Spiropentane was obtained free of unsaturated impurities by rough titration of a 20% (by volume) solution of the hydrocarbon in ethylene dibromide with bromine, followed by distillation through a 4.5-ft. spiral-wire column. The product (b.p. 36.5–37.5°) had an infrared spectrum in agreement with the published spectrum[9] of spiropentane.

Acetylacetone was tried as a sequestering agent also and was found to be less satisfactory than ethylenediaminetetraacetate. When the theoretical amounts of acetylacetone and sodium carbonate were used to chelate the zinc ion generated in the reaction, a 60% yield of hydrocarbon containing 76% spiropentane (by base-line infrared analysis) was obtained. Smaller amounts of acetylacetone and sodium carbonate gave much smaller yields of spiropentane.

Methylenecyclobutane (II) in pure form for infrared and vapor chromatographic analysis was prepared by the method of Roberts and Sauer.[2] The reaction of 6 g. of zinc bromide, 18 ml. of ethanol, 700 ml. of water, 225.6 g. of zinc, and 406.8 g. of pentaerythrityl tetrabromide gave methylenecyclobutane in 19% yield. The product, b.p. 40.5°, was purified by distillation through a 4-ft. spinning-band column, and its infrared spectrum agreed with the published spectrum.[2]

Acknowledgment. This research was supported in part by a grant from the Petroleum Research Fund administered by the American Chemical Society. Grateful acknowledgment is hereby made to the donors of said fund. We would also like to thank Mr. James Brader and his associates for the infrared spectra.

URBANA, ILL.

(8) American Petroleum Institute, Research Project 44 at National Bureau of Standards, *Infrared Absorption Spectrograms*, *Vol. I*, No. 196.

(9) F. F. Cleveland, M. J. Murray, and W. S. Gallaway, *J. Chem. Phys.*, **15**, 742 (1947).

[CONTRIBUTION FROM THE INSTITUTE OF PAPER CHEMISTRY]

Chlorination of Cellulose with Thionyl Chloride in a Pyridine Medium

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Activated cotton linters were treated with thionyl chloride in anhydrous pyridine to form cellulose derivatives containing up to 1.3 stable chlorine atoms per anhydroglucose unit. Unstable sulfur groupings, presumably in the form of sulfurous acid esters, were also introduced. Chlorocelluloses were hydrolyzed in aqueous sulfuric acid solution without loss of chlorine, but resistance to hydrolysis was encountered as the degree of chlorine substitution was increased. A hydrolyzate was fractionated chromatographically; glucose was isolated from one fraction and a monochloroglucose from another.

The chemical literature contains very little information concerning the halogen derivatives of cellulose. Past investigations revealed that halogens had been introduced into cellulose during the preparation of the tosyl and mesyl esters,[1] but the presence of halogens was generally considered to be of only secondary importance. The tosylation of carbohydrates in general and accompanying chlorination has been extensively reviewed by Tipson.[2] Pacsu and Schwenker[3] have recently prepared 6-mesyl chloro, 6-mesyl bromo, and 6-mesyl iodocelluloses by partial replacement of the 6-mesyl group by the appropriate halogen.

(1) K. Hess and N. Ljubitsch, *Ann.*, **507**, 62 (1933); F. B. Cramer and C. B. Purves, *J. Am. Chem. Soc.*, **61**, 3458 (1939); A. L. Bernoulli and H. Stauffer, *Helv. Chim. Acta*, **23**, 627 (1940); M. L. Wolfrom, J. C. Sowden, and E. A. Metcalfe, *J. Am. Chem. Soc.*, **63**, 1388 (1941); J. F. Mahoney and C. B. Purves, *J. Am. Chem. Soc.*, **64**, 9 (1942); C. J. Malm, L. J. Tanghe, and B. C. Laird, *J. Am. Chem. Soc.*, **70**, 2740 (1948); E. Heuser, M. Heath, and W. H. Shockley, *J. Am. Chem. Soc.*, **72**, 670 (1950); R. Roberts, *J. Am. Chem. Soc.*, **79**, 1175 (1957).

(2) R. S. Tipson, *Advances in Carbohydrate Chemistry*, Academic Press, New York, Volume 8, p. 107.

(3) E. Pacsu and R. F. Schwenker, Jr., *Textile Research J.*, **27**, 173 (1957)

Carré and Mauclère[4] studied the reaction of cotton linters with thionyl chloride in a pyridine medium and obtained a substance with the formula ($C_6H_9O_4Cl$). The cotton was darkened during the course of the reaction and suffered a loss in tenacity. A more detailed investigation is given in this paper.

EXPERIMENTAL

Cotton linters. A commercially purified grade[5] contained 98.5% alpha-cellulose, 0.06% ash, had a solubility of 4.1% in hot sodium hydroxide solution, and a degree of polymerization of 1200. It was treated in a laboratory Wiley mill and screened; the fraction which passed through a 100-mesh screen and was retained on a 325-mesh screen was collected.

The linters were activated with 18% sodium hydroxide (25 ml. per gram of linters) for 4 hr. at 24–26°, washed on a tared coarse fritted-glass crucible with absolute methanol until the washings were no longer alkaline to phenolphthalein, and then five successive times with anhydrous pyridine (distilled over barium oxide). Care was taken to prevent drying of the cellulose on the filter. The quantity of activated linters available for the chlorination reaction was calculated from the yield of mercerized linters.

Thionyl chloride. Practical-grade thionyl chloride was purified by three distillations over sulfur and acetone, quinoline, and linseed oil.[6] The purity (100%) was ascertained[7] by allowing samples to distill quantitatively into a known excess of sodium hydroxide solution overnight at room temperature, and back-titrating with hydrochloric acid to phenolphthalein endpoint.

Chlorination of cellulose. Anhydrous pyridine and thionyl chloride (50.0 and 10.0 moles per mole of anhydroglucose unit, respectively) were added to the activated pyridine-moist linters, with cooling, if necessary. Reaction solutions at room temperature were shaken mechanically; those at elevated temperatures were agitated in a water bath with a mercury-sealed stirrer.

The products were then suspended in water and aqueous sodium hydroxide gradually introduced to 0.15*N* strength. After standing overnight, the suspensions were neutralized with dilute sulfuric acid; the products were washed with water until the filtrates were colorless and then air-dried.

Acidic chlorite treatment. The crude chlorocelluloses were purified by a wood pulp chloriting technique.[8] Samples (6–7.5 g.) were suspended in 300 ml. of water, acidified with 0.75 ml. of glacial acetic acid, treated with 3.0 g. of sodium chlorite, heated at 70–80° for 0.5 hr., filtered, and washed with water until free of chloride ion. In two cases (B and C) the treatment was repeated twice.

Preparation of chlorocelluloses with high sulfur content. Terminating the chlorination reaction by adding the reaction mixture slowly to cold water, filtering after 1 hr., soaking overnight in half-saturated sodium bicarbonate solution, and washing until the filtrates were colorless, gave a sample (D) with a higher sulfur content.

Pouring another chlorination mixture into absolute methanol, filtering after 1 hr., soaking in methanol overnight, and then extracting the product in a Soxhlet apparatus (*in vacuo* at 30–40°) gave a sample (E) with a still higher sulfur content.

Chemical analyses. All samples were dried to constant weight *in vacuo* at 45°. Gravimetric determinations of chlorine, as silver chloride, and sulfur, as barium sulfate, were carried out by the Parr peroxide bomb method.[9]

Cuprammonium study. The viscosity of 1% solutions in cuprammonium solution (200 g. ammonia and 15.0 g. copper per liter) ranged from 1.80–3.62 centipoises for samples A, B, C, and E. After purification with chlorite, samples A′, B′, and C′ gave values ranging from 1.80–2.48 centipoises.

Hydrolysis study. Samples (0.1–0.15 g.) of chlorocelluloses were dispersed in 2.00 ml. of 72% sulfuric acid (previously cooled to 12–15°) after 2 hr. at 18–20°. Sulfur dioxide was evolved during this period. Each solution was diluted to 3% acid and boiled under reflux for 4 hr.; in some cases material precipitated on dilution and remained insoluble during subsequent boiling. The cooled and filtered solutions were neutralized with barium carbonate, refiltered, acidified with acetic acid to a litmus endpoint, and concentrated to a thick sirup (0.1–0.2 ml.) *in vacuo* at 50°.

Paper chromatography. Chromatograms of each concentrated hydrolyzate were run on Whatman No. 1 filter paper in 10:3:3 butanol-pyridine-water for 12–72 hr., and sprayed with aniline–hydrogen phthalate reagent.

Cellulose chromatographic column. A sirup (2.35 g.) concentrated from a large scale hydrolyzate of A was placed on a developer-saturated Whatman standard grade cellulose powder column (22 × 2.25 in.). The developer solution, butanol half-saturated with water, was allowed to flow at a rate of 140 ml. per hr. for the first 700 ml., then at 20–25 ml. per hr. thereafter. The effluent was collected in fractions,[10] and the fractionation followed by means of paper chromatograms. The column was finally washed with 1200 ml. of 50% ethanol. All fractions were evaporated to constant weight *in vacuo* at 50°.

Identification of glucose. Glucose was crystallized from fraction 6–1 by seeding the concentrated decolorized sirup. The isolated crystals melted at 145°, and exhibited rotation in water of $[\alpha]_D^{25}$ +52°; the phenylosazone m.p. 204–205°. A mixture of the isolated compound and D-glucose m.p. 145°.

Identification of a monochloroglucose. Crystalline fraction 2 melted sharply at 134–135°, reduced Fehling solution strongly, and formed only small quantities of silver chloride when treated with silver nitrate solution. It showed a rotation in absolute ethanol of $[\alpha]_D^{25}$ +100 ± 3° (c 0.5) and in water a rotation of $[\alpha]_D^{25}$ +43 ± 3° (c 0.5). Helferich and Brederick[11] found that 6-chloro-D-glucose melted at 135–136°, reduced Fehling solution rapidly, and gave a rotation in water of $[\alpha]_D$ +35.0°.

Anal. Calcd. for $C_6H_{11}O_5Cl$: C, 36.28; H, 5.58; Cl, 17.85. Found: C, 36.82; H, 5.85; Cl, 18.66.

RESULTS AND DISCUSSION

Upon addition of thionyl chloride to mixtures of cellulose and pyridine, an exothermal reaction takes place, and the mixture gradually darkens. This color effect increases with increasing tempera-

(4) P. Carré and P. Mauclère, *Compt. rend.*, **192**, 1567 (1931).

(5) This material was supplied by courtesy of Dr. M. Heath of The Buckeye Cellulose Corp., Memphis, Tenn. The degree of polymerization was calculated from the viscosity of a 2.5% solution in cuprammonium according to the ACS method (conversion chart 803-2M published by Hercules Powder Co.).

(6) H. R. C. Pratt, British Patent **538,028** (July 17, 1941); *Chem. Abstr.*, **36**, 1744; D. L. Cottle, *J. Am. Chem. Soc.*, **68**, 1380 (1946); L. F. Fieser, *Experiments in Organic Chemistry*, 2nd ed., especially p. 367–368, Heath, New York, 1941.

(7) G. Jander, B. Gruttner, and G. Scholz, *Ber.*, **80**, 279 (1947).

(8) P. F. Cundy and M. M. Beck, *Paper Trade J.*, **124**, 18, 36 (May 1, 1947).

(9) *Peroxide Bomb: Apparatus and Methods*, Manual No. 121, Parr Instrument Co., Moline, Ill., 1950, p 47.

(10) L. Hough, J. K. N. Jones, and W. H. Wadman, *J. Chem. Soc.*, 2511 (1949).

(11) B. Helferich and H. Brederick, *Ber.*, **60B**, 1995 (1927).

TABLE I

DESCRIPTION OF CHLOROCELLULOSES

Product	A	A′[a]	B	B′	C	C′	D	E
Reaction temp., °C.	26		50		69		25	25
Reaction time, hr.	4		4		1		4	4
Reaction ended with	NaOH		NaOH		NaOH		$NaHCO_3$	MeOH
Chlorine, %	6.12	6.96	12.90	13.50	19.66	20.16	4.42	5.23
Sulfur, %	0.70	0.13	2.30	0.30	2.04	0.93	4.86	11.65
Chlorine, D.S.[b]	0.29	0.33	0.67	0.67	1.04	1.04	0.22	0.30[c]
Sulfur, D.S.[b]	0.04	0.01	0.13	0.02	0.12	0.05	0.27	0.73[c]
Yield, based on A, B, and C, resp.		96.8		83.0		84.4		
Carbon, %		43.67		42.43		41.26		
Hydrogen, %		5.42		4.86		4.43		
Ash, %	0.09	0.08	0.08	0.20	0.10	0.27		
Material not dissolved by acid hydrolysis, %		None		4.9		8.3		

[a] A′, B′, and C′ represent A, B, C, respectively, after purification with chlorite. [b] The D.S. (degree of substitution) of the chlorocelluloses were calculated from the following simultaneous equations.

$$\text{Sulfur, \%} = 3206x/(162.1 + 46.04x + 18.45y)$$

$$\text{Chlorine, \%} = 3546y/(162.1 + 46.04x + 18.45y)$$

where y = degree of chlorine substitution, and x = degree of sulfite ester substitution (—OSOO—). [c] Treatment of sample E with 0.15N NaOH at 25° gave a 76% yield of material, analyzing for 6.44% chlorine and 0.62% sulfur, or D.S. of 0.31 and 0.04, respectively.

TABLE II

CHROMATOGRAPHIC FRACTIONATION OF HYDROLYZATE A

Fraction	R_g[a]	Dried Fraction, G.	Specific $[\alpha]_D^{25°}$	Rotation Solvent	Cl, %	Cl in Fraction, G.	Fehling's Test	$AgNO_3$ Test
1	4.3	0.0163	0	Abs. EtOH	13	0.0021	+	−
2	3.5	0.1303	+41.0 ± 0.4	Abs. EtOH	11.7	0.0152	+	−
3	2.7	0.0677	+13 ± 1	Abs. EtOH	11.2	0.0075	+	−
4	1.8	0.0402	+2 ± 1	Abs. EtOH	13.5	0.0054	+	+
5-1[b]	1.3	0.0803	−41 ± 1	H_2O	4.9	0.0039	+	−
5-2	1.3	0.0154	−3 ± 3	Abs. EtOH	6.4	0.0010	−	−
6-1[c]	1.0	1.1086	+40.2 ± 0.4	H_2O	1.48	0.0164	+	−
6-2	—	0.2071	0	EtOAc	0.4	0.0008	sl. +	−
7	Column Wash	1.6104	+2.9 ± 0.1	H_2O	2.12	0.0341	+	+
Total		3.2763				0.0864		
Residual[d]		0.594			8.9	0.053		
Original[e]		3.870			3.59	0.139		

[a] The R_g value is the rate of movement relative to the rate of movement of glucose. [b] Only a portion of fraction 5 was soluble in water (5/1), and the remainder (5/2) was soluble in ethanol. [c] Only a portion of fraction 6 was soluble in water (6/1), and the remainder (6/2) soluble in ethyl acetate. [d] This is the material (calculated by difference) remaining on the column after washing with 50% ethanol. [e] The original hydrolyzate contained 1.52 g. barium acetate and 2.35 g. hydrolyzed product.

ture. Thionyl chloride and pyridine alone also react exothermally, to form a dark solid which may be responsible for the color of the fibrous products. The chlorine content of chlorocelluloses increases with increased reaction time and temperature. Excessive reaction temperatures, however, result in the formation of black gritty nonfibrous materials.

The reaction is best terminated by treating the crude products with dilute alkali, which reduces the sulfur content to a small value. Further treatment with acidic sodium chlorite removes more sulfur and gives a lighter color to the product. The residual sulfur appears to be present as sulfurous acid esters, since sulfur dioxide is evolved upon treatment with 72% sulfuric acid or 85% phosphoric acid.

All the chlorocelluloses, except those with high chlorine content, appear to be largely soluble in cuprammonium solution. Only small amounts of material can be regenerated from these solutions, however. The viscosities of the solutions are extremely low, so it is evident that the chlorination of cellulose with thionyl chloride in pyridine is also a strong degrading action.

The chlorine in the chlorocelluloses seems to be firmly bound, as shown by acid hydrolysis; only traces of silver chloride are formed when the acidic solution is treated with silver nitrate and nitric acid. Resistance to hydrolysis increases as the chlorine

content of the chlorocelluloses is increased, as shown by a larger amount of insoluble material in the hydrolyzate. Paper chromatography of the hydrolyzates gives spots for cellobiose and glucose, and also five additional spots of higher R_f value. The intensity of the glucose spot diminishes as the chlorine content of the original chlorocellulose is increased.

The hydrolyzate of a large sample of A was fractionated on a cellulose column and the data are presented in Table II. The presence of glucose in fraction 6–1 was definitely established, amounting to 47% of the total hydrolyzate. This large amount of glucose is commensurate with the low degree of chlorine substitution (0.29) of the original sample.

The resistance of chlorocelluloses to hydrolysis is again shown by the presence of two incompletely hydrolyzed components (fraction 7 and the residual material on the column), which contained 63% of the chlorine originally present in hydrolyzate A.

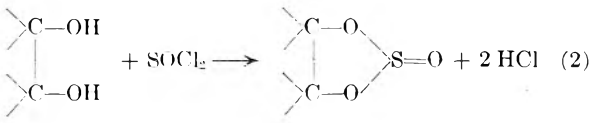
Fractions 1 through 4 possess chlorine contents slightly below the theoretical amount (17.85%) required for a monochlorohexose; they represent 22% of the chlorine originally present in the hydrolyzate. Attempts to obtain crystalline compounds from these fractions were largely unsuccessful. Gradual addition of petroleum ether (b.p. 30–60°) to an ethyl acetate solution of fraction 2 finally gave crystalline needles, analyzing for a monochlorohexose, and tentatively identified as 6-chloro-D-glucose.

Terminating the original chlorination reaction by soaking the products in either aqueous sodium bicarbonate or in methanol gave products with much higher sulfur contents (D and E in Table I). Treatment of the methanol-soaked product with dilute alkali (E) gave a product with a much reduced sulfur content; the chlorine content, when calculated as degree of substitution, showed no change. Acidification of the alkaline solution gave an evolution of sulfur dioxide. So it seems possible that the sulfur in these crude chlorocelluloses exists as cyclic sulfites, probably linked in either the 2,3- or 3,6-position, and of low stability.

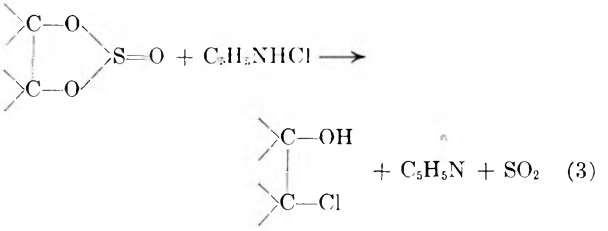
A mechanism for chlorination occurring during tosylation has been suggested by Hess and Stenzel,[12] the formation of a tosyl ester precedes chlorination, and pyridinium chloride, rather than the sulfonyl chloride is the chlorinating agent (reaction 1).

$$ROSO_2C_7H_7 + C_5H_5NHCl \longrightarrow RCl + C_5H_5NHSO_3C_7H_7 \quad (1)$$

A similar type of mechanism applied to chlorination with thionyl chloride and pyridine would suggest the formation of a sulfite ester, probably from carbons 2 and 3, or carbons 3 and 6, as a first step (Equation 2), and then a subsequent



chlorination step with pyridinium chloride, leading to the formation of either a chlorohydrin (Equation 3) or a dichloro derivative. It is interesting that



none of the fractions isolated from the chlorocellulose hydrolyzate (Table II) has sufficient chlorine to be considered a dichloro derivative; hence reaction 3 must predominate.

Several workers have reported the formation of cyclic sulfites from polyhydroxy compounds. Price and Berti[13] prepared both the cis and trans forms of the 1,2-cyclohexandiol sulfites, using a mixture of thionyl chloride and pyridine as reagent. No chlorination was reported in this reaction. De la Mare and co-workers[14] prepared 3-chlorotrimethylene sulfite, using thionyl chloride and a neutral solvent. When pyridine was used as the solvent, chlorination resulted, with the formation of a mixture of dichlorohydrins and trichloropropane. This again emphasizes the possible role of pyridinium chloride as the chlorinating agent, and the intermediate role of a sulfite ester.[15]

A second mechanism postulates the formation of an unstable chlorosulfite ester as an intermediate, and involves the attack of only one hydroxyl group (Equations 4 and 5). This has been investigated in detail for simple alcohols by Ingold and co-workers,[16] by Lewis and Boozer,[17] and by Cram.[18] Studies with stereoisomers have shown that an S_Ni mechanism gives retention of configuration, whereas inversion occurs with the S_N2 mechanism. In some cases a mixture of retention and inversion has been observed. Most of the reactions have been

(12) K. Hess and H. Stenzel, *Ber.*, **68**, 981 (1935).

(13) C. C. Price and G. Berti, *J. Am. Chem. Soc.*, **76**, 1211 (1954).

(14) P. B. D. de la Mare, W. Klyne, D. J. Millen, J. G. Pritchards, and D. Watson, *J. Chem. Soc.*, 1813(1956).

(15) A recent patent [German Patent **875,804**, *Chem. Abstr.*, **52**, 9196e] gives the preparation of pentaerythritol dichlorohydrin sulfurous acid ester from the polyol and thionyl chloride in pyridine. This compound, purified by distillation *in vacuo* to a solid, m.p. 30°, was converted by hot alcoholic potassium hydroxide to the dichlorohydrin, m.p. 75–80°.

(16) W. A. Cowdrey, E. D. Hughes, C. K. Ingold, S. Masterman, and A. D. Scott, *J. Chem. Soc.*, 1267 (1937).

(17) E. S. Lewis and C. E. Boozer, *J. Am. Chem. Soc.*, **74**, 308 (1952).

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

$$ROH + SOCl_2 \longrightarrow ROSOCl + HCl \quad (4)$$

$$ROSOCl \longrightarrow RCl + SO_2 \quad (5)$$

carried out in thionyl chloride, without the use of pyridine, and the chlorosulfite esters have shown very low stability, in contrast to the cyclic sulfite esters formed from glycols and the sulfur groupings encountered in the present work. The isolation of products D and E, with a higher degree of sulfur substitution than of chlorine substitution, seems to be evidence against the presence of chlorosulfite esters in the chlorocelluloses.

Since only three isomeric monochloroglucoses (2-, 3-, and 6-) are possible, the isolation of four isomers from a chlorocellulose hydrolyzate raises the possibility of Walden inversion on either carbon 2 or 3 to give a monochloromannose or aldose. This type of alkyl-oxygen fission can occur either by reaction 3 or reaction 5. There is also a possibility of 2,3- and 3,6-anhydro derivatives being formed, either with or without chlorine. The latter possibility is shown by the isolation of three crude fractions (5–1, 5–2, and 6–2) with low chlorine contents. Ohle and co-workers[19] have reported the isolation of a 3,6-anhydro-1,2-isopropylidene-5-*O*-tosyl-D-glucose by the action of tosyl chloride and pyridine on 1,2-*O*-isopropylidene-D-glucofuranose.

Assuming that each sulfur atom in a chlorocellulose is linked to three oxygen atoms as a sulfite ester, it can be calculated that the empirical formulas of chlorocelluloses A, B, and C contain 0.6, 0.86, and 0.77 oxygen atoms in excess of the number necessary to combine with hydrogen as hydroxyl groups. This is a further indication of the possible presence of anhydro-ring formation.

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APPLETON, WIS.

(19) H. Ohle and E. Dickhauser, *Ber.*, **58**, 2593 (1925); H. Ohle, L. von Vargha, and H. Erlbach, *Ber.*, **61**, 1211 (1928).

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, THE UNIVERSITY, ABERDEEN]

Acid-Catalyzed Rearrangements in the Nepenthone Series

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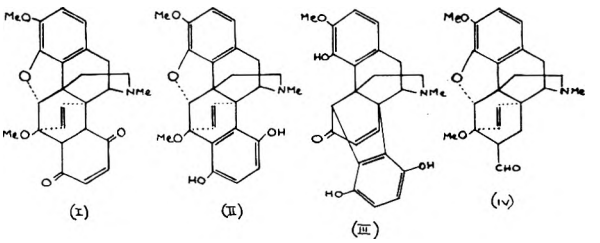
Thebaine on condensation with phenyl vinyl ketone affords a Diels-Alder adduct, nepenthone,[1] which has been rearranged in acid solution. Reduction affords nepenthol, which has been dehydrated to an olefin, nepenthene, and both nepenthol and nepenthene have been rearranged to flavonepenthone, an analog of flavothebaone. Mechanisms are advanced for the changes reported.

Thebaine, on condensation with *p*-benzoquinone affords the adduct (I)[2,3] which can be isomerized by acids to the quinol (II), and this on heating with hydrochloric acid undergoes a concerted opening of the cyclic ether and 1:2-shift of the quinol nucleus, giving flavothebaone[3–5] which has the structure (III).[4,5] During work on the structure of the last named base attempts were made to effect a similar rearrangement in somewhat simpler compounds.



(I) (II) (III) (IV)

The simplest thebaine adduct reported in the literature is thebaine-acrolein (IV),[6] but attempts to rearrange this in acid solution led to the immediate production of black intractable materials. The adduct of thebaine and phenyl vinyl ketone (V) was obtained from the two components in excellent yield, and was subjected to a variety of transformations. On account of the extremely

(1) K. W. Bentley and J. C. Ball, *Chem. & Ind. (London)*, 1428 (1956).

(2) W. Sandermann, *Ber.*, **71**, 648 (1938).

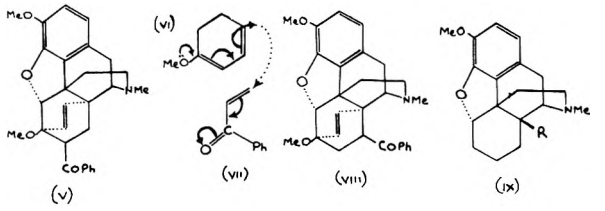
(3) C. Schöpf, K. von Gottberg, and W. Petri, *Ann.*, **536**, 216 (1938).

(4) K. W. Bentley, J. Dominguez, and J. P. Ringe, *Chem. & Ind. (London)*, 1353 (1956); *J. Org. Chem.*, **21**, 1348 (1956); **22**, 409, 418, 422, 424, 599 (1957).

(5) J. Meinwald and G. A. Wiley, *Chem. & Ind. (London)*, 957 (1956); *J. Am. Chem. Soc.*, **79**, 2569 (1957).

(6) S. I. Kaneveskaya and S. F. Mitryagina, *J. Gen. Chem. U.S.S.R.*, **17**, 1023 (1947).

cumbersome nature of the systematic names for the Diels-Alder adducts of thebaine in general and of the phenyl vinyl ketone adduct in particular this



substance was assigned the trivial name "nepenthone" in order to simplify subsequent discussion of the results.

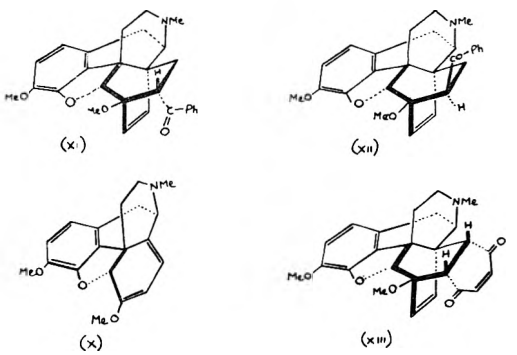
The adduct was formulated as V rather than as VIII on consideration of the potential electronic shifts shown in VI and VII, in which electrons are most available at $C_{(14)}$ of thebaine and the terminal carbon atom of the vinyl group in the unsaturated ketone is electron-deficient. The adduct appeared to consist exclusively of one isomer, and a careful examination of the mother liquors failed to reveal any of the isomeric VIII. However, in order to place any interpretation of the complex reactions of nepenthone on a sure foundation it soon became essential to have definite evidence on this structural point. The assignment of structure V to nepenthone was strongly supported by the basic strengths of the adduct, its derivatives, and several other bases of the morphine-thebaine group. The basic strengths of the compounds examined were found to be quite sharply divided into three groups (see table) as follows: (a) Bases of the type IX, where R = H or OH, with *p*K about 6.70; (b) Bases of the nepenthone series, where on the basis of structure V R = CH—CH_2, with *p*K about 5.80; (c) Bases such as the adduct I where R = CH—C=O or O—C=O, with *p*K about 5.0.

The marked difference in the basic strengths of the bases of groups (a) and (c) is due partly to steric hindrance at the nitrogen atom by the substituent at $C_{(14)}$ and partly to interaction between the nitrogen atom and the unsaturated carbonyl group suitably placed, in space. Adducts such as nepenthone, thebaine-acrolein and, thebaine–methyl vinyl ketone show a much smaller reduction in basic strength, indicating that the carbonyl group is further removed from the nitrogen atom than it is in, say, thebainequinone (I), and the possibility that nepenthone has the structure (VIII) may thus be discounted. The potentiometric titrations by which the basic strengths were determined provided a very accurate method of determination of the molecular weights of the bases, and this proved of great value in the investigation. The stereochemistry of nepenthone is of importance in a consideration of the transformations of this base. Addition of the dienophile to thebaine would be expected to occur on the least hindered side of the molecule (X) and to give the *endo* product XI, rather than

TABLE I

Base	*p*K	Mol. Wt., Found	Mol. Wt., Calcd.
Morphine	6.85	285	285
Thebaine	6.80	313	311
14-Hydroxycodeinone	6.65	310	313
Codeine	6.60	300	299
Nepenthone	5.80	443	443
Nepenthol	5.80	443	445
Flavonepenthone	5.80	417	413
Thebaine-acrolein	5.80		
Thebaine–methyl vinyl ketone	5.80	381	381
Dihydrothebaine-quinone	5.25	419	421
14-Acetoxycodeinone	5.25	358	355
Thebainequinone	4.90	—	—
Dimethylthebaine-maleate	4.80	—	—

the epimeric *exo* compound (XII), as the production of the former would involve the greatest overlap of the two unsaturated groups during the addition process. In support of this view it was found impossible to hydrogenate the double bond of nepenthone, as would be expected on the basis of the structure (XI), in which the ethylenic bridge is shielded by the other parts of the molecule, whereas in the epimeric structure (XII) such screening is not present. It may be noted that the ethylenic bridge in thebaine quinone, assigned the structure (XIII) by Schöpf,[8] is unreducible. Two oximes, presum-

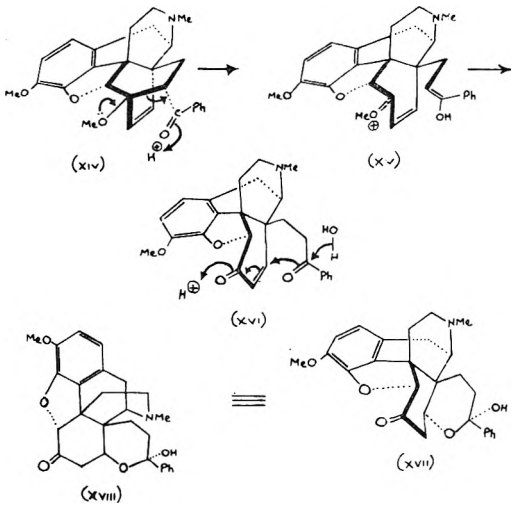


ably geometrical isomers, can be prepared from nepenthone.

Nepenthone was found to be stable in dilute acids, being recovered unchanged after boiling for four hours with 5% hydrochloric acid, but on heating with concentrated hydrochloric acid and glacial acetic acid at 100° (the conditions of the thebainequinol→flavothebaone transformation) it afforded two bases, neonepenthone-A and neonepenthone-B, in yields of approximately 25% and 10%, respectively.

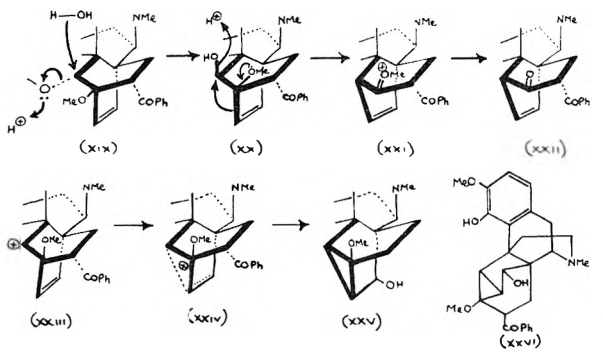
Neonepenthone-A, m.p. 135°, is nonphenolic and has the composition $C_{27}H_{29}O_5N$, *i.e.* nepenthone $C_{28}H_{29}O_4N$ − CH_2 + H_2O. The infrared spectrum shows a hydroxyl band at 3430 cm.$^{-1}$ (2.94μ), and one carbonyl band at 1717 cm.$^{-1}$

(5.83μ), indicating that the compound contains only a saturated ketone system.



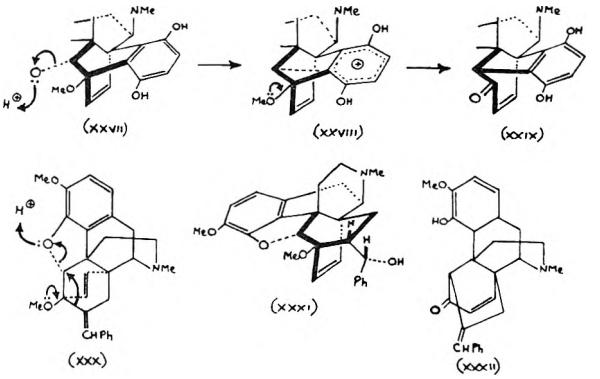
Clearly the transformation involved in the production of neonepenthone-A from nepenthone is different from the flavothebaone rearrangement, and the processes XIV → XVI might be initiated by attack of the aromatic carbonyl group of nepenthone by a proton. This is in essence an acid-catalyzed dealdolization, and the product may well exist in the acid mixture as XIV, which, during isolation and purification, could suffer addition of the aromatic carbonyl group to the $\alpha\beta$-unsaturated ketone system, XVI → XVII. This would lead to the formulation of neonepenthone-A as the saturated ketone (XVIII). Only in this way can the single carbonyl infrared absorption at 1717 cm.$^{-1}$ (5.83μ) be rationally accounted for. Nothing further is known about neonepenthone-A.

Neonepenthone-B, m.p. 275°, obtained in about 10% yield, is phenolic and has the composition $C_{28}H_{31}O_5N$ (mol. wt. calcd. 461, found 464) *i.e.* nepenthone $C_{28}H_{29}O_4N$ + H_2O; the infrared spectrum contains a hydroxyl band at 3470 cm.$^{-1}$ (2.85μ) and a carbonyl band at 1670 cm.$^{-1}$ (5.98μ). One simple explanation of these properties would be that a hydrolytic fission of the oxide bridge of nepenthone had taken place as depicted in the partial structures XIX → XX, but it seems highly unlikely that this explanation is correct, as XX, under the strongly acid conditions, would be expected to undergo the geometrically favorable 1:2-shift of the ethylenic bridge, giving finally the ketone XXII.



A more plausible process is depicted in the partial-structures (XXIII) → (XXV), in which the classical carbonium ion resulting from opening of the oxide ring becomes the non-classical bridged ion (XXIV), which then adds a hydroxyl group at the least hindered position giving XXV. On the basis of these changes neonepenthone-B may be represented as XXVI. Zeisel determination shows the presence of only one methoxyl group in neonepenthone-B, whereas, the structure XXVI contains two such groups; however the methoxyl group of XXV, which is highly hindered might not be affected under the conditions normally used in the Zeisel determination, though the low methoxyl value may be due to solubility reasons.[7]

It was inferred from the failure of the acid treatment of nepenthone to give an analog of flavothebaone that the production of the latter from thebainequinol involves the participation of the aromatic nucleus in a nonclassical ion as shown in the partial-structures XXVII → XXVIII → XXIX, and that when formation of such an ion cannot take place, the reaction can take a different course with the participation of the ethylenic bridge instead, XXIII → XXV. Accordingly we



felt that it should be possible to prepare an analog of flavothebaone from the styrene (XXX).

Nepenthone on reduction with aluminium isopropoxide or with sodium borohydride affords the related alcohol, nepenthol. Models indicate that on steric grounds the reduction will afford the epimer (XXXI). Unlike nepenthone, nepenthol is rearranged in 90% yield in hot concentrated hydrochloric acid and glacial acetic acid solution, giving a new base, named flavonepenthone by analogy with flavothebaone, although the characteristic yellow color of the last named base is not observed.

Color reaction with diazotized sulfanilic acid and with quinone chloroimine, together with the

(7) Phenyldihydrothebaine derivatives consistently give methoxyl values for one methoxyl group less than actually present under the normal conditions of the Zeisel determination, presumably for solubility reasons [L. F. Small, L. J. Sargent, and J. A. Bralley, *J. Org. Chem.*, 12, 839 (1947)].

alkali-solubility of flavonepenthone clearly demonstrate that this base is phenolic, and in confirmation of this a monoacetyl derivative and a monomethyl ether have been prepared. Analyses indicate the composition $C_{27}H_{27}O_3N$, showing that H_2O as well as CH_2 is lost during the rearrangement, and in agreement with this the ultraviolet absorption spectrum is styrenoid; the spectrum also shows the long wave length band with λ_{max} 3,400 A and ϵ_{max} 2,500, which is an outstanding feature of the ultraviolet spectrum of flavothebaone. The infrared spectrum of flavonepenthone shows an $\alpha\beta$-unsaturated carbonyl absorption band at 1675 cm.$^{-1}$ (5.96μ), which is shifted to 1710 cm.$^{-1}$ (5.85μ) when the base is reduced to a tetrahydro derivative with sodium amalgam; the styrenoid ultraviolet absorption also disappears during this reduction.

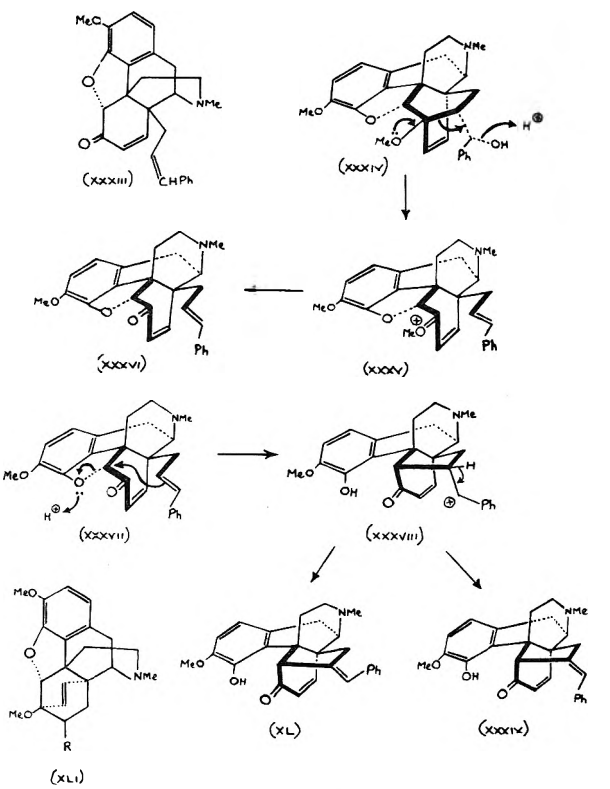
All these properties clearly point to the structure (XXXII) for flavonepenthone, which could arise as a result of the dehydration of nepenthol (XXXI) to the olefin (XXX) followed by the predicted 1:2-shift of the PhCH=C—CH_2-bridge. The similarity of the ultraviolet spectra of flavonepenthone and flavothebaone in the region 3,200–3,600 Å is, as already indicated,[4] strong support for the view that the long wave length band common to these spectra is due to perturbation of the orbitals of the cyclohexenone system by the other unsaturated group (styrene and quinol, respectively) present in the molecules of these bases.

The separation of the rearrangement of nepenthol to flavonepenthone into two distinguishable and perhaps non-simultaneous steps led logically to an attempt to prepare the olefin (XXX) and realize the 1:2-shift of the bridge as a separate reaction. The dehydration of nepenthol was accomplished by heating with anhydrous formic acid at 100° for sixteen hours, and the new base, nepenthene, so obtained was found to give flavonepenthone when heated with concentrated hydrochloric acid. However, the dehydration is not the simple process envisaged, since nepenthene shows a prominent unsaturated carbonyl absorption band at 1663 cm.$^{-1}$ (6.01μ) in its infrared spectrum. The analytical data indicate a composition $C_{27}H_{27}O_3N$ isomeric with that of flavonepenthone. The ultraviolet spectrum is styrenoid, and this together with the absence of hydroxyl absorption bands in the infrared spectrum shows that dehydration has certainly occurred. The oxide ring is still intact since nepenthene is non-phenolic. Catalytic reduction involves saturation only of the styrenoid double bond, giving dihydronepenthene, whereas sodium amalgam reduction gives only a non-crystalline product in which the carbonyl group is saturated as shown by the infrared spectrum which contains only one carbonyl absorption band, and that at 1703 cm.$^{-1}$ (5.86μ) compared with 1663 cm.$^{-1}$ (6.01μ) in nepenthene.

Only the structure XXXIII appears satisfactorily to account for these facts. The dehydration of nepenthol to nepenthene may be depicted as in the structures XXXIV→XXXVI. The conversion of nepenthene into flavonepenthone presents no real problem, and may be represented as in XXXVII→XXXIX. On steric grounds there seems little to choose between the structures XXXIX and XL for flavonepenthone, and under acid conditions interconversion through an ion such as XXXVIII is possible. If anything XXXIX involves the least steric compression of groups.

Attempts to degrade nepenthone and flavonepenthone proved fruitless. No quaternary salts or *N*-oxides could be formed, presumably as a result of steric hindrance at the nitrogen atom; no adduct could be prepared from thebaine methiodide and phenyl vinyl ketone. Neither double bond in flavonepenthone could be attacked with peracids or with alkaline hydrogen peroxide.

Thebaine has also been condensed with methyl vinyl ketone and with acrylonitrile to give the adducts (XLI, R = $CO.CH_3$) and (XLI, R = CN), respectively; the second of these has also been prepared by the dehydration of the oxime (XLI, R = CH=N.OH) of the acrolein adduct IV.



EXPERIMENTAL

Phenyl vinyl ketone. The method described by Mannich[8] was modified as follows. Acetophenone (80 g.), powdered paraformaldehyde (20 g.), and dimethylamine hydrochloride (55 g.) were heated together under reflux in ethanol (100 ml.). After 10 min. a clear solution was obtained, and after 0.5 hr. 80 ml. of ethanol were removed by distillation

(8) C. Mannich and G. Heilner, *Ber.*, **55**, 356 (1922).

Acetone (300 ml.) was added to the hot residue and the resulting solution transferred at once to a beaker. Colorless crystals of ω-dimethylaminopropiophenone hydrochloride, m.p. 156° (98 g.) separated rapidly. The salt was collected and dried and steam distilled until about two liters of distillate had been collected. A small amount of quinol was added to the distillate which was then extracted with ether. The ether extract was dried over sodium sulfate and evaporated, and the residue distilled, when 21 g. of phenyl vinyl ketone, b.p. 98–97°/15 mm., was obtained.

Nepenthone (V). Freshly distilled phenyl vinyl ketone (26 g.) together with a small amount of quinol, was added to a solution of thebaine (60 g.) in boiling benzene (240 ml.), and the resulting solution boiled under reflux for 2 hr. The benzene was removed by distillation *in vacuo*. Hot alcohol (450 ml.) was added and the solution allowed to cool, when *nepenthone* separated as irregular plates, m.p. 155°, after recrystallization from ethanol. Yield 60 g. $[\alpha]_D^{20}$ −232° ($CHCl_3$, *c* 1.09). λ_{max} 2,400 Å; ϵ_{max} 2,630.

Anal. Calcd. for $C_{28}H_{28}O_4N$: C, 75.8; H, 6.6; (2)OMe, 14.4. Found: C, 75.6; H, 6.4; OMe, 14.4%.

In an attempt to prepare a methiodide of nepenthone thebaine methiodide was recovered unchanged after heating under reflux with phenyl vinyl ketone in chloroform for 4 hr.

Oximes. Nepenthone (10 g.), hydroxylamine hydrochloride (10 g.), water (100 ml.), and ethanol (10 ml.) were heated together under reflux for 5 hr. Ammonia solution was added to the cooled mixture and the precipitated material triturated with ether. The resulting solid matter was collected, dissolved in 2-ethoxyethanol (150 ml.), and the solution was filtered, evaporated to about 70 ml., and diluted with water (20 ml.). On cooling 5.7 g. of crystalline material was obtained, and this was recrystallized from 80% 2-ethoxyethanol, when *nepenthoxime*-I was obtained as colorless prisms, m.p. 270°, $[\alpha]_D^{22}$ −254° ($CHCl_3$, *c* 0.83).

Anal. Calcd. for $C_{28}H_{30}O_4N_2$: C, 73.3; H, 6.6; N, 6.1. Found: C, 73.3; H, 6.7; N, 6.2%.

Evaporation of the mother liquors from the isolation of nepenthoxime-I afforded a viscous gum, which crystallized readily from acetone. Recrystallization from acetone afforded 3.1 g. of *nepenthoxime-II*, m.p. 188°, $[\alpha]_D^{21}$ −242° ($CHCl_3$, *c* 1.09). This oxime was much more soluble than nepenthoxime-I in organic solvents.

Anal. Calcd. for $C_{28}H_{30}O_4N_2$: C, 73.3; H, 6.6; N, 6.1. Found: C, 73.1; H, 6.6; N, 5.9%.

Acid-catalyzed rearrangement of nepenthone: neonepenthone-A and neonepenthone-B. Nepenthone (10 g.) was dissolved in glacial acetic acid (30 ml.) and concentrated hydrochloric acid (30 ml.), and the mixture was heated on the steam bath for 6 hr., during which time it became deep green. Removal of volatile material *in vacuo*, followed by treatment of the resulting sirup with methanol afforded a colorless crystalline salt (2.90 g.), which was collected and dissolved in water and the solution treated with hot aqueous sodium carbonate, when *neonepenthone-A* was obtained. This was recovered as colorless rods, m.p. 135°.

Anal. Calcd. for $C_{27}H_{29}O_5N$: C, 72.5; H, 6.6; (1)OMe, 6.9%; M.W. 447. Found: C, 72.5; H, 6.6; OMe, 7.4; mol. wt. (potentiometric titration), 442.

The base was appreciably soluble in organic solvents, and gave negative color reactions with diazotized sulfanilic acid and quinone chloroimine.

The mother liquors from the isolation of neonepenthone-A were basified with ammonia and diluted with water. The precipitated material crystallized on trituration with ether. When this material was recrystallized from 2-ethoxyethanol (50 ml.) 1.0 g. of *neonepenthone*-B, m.p. 273°, was obtained.

Anal. Calcd. for $C_{28}H_{31}O_5N$: C, 72.8; H, 6.7; (2)OMe, 13.5%; M.W., 461. Found: C, 72.9; H, 6.7; OMe, 7.8%; mol. wt. (potentiometric titration), 464.

Unlike neonepenthone-A this base is sparingly soluble in organic solvents and gives a deep red color on coupling with diazotized sulfanilic acid in alkaline solution and gives a deep green color with quinone chloroimine.

Nepenthol. (a) Nepenthone (64 g.) was heated with aluminum isopropoxide (120 g.) in boiling 2-propanol (320 ml.) with mechanical stirring. The mixture was slowly distilled through a fractionating column in such a way that a distillate was collected at the rate of about five drops per minute. Distillation was continued until the distillate no longer gave a precipitate with 2,4-dinitrophenylhydrazine hydrochloride solution (about 2.5 hr.). The reaction mixture was then poured into ice water (1500 ml.) containing concentrated hydrochloride acid (200 ml.). An excess of Rochelle salt solution was then added, and the mixture basified with aqueous sodium hydroxide, and the precipitated organic base extracted with chloroform. Evaporation of the extract and recrystallization of the residue from 2-ethoxyethanol gave 54.5 g. of nepenthol as colorless rods, m.p. 210°, $[\alpha]_D^{21}$ −136° ($CHCl_3$, *c* 1.25). λ_{max} 2400, 2890 Å; ϵ_{max} 6,310, 1,738.

Anal. Calcd. for $C_{29}H_{31}O_4N$: C, 75.4; H, 7.1. Found: C, 75.0, 75.8; H, 7.1, 7.1%.

(b) Sodium borohydride (0.40 g.) in methanol (10 ml.) was added to a suspension of nepenthone (5 g.) in cold methanol (100 ml.). When the mixture was heated to the boiling point and allowed to cool to room temperature nepenthol (1.5 g.), was obtained, melting point and mixed melting point with nepenthol prepared as in (a), 210°, $[\alpha]_D^{18}$ −136° ($CHCl_3$, *c* 0.87).

The *acetyl derivative* was obtained by the usual acetic anhydride/pyridine treatment, and on recrystallization from methanol was recovered as prisms m.p. 153°.

Anal. Calcd. for $C_{30}H_{33}O_5N$: C, 73.9; H, 6.8; OAc, 8.8. Found: C, 73.6; H, 6.9; OAc, 9.3%.

Nepenthene (XXXI). Nepenthol (1.94 g.) was dissolved in 98–100% formic acid (20 ml.) and the mixture was heated under reflux for 16 hr. The resulting solution was diluted with water, made alkaline with ammonia, and the white precipitate collected and recrystallized from a methanol/2-ethoxyethanol mixture, when *nepenthene* (1.38 g.) was obtained as needles m.p. 225°, $[\alpha]_D^{24}$ +87° ($CHCl_3$, *c* 0.41), λ_{max} 2400, 2860 (inflexion) Å; ϵ_{max} 24,000, 7,080.

Anal. Calcd. for $C_{27}H_{27}O_3N$: C, 78.4; H, 6.6; (1)OMe, 7.5. Found: C, 78.7; H, 6.5; OMe, 7.8%.

The base was insoluble in alkali, and gave no indication of coupling with diazotized sulfanilic acid.

Dihydronepenthene. Nepenthene (3.0 g.) in glacial acetic acid (30 ml.) was shaken under hydrogen at room temperature and pressure in the presence of platinum oxide (0.1 g.). Absorption of hydrogen was slow, and a further 0.1 g. of platinum oxide was added after 2.5 hr. After 6 hr. one mole of hydrogen had been absorbed, and the rate of hydrogenation slowed down, but the reaction did not cease entirely. The solution was freed from catalyst, evaporated *in vacuo* and the residue was dissolved in water and the solution made alkaline with ammonia. The precipitated base was collected and recrystallized from a methanol/2-ethoxyethanol mixture, when *dihydronepenthene* was obtained as plates, m.p. 179°, λ_{max} 2750 Å; ϵ_{max} 3,550.

Anal. Calcd. for $C_{27}H_{29}O_3N$: C, 78.0; H, 7.0. Found: C, 77.7; H, 7.1%.

Flavonepenthone (XXXII). (a) Nepenthol (51 g.) was dissolved in hot glacial acetic acid (150 ml.), and concentrated hydrochloric acid (150 ml.) added. The mixture was then heated on the steam bath for 4 hr.; after 1 hr. a pale yellow crystalline solid separated. The mixture was cooled and the solid matter collected (43.5 g.) and washed with concentrated hydrochloric acid. Flavonepenthone hydrochloride thus obtained had m.p. over 300°.

Anal. Calcd. for $C_{27}H_{27}O_3N.HCl.{}^1/_2H_2O$:C, 70.6; H, 6.4; Cl, 7.7. Found: C, 70.4; H, 6.4; H, 7.8%.

The free base was recovered from the hydrochloride by treating the salt with hot aqueous sodium carbonate. Recrystallization from 2-ethoxyethanol afforded flavonep-

enthone as colorless rods m.p. 263°, $[\alpha]_D^{18}$ +33° ($CHCl_3$-*c* 0.65) λ_{max} 2500, 3400 Å: ϵ_{max} 21,880, 2,500.

Anal. Calcd. for $C_{27}H_{27}O_3N$: C, 78.3; H, 6.6%; M.W., 413. Found: C, 78.2; H, 6.5%; mol. wt. (potentiometric titration), 417.

The base was readily soluble in alkalis, and the solution gave a deep red color on treatment with diazotized sulfanilic acid. It gave a deep green color with quinone chloroimine, a green color with ferric chloride, and an orange color with concentrated sulfuric acid.

(b) Nepenthene (0.81 g.) was dissolved in a mixture of glacial acetic acid (5 ml.) and concentrated hydrochloric acid (5 ml.) and the mixture heated on the steam bath for 6 hr. Water was added and the solution made alkaline with ammonia, which precipitated the free base. This was collected and recrystallized from 2-ethoxyethanol when flavonepenthone was obtained as colorless rods m.p. 263° alone or mixed with a specimen prepared as in (a).

Acetylflavonepenthone. Flavonepenthone (1.0 g.) was acetylated with acetic anhydride (1 ml.) in pyridine (10 ml.). The product was isolated in the usual way and recrystallized from ethanol, when *acetylflavonepenthone* was obtained as colorless rods m.p. 268°, mixed m.p. with flavonepenthone 235°.

Anal. Calcd. for $C_{29}H_{29}O_4N$: C, 76.5; H, 6.4. Found: C, 76.4; H, 6.3%.

Flavonepenthone methyl ether. Flavonepenthone hydrochloride (5 g.) was suspended in methyl sulfate (17 ml.) and a solution of sodium hydroxide (6.25 g.) in water (20 ml.) added slowly with vigorous stirring. When all the alkali had been added the mixture was heated to the boiling point to decompose excess of methyl sulfate, 10 ml. of 30% sodium hydroxide solution being added. The mixture was cooled and the insoluble material collected and crystallized and recrystallized from methanol, when *flavonepenthone* methyl ether was obtained as colorless needles m.p. 140°, $[\alpha]_D^{20}$ −4° ($CHCl_3$, *c* 0.46).

Anal. Calcd. for $C_{29}H_{29}O_3N$: C, 78.6; H, 6.8; (2)OMe, 14.6. Found: C, 78.5; H, 6.8; OMe, 14.7%.

The base was insoluble in alkali and gave no color with diazotized sulfanilic acid, quinone chloroimine, or ferric chloride.

Tetrahydroflavonepenthone. Flavonepenthone hydrochloride (10 g.) was suspended in boiling ethanol (250 ml.) and treated with 510 g. of 2% sodium amalgam. The reaction mixture was kept for 4 hr. under reflux on the steam bath. Within the first few minutes the solid dissolved, and a solid subsequently separated but later dissolved again. The following day the alcoholic solution was diluted with water (1500 ml.), the mercury removed and the mixture extracted with chloroform. (300 ml.). Evaporation of the extract gave an amorphous solid (8 g.) which readily dissolved in methanol. After several days the methanol solution deposited 3.3 g. of crystalline material. This was collected and recrystallized from methanol, when *tetrahydroflavonepenthone* was obtained as colorless prisms, m.p. 100°, $[\alpha]_D^{20}$ −162° ($CHCl_3$, *c* 0.71), λ_{max} 2830 Å; ϵ_{max} 1,778.

Anal. Calcd. for $C_{27}H_{31}O_3N.CH_3OH$: C, 74.8; H, 7.8. Found: C, 74.7; H, 8.0%.

Found (dried at 160°/0.05 mm.): C, 77.4; H, 7.6%.

Thebaine–methyl vinyl ketone adduct (XLI, R = $CO.CH_3$). A solution of thebaine (15 g.) in methyl vinyl ketone (95 g.) was heated under reflux for 18 hr. and the excess of methyl vinyl ketone removed by distillation *in vacuo*. The product crystallized from methanol (60 ml.) as irregular plates (17 g.) m.p. 120°, but it contained rubbery impurities which were best removed by dissolving the product in hot concentrated hydrochloric acid, diluting with water, and filtering from black tarry matter. Recovery of the base from the acid solution followed by crystallization from ethanol afforded *thebaine–methyl vinyl ketone* as colorless plates m.p. 122°.

Anal. Calcd. for $C_{24}H_{27}O_4N$: C, 72.3; H, 7.2. Found: C, 72.5; H, 7.1%.

Dehydration of thebaine-acrolein oxime. Thebaine-acrolein oxime[6] (3 g.) in chloroform solution (20 ml.) at 0° was treated with ice cold thionyl chloride (3 ml.) in chloroform (10 ml.). The resulting yellow solution was evaporated *in vacuo* at room temperature and the residue was shaken with chloroform and aqueous ammonia. Separation of the chloroform and evaporation of the solvent gave a residue that was crystallized from methanol, when *thebaine-acrylonitrile* (2.25 g.) was obtained as colorless plates m.p. 177°, raised to 185° by recrystallization.

Anal. Calcd. for $C_{22}H_{24}O_3N_2$: C, 72.4; H, 6.7; N, 7.5. Found: C, 72.4; H, 6.9; N, 7.3%.

Condensation of thebaine and acrylonitrile. Thebaine (10 g.) was heated under reflux with freshly distilled acrylonitrile (50 ml.) containing a small quantity of quinol, for 8 hr. The excess of acrylonitrile was removed by distillation *in vacuo* and the residue crystallized from ethanol, when thebaine-acrylonitrile was obtained as plates m.p. 177°. The identity of this material with that prepared by the dehydration of thebaine–acrolein oxime was demonstrated by the identity of their infrared spectra.

Acknowledgment. One of us (J.C.B.) wishes to thank the Department of Scientific and Industrial Research for a maintenance grant.

ABERDEEN, SCOTLAND

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, THE UNIVERSITY, ABERDEEN]

Base-Catalyzed Rearrangements in the Nepenthone Series

K. W. BENTLEY AND J. C. BALL

Received January 20, 1958

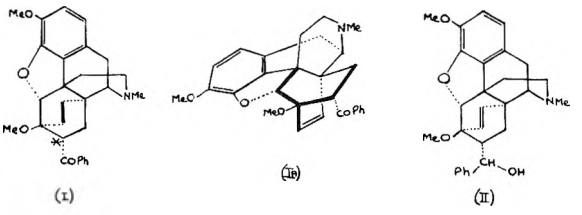
The thebaine–phenyl vinyl ketone adduct, nepenthone, on heating with alkali is isomerized to isonepenthone. This is formulated as a molecular rearrangement of a type hitherto unobserved in the morphine series. Isonepenthone may be hydrolyzed to ψ-nepenthone, and has been related through isonepenthol and ψ-nepenthol to flavonepenthone. Two other products of base-catalyzed transformation of nepenthone, both of which yield ψ-nepenthone on hydrolysis, are reported and formulated.

Thebaine condenses readily with phenyl vinyl ketone to give the adduct (I), named nepenthone[1,2] to facilitate discussion. This adduct, which is formulated as the *endo*-compound (Ia), was heated

(1) K. W. Bentley and J. C. Ball, *Chem. & Ind. (London)*, 1428 (1956).

(2) K. W. Bentley and J. C. Ball, *J. Org. Chem.*, **23**, 1720 (1958).

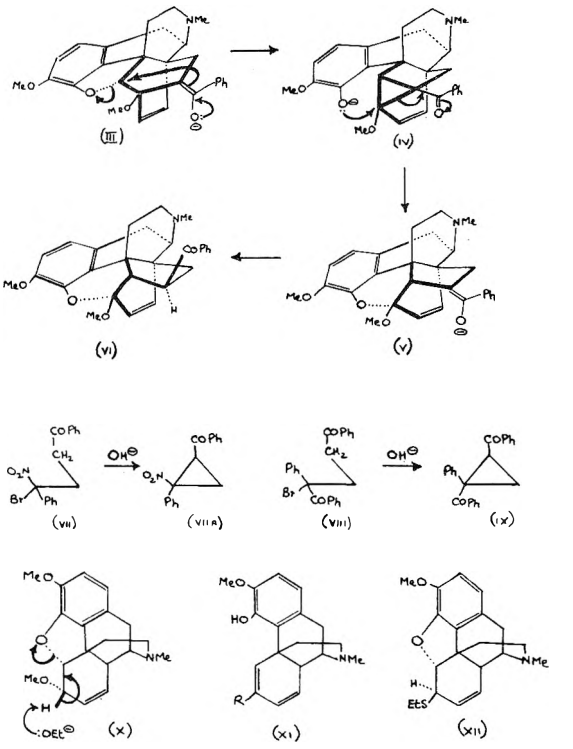
with alkali in an attempt to bring about epimerization at the asterisked carbon atom to the *exo*-compound. In the initial experiments poor yields of two substances were obtained after four hours heating under reflux with 5% methanolic sodium hydroxide. In a later experiment however, crystallization occurred in the boiling solution after ten minutes, and a 75% yield of a third base, isonepenthone, was obtained. Subsequently this base could always be obtained in good yield by seeding the reaction mixture after five or ten minutes' treatment with alkali.



Isonepenthone is isomeric with nepenthone, is non-phenolic, and still contains the benzoyl group (infrared band at 1677 cm.$^{-1}$, 5.96μ). The benzoyl group is essential for this change, since the secondary alcohol, nepenthol (II), derived from nepenthone does not undergo a similar change on heating with alkalis. Isonepenthone may, however, be converted into a secondary alcohol, isonepenthol, isomeric with nepenthol, by reduction with sodium borohydride.

Isonepenthone differs from nepenthone in being extremely sensitive to acid hydrolysis. Whereas the latter is recovered unchanged after boiling for four hours with 5% hydrochloric acid, the former is very rapidly hydrolyzed by this reagent, and even by cold acetic acid or picric acid, to ψ-nepenthone, $C_{27}H_{27}O_4N$, and this difference in the behavior of the two isomers makes it very unlikely that isonepenthone is the expected epimer of nepenthone. This possibility will, however, be considered in detail later.

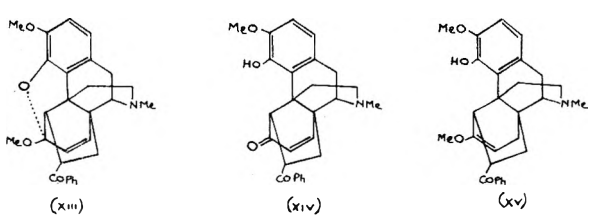
As nepenthol is stable to base undoubtedly the first stage in the conversion of nepenthone into isonepenthone is the removal of a proton from the PhCOCH group, with the formation of the enolate ion (III). A reasonable second step is then the displacement of the phenate ion with the formation of the cyclopropane ring, as in III → IV. Analogies for this may be cited in the formation of a cyclopropane ring with the displacement of a bromide ion from the compounds VII and VIII, which give the compounds VIIA and IX, respectively on treatment with alkali[3,4] and the formation of thebainone $\Delta^{5,7}$-enol methyl ether (XI, R = OMe) from codeine methyl ether (X) on treatment with sodium



ethoxide[5] and of β-ethylthiocodide (XI, R = SEt) on treatment of α-ethylthiocodide (XII) with alkali.[6,7]

If this process is involved, however, some subsequent changes must take place, as isonepenthone in non-phenolic. A plausible further step is the opening of the cyclopropane ring by attack by the phenate ion, as in IV → V, giving the enolate ion V, which would be discharged under reversible conditions to give the most stable epimer of the ketone. Examination of models shows that the non-bonded interactions are least in the epimer VI; a model of this substance can be constructed without strain, and this is assumed to be the structure of isonepenthone. All the reactions may be regarded as reversible, but presumably isonepenthone is less strained than nepenthone; in any case it is removed from the reaction mixture by crystallization, and thus the reactions would proceed in one way only.

The structure VI ≡ XIII represents isonepenthone as the mixed acetal of an α,β-unsaturated



(3) C. F. H. Allen and H. P. Bridges, *J. Am. Chem. Soc.*, **51**, 2151 (1929).

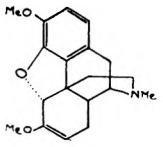
(4) C. F. H. Allen and W. E. Barker, *J. Am. Chem. Soc.*, **54**, 736 (1932).

(5) L. F. Small and G. L. Browning, *J. Org. Chem.*, **3**, 618 (1939).

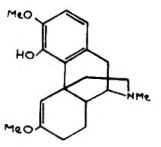
(6) R. Pschorr, *Ann.*, **373**, 1 (1910).

(7) D. E. Morris and L. F. Small, *J. Am. Chem. Soc.*, **56**, 2159 (1934).

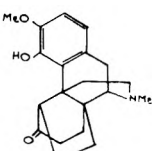
ketone, and acid hydrolysis would be expected to proceed readily, as is actually observed, to give the phenolic α,β-unsaturated ketone, ψ-nepenthone (XIV). A model of the structure VI shows that the double bond of isonepenthone is less hindered than that of nepenthone, and whereas the latter is resistant to hydrogenation, isonepenthone can be reduced in ethanolic solution at 50° to dihydroisonepenthone, which is phenolic. In VI ≡ XII the double bond is part of an allylic ether system, which could suffer 1:4-reduction to give the phenol XV, which structure is proposed for dihydroisonepenthone; the double bond of XV, being part of an enol ether system, would be expected to resist further reduction. Bases in the morphine series in which the oxide ring is part of such an allylic ether system are readily reduced with the opening of the oxide ring and the production of phenols, *e.g.* dihydrothebaine (XVI) can be re-



(XVI)



(XVII)



(XVIII)

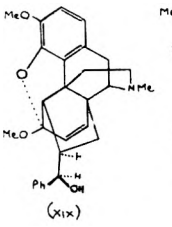
duced to dihydrothebainone Δ^5-enol methyl ether (XVII).[8]

As formulated in XV dihydroisonepenthone is an enol ether and, like dihydrothebainone Δ^5-enol methyl ether (XVII), would be expected to be very readily hydrolyzed to the corresponding ketone, and in fact on treatment with dilute acid this base affords dihydro-ψ-nepenthone (XVIII), also obtainable by the catalytic reduction of ψ-nepenthone (XIV). This ketone, as expected on the basis of the structure XVIII, shows bands at 1703 cm.$^{-1}$ (5.86μ) and 1668 cm.$^{-1}$ (6.0μ) in the infrared spectrum, attributable to the saturated and aromatic carbonyl groups, respectively.

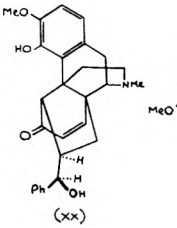
Isonepenthone on reduction with sodium borohydride affords isonepenthol (XIX), and this, like the parent ketone, is very readily hydrolyzed by acids, giving ψ-nepenthol (XX), also obtainable by the sodium borohydride reduction of ψ-nepenthone (XIV). The reduction of only one of the two carbonyl groups of ψ-nepenthone under these conditions may be attributed to the fact that, as shown in XXI, only the aromatic carbonyl group of this compound is easily accessible to attack by a hydride ion; the $\alpha\beta$-unsaturated carbonyl group is effectively screened by the other parts of the molecule.

The structures assigned to ψ-nepenthone (XIV) and ψ-nepenthol (XX) show a skeletal resemblance to that proposed for flavonepenthone (XXIII),[2] and in fact ψ-nepenthol should give flavonepen-

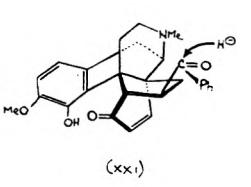
(8) K. W. Bentley, Sir Robert Robinson, and A. E. Wain, *J. Chem. Soc.*, 958 (1952).



(XIX)

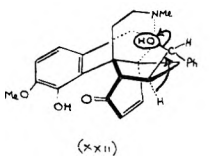


(XX)

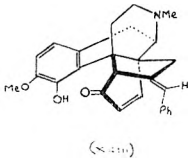


(XXI)

thone simply on dehydration. This dehydration was effected with formic acid, but it was also found that the hydrolysis of isonepenthol (XIX) to ψ-nepenthol (XX) with hot 5% hydrochloric acid was always accompanied by some dehydration of the product and flavonepenthone was recovered from the products of this reaction in about 50% yield. The production of flavonepenthone under such mild conditions strongly supports the view that the 1:2-shift of the bridge occurs in the original base-catalyzed conversion of nepenthone into isonepenthone, and hence the formulas assigned above to the compounds of the isonepenthone–ψ-nepenthone series. Flavonepenthone is easily obtained in very good yield from isonepenthol and ψ-nepenthol by heating with concentrated hydrochloric acid and acetic acid, but as this treatment also brings about the rearrangement of nepenthol to flavonepenthone,[2] only the production of the last-named base under the milder conditions reported above has significance to the present discussion.



(XXII)



(XXIII)

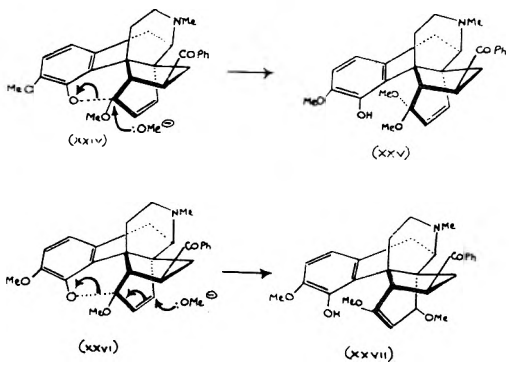
As previously mentioned, in the early experiments two bases different from isonepenthone were obtained after heating nepenthone for five hours with 5% methanolic sodium hydroxide. These two bases, compound-X and compound-Y, were obtained in yields of about 10%.

Compound-X has the composition $C_{29}H_{33}O_5N$ (*i.e.* isonepenthone + CH_3OH) and contains three methoxyl groups. It is phenolic and ketonic (infrared band at 1680 cm.$^{-1}$, 5.96μ), and on hydrolysis with dilute acid it affords ψ-nepenthone in good yield. Compound-Y, which also contains three methoxyl groups, is isomeric with compound-X, is phenolic but non-ketonic, and also affords ψ-nepenthone in good yield on hydrolysis with dilute acid.

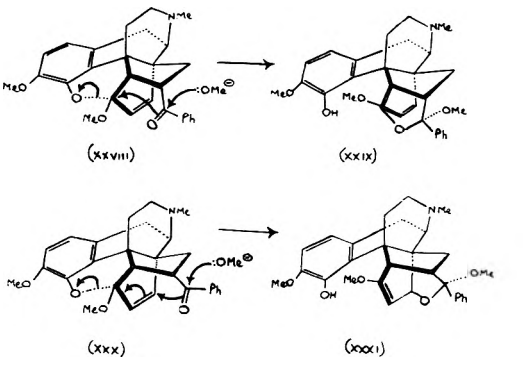
As both these substances are produced after prolonged treatment of nepenthone with alkali it is reasonable to suppose that they are further transformation products of isonepenthone, which is known to be present in the mixture after ten minutes. The hydrolysis of each of them to ψ-nepenthone with the loss of CH_3 and CH_3O indicates that no skeletal rearrangement is involved

in their production from isonepenthone, and suggests that they are both acetals of ψ-nepenthone, and the non-ketonic nature of compound-Y indicates that if this is so the aromatic carbonyl group must also be involved in some way in the acetal system in this base.

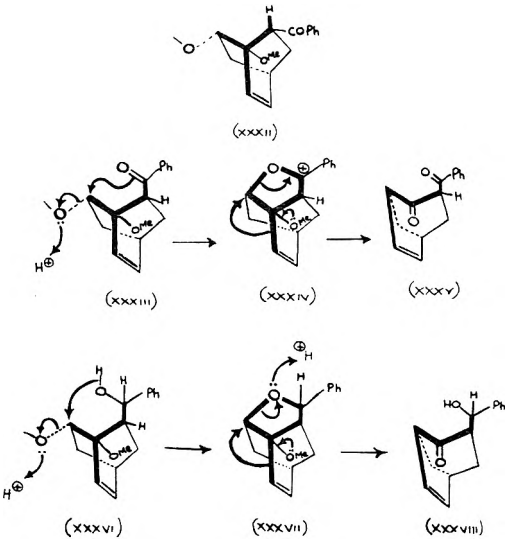
Mechanistically the formation of compound-X could be represented as the displacement of the phenate ion in isonepenthone by the direct attack of a methoxide ion, as in XXIV, giving XXV as the structure of compound-X, which would then be ψ-nepenthone dimethyl acetal. Such a process is stereochemically acceptable, as the site of the attack by OMe is relatively unhindered. ψ-Nepenthone would then arise from compound-X by the simple hydrolysis of the acetal system of XXV. Alternatively the phenate ion could be displaced as shown in XXVI, in which case compound-X would have the structure XXVII, and would be methoxydihydroisonepenthone. The hydrolysis of this enol ether would give the β-methoxyketone, from which methanol would be easily eliminated, giving ψ-nepenthone.



If the aromatic carbonyl group is to participate in the acetal formation, as it apparently does in the formation of compound-Y, epimerization of the —CHCOPh group of isonepenthone must occur as a first step. Presumably in alkaline solution isonepenthone (VI) will be in equilibrium with the presumably less stable epimer XXVIII, and in this attack by OMe^- could occur with displacement of the phenate ion as shown in XXVIII, giving XXIX as the structure of compound-Y. The alternative process shown in XXX can be envisaged, giving XXXI as the structure of compound-Y, but seems less likely on steric grounds. Both XXIX and XXXI on treatment with dilute acid would be expected to give ψ-nepenthone XXI → XIV with the regeneration of the two carbonyl groups, and the epimerization of the —CHCOPh group to the more stable form.



Attempts to probe the structures of the compounds of the isonepenthone–ψ-nepenthone series further by degradation proved unsuccessful; none of the compounds could be induced to form quaternary salts or *N*-oxides, and the various oxidation processes that were tried gave intractable materials. Accordingly the validity of the structures proposed above rests on their success in explaining a complex of data. That being so the possibility that isonepenthone is the originally expected epimer of nepenthone cannot be rejected without serious consideration. It was discounted earlier in this discussion on the basis of the marked difference in stability of nepenthone and isonepenthone towards dilute acids. Nepenthone is assigned the part-structure XXXII, and it is conceivable that the epimeric structure XXXIII might undergo oxide ring fission in acids under conditions in which XXXII does not, as a result of the participation of the carbonyl group as shown in XXXIII → XXXIV. However, the resulting carbonium ion XXXIV could reasonably be expected to have only two alternative fates, *viz.* reaction with water with the addition of a hydroxyl group and the formation of a non-ketonic hemi-acetal, or the stereochemically favorable further rearrangement with a 1:2-shift of the ethylenic bridge, to give the β-diketone represented by the part-structure XXXV. If this occurred then ψ-nepenthone would have the structure XXXVI, which it cannot have if the structure XXIII assigned to flavonepenthone[2] is correct.



A rearrangement of the type shown in XXXIII → XXXV would be expected to require much more

vigorous conditions than those found to be required for the conversion of isonepenthone into ψ-nepenthone. Moreover the transformation of isonepenthol into ψ-nepenthol by a similar process would involve the participation of the alcoholic hydroxyl group as shown in XXXVII, and would lead to the cyclic ether XXXVIII, from which a ketone can be obtained only by the further rearrangement XXXVIII→XXXIX, which would result in the representation of ψ-nepenthol by the part-structure XXXIX, *i.e.* as a saturated ketone, which is contrary to observation. Finally, if isonepenthone were the epimer of nepenthone there is no reason why the reduction of the former should afford a phenolic dihydro-compound (dihydroisonepenthone) that gives a ketone (dihydro-ψ-nepenthone) on hydrolysis. Attempts to prepare enol acetates of nepenthone and isonepenthone, which would be identical if the two compounds were epimers, were unsuccessful; nepenthone was always recovered unchanged, and isonepenthone gave acetyl-ψ-nepenthone enolacetate.

These arguments must lead to the rejection of the possibility that isonepenthone is the epimer of nepenthone, and indirectly support the structures assigned above to the compounds of the isonepenthone–ψ-nepenthone series.

EXPERIMENTAL

Isonepenthone. Nepenthone (15 g.) was heated under reflux in methanol (300 ml.) and sodium hydroxide (15 g.) was added to the boiling solution. After the sodium hydroxide had completely dissolved (in about 5–10 min.) the solution was seeded with isonepenthone, when extensive crystallization occurred in the reaction mixture. In the absence of seeds crystallization either occurred spontaneously after some time or could be induced by vigorous scratching of the walls of the reaction flask. If crystallization did not occur and the heating was continued for 4 hr. no isonepenthone could be recovered from the mixture, only compounds X and Y (see below) being obtained. The *isonepenthone* was collected, washed with cold methanol, and recrystallized from ethanol, when it was obtained as colorless needles, m.p. 174°, followed by resolidification and remelting at 188°, $[\alpha]_D^{20}$ −37° ($CHCl_3$, *c* 0.39); λ_{max} 244, 289 mμ, ϵ_{max} 21,880, 2,180.

Anal. Calcd. for $C_{28}H_{-9}O_4N$: C, 75.8; H, 6.6; (2)OMe, 14.0. Found: C, 75.7; H, 6.6; OMe, 14.5%.

Attempts to prepare salts of this base afforded only derivatives of ψ-nepenthone.

Compounds X and Y. Nepenthone (15 g.) was heated under reflux with methanol (300 ml.) and sodium hydroxide (15 g.) for 4 hr. In the initial experiments crystallization of isonepenthone did not occur. The methanol was removed under reduced pressure and water (200 ml.) was added. The organic material was extracted with ether, and the washed and dried ether extract was evaporated, leaving a mass of yellow crystals (3.0 g.), m.p. about 195°, $[\alpha]_D^{18}$ −69° ($CHCl_3$, *c* 0.62). This material consisted of a mixture of two bases which were separated as follows. The mixture was dissolved in chloroform (50 ml.) and the solution evaporated to a sirup, and diluted with ethanol (30 ml.). After several days a mat of colorless needles had separated, and in this was embedded clumps of yellow needles. The two types of crystal were separated by hand picking, and the bases recrystallized from ethanol.

Compound-X was obtained as regular colorless rods, m.p. 216°, $[\alpha]_D^{20}$ −10° ($CHCl_3$, *c* 0.50), λ_{max} 2400, 2810 Å, ϵ_{max} 27,540, 10,470.

Anal. Calcd. for $C_{29}H_{33}O_5N$: C, 73.2; H, 7.0; (3)OMe, 19.6. Found: C, 73.6; H, 7.2; OMe, 20.0%.

This base gave an immediate red color with diazotized sulfanilic acid in alkaline solution, and gave a blue-green color with quinone chloroimine.

Compound-Y. This was obtained as bunches of pale yellow needles m.p. 225°, $[\alpha]_D^{25}$ −101° ($CHCl_3$, *c* 0.39), λ_{max} 240, 281 mμ, ϵ_{max} 19,950, 3,390.

Anal. Calcd. for $C_{29}H_{33}O_5N$: C, 73.2; H, 7.0; (3)OMe, 19.6. Found: C, 73.2; H, 7.1; OMe, 20.0%.

This base gave an immediate red color with diazotized sulfanilic acid, in alkaline solution, and a blue-violet color with quinone chloroimine.

Dihydroisonepenthone. Isonepenthone (5.0 g.) was shaken with hydrogen in alcohol (200 ml.) in the presence of platinum oxide (0.1 g.) at 50°. After 2.5 hr. about three quarters of a molar equivalent of hydrogen had been absorbed and hydrogenation had become very slow. The catalyst was removed and the solution concentrated to 75 ml. and cooled, when 3.77 g. of *dihydroisonepenthone* was obtained. Recrystallization of this material from ethanol gave the base as colorless needles, m.p. 195°, $[\alpha]_D^{22}$ −118° ($CHCl_3$, *c* 0.57), λ_{max} 240, 279 mμ, ϵ_{max} 20,890, 2,630.

Anal. Calcd. for $C_{28}H_{31}O_4N$: C, 75.4; H, 7.0. Found: C, 75.3; H, 6.9%.

The base gave an immediate red color with diazotized sulfanilic acid in alkaline solution, a deep blue color with quinone chloroimine and an olive-green color with alcoholic ferric chloride.

Isonepenthol. Isonepenthone (5.0 g.) was suspended in methanol (100 ml.) and heated under reflux with sodium borohydride (0.40 g.) until a clear solution was obtained. The mixture was then evaporated to small bulk and diluted with water, when *isonepenthol* (4.4 g.) was obtained. Recrystallization of this material from 60% ethanol afforded the base as colorless prisms m.p. 238°, $[\alpha]_D^{18}$ +69° ($CHCl_3$, *c* 1.13).

Anal. Calcd. for $C_{28}H_{31}O_4N$: C, 75.4; H, 7.0. Found: C, 75.5; H, 7.1%.

The base gave no color with diazotized sulfanilic acid or with quinone chloroimine.

The Meerwein-Ponndorf reduction of isonepenthone was complicated by the difficulty of isolating the product in the presence of aluminum hydroxide without acidification of the mixture. However isonepenthol was clearly formed since acidification of the mixture resulted in the isolation of ψ-nepenthol (see below).

ψ-Nepenthone. (a) *From isonepenthone.* Isonepenthone (2.0 g.) was dissolved in boiling ethanol (50 ml.) and a boiling solution of picric acid (2 g.) in ethanol (25 ml.) was added to the solution. Yellow crystals of *ψ-nepenthone picrate* (2.90) separated almost at once. The salt was collected and washed with ethanol, when it was obtained as yellow needles, m.p. 245°.

Anal. Calcd. for $C_{27}H_{27}O_4N.C_6H_3O_7N_3$: C, 60.1; H, 4.6; N, 8.5. Found: C, 60.0; H, 4.6; H, 8.1%.

ψ-Nepenthone was recovered from the picrate by shaking the salt (2.0 g.) with dilute ammonia solution and benzene. The benzene layer was separated, washed once with dilute ammonia solution, and evaporated, when 1.32 g. of the base was obtained. This was recrystallized from ethanol, when it was recovered as colorless rods, m.p. 202°, $[\alpha]_D^{23}$ −68° ($CHCl_3$, c 0.73), λ_{max} 238, 284 mμ, ϵ_{max} 20,890, 3,160.

Anal. Calcd. for $C_{27}H_{27}O_4N$: C, 75.5; H, 6.3; (1)OMe, 7.2. Found: C, 75.4; H, 6.4; OMe, 7.8%.

The base gave an immediate red color with diazotized sulfanilic acid in alkaline solution, and a blue-green color with quinone chloroimine.

ψ-Nepenthone was also obtained from isonepenthone by dissolving the latter in hydrochloric acid and pouring the solution into hot water. The crystalline salt so obtained was shaken with ammonia and benzene, when ψ-nepenthone

was recovered from the benzene layer. It was also obtained by dissolving isonepenthone in cold glacial acetic acid, diluting the solution at once with water, and neutralizing with sodium carbonate. In both cases the base was identical with that prepared as above through the picrate.

(b) *From compound-X.* Compound-X (0.50 g.) was dissolved in concentrated hydrochloric acid (4 ml.) and the solution immediately poured into hot water (20 ml.). Colorless crystals (0.50 g.) separated and were collected and converted into the base by shaking with warm aqueous sodium carbonate and benzene. The dried benzene solution was evaporated and the residue recrystallized from methanol, when ψ-nepenthone was obtained (0.32 g.) as colorless rods, m.p. 203° undepressed on mixing with material prepared from isonepenthone.

(c) *From compound-Y.* Compound-Y (0.50 g.) was hydrolyzed under the same conditions as those used from the hydrolysis of Compound-X, and afforded 0.34 g. of ψ-nepenthone, m.p. 203°, undepressed on mixing with material prepared from isonepenthone.

Acetyl-ψ-nepenthone. ψ-Nepenthone (1 g.) was allowed to stand for 17 hr. at room temperature in acetic anhydride (10 ml.) and pyridine (10 ml.). The mixture was then poured into water, treated with aqueous ammonia, and the precipitated base extracted with ether-chloroform mixture. The extracts on evaporation afforded a residue that crystallized from methanol, when *acetyl-ψ-nepenthone* (0.67 g.) was obtained as colorless needles m.p. 174°.

Anal. Calcd. for $C_{29}H_{29}O_5N$: C, 73.9; H, 6.2; OAc, 9.1. Found: C, 73.8; H, 6.4; OAc, 9.8%.

Acetyl-ψ-nepenthone enol acetate. ψ-Nepenthone (0.80 g.) was heated under reflux with acetic anhydride (50 ml.) and fused sodium acetate (0.2 g.) for 8 hr. The volatile materials were removed under reduced pressure at 100° and the residue was repeatedly extracted with acetone. Evaporation of the acetone extracts and recrystallization of the residue from methanol afforded *acetyl-ψ-nepenthone enol acetate* (0.64 g.) as colorless needles, m.p. 204°, depressed to 184° on mixing with ψ-nepenthone.

Anal. Calcd. for $C_{31}H_{31}O_6N$: C, 72.5; H, 6.0. Found: C, 72.3; H, 5.8%.

The same substance was obtained when isonepenthone was treated in the same way, but a similar experiment with nepenthone yielded only unchanged starting material.

Dihydro-ψ-nepenthone. (a) *From ψ-nepenthone.* ψ-Nepenthone (3.28 g.) was shaken under hydrogen at 50° in ethanol (200 ml.) in the presence of platinum oxide (0.1 g.). After about 2 hr. one molar equivalent of hydrogen had been absorbed. The mixture was then filtered from catalyst and evaporated, and the residue was recrystallized from ethanol, when *dihydro-ψ-nepenthone* (2.25 g.) was obtained as colorless rods, m.p. 191°, $[\alpha]_D^{19}$ −77° ($CHCl_3$, *c* 0.34). λ_{max} 235, 277 mμ, ϵ_{max} 19,950, 3,390.

Anal. Calcd. for $C_{27}H_{29}O_4N$: C, 75.2; H, 6.8. Found: C, 75.2; H, 6.7%.

The base gave an immediate red color with diazotized sulfanilic acid in alkaline solution, an olive-green color with alcoholic ferric chloride and a blue-green color with quinone chloroimine.

(b) *From dihydroisonepenthone.* Dihydroisonepenthone (0.50 g.) was dissolved in hydrochloric acid (5 ml.) and the solution was poured into hot water (20 ml.). The solution was basified with ammonia after 1 min., and the precipitated organic base was extracted with ether. Evaporation of the ether extract afforded a solid residue, which was recrystallized from methanol, when dihydro-ψ-nepenthone (0.4 g.) was obtained as colorless rods, m.p. 191° undepressed on mixing with material prepared by the reduction of ψ-nepenthone, $[\alpha]_D^{19}$ −79° ($CHCl_3$, c 0.24).

ψ-Nepenthol. (a) *From ψ-nepenthone.* ψ-Nepenthone (2.0 g.) was heated under reflux with methanol (100 ml.) and sodium borohydride (0.35 g.) for 10 min. The solution was concentrated to 50 ml., and hot water (60 ml.) was added, causing the separation of 1.35 g. of fine needles. These were collected and recrystallized from 70% ethanol, when *ψ-nepenthol* was obtained as colorless needles, m.p. 313°, $[\alpha]_D^{19}$ +64° ($CHCl_3$, *c* 0.84).

Anal. Calcd. for $C_{27}H_{29}O_4N$: C, 75.2; H, 6.8. Found: C, 75.5; H, 6.9%.

The base gave an intense red color immediately with diazotized sulfanilic acid in alkaline solution, and a deep green color with quinone chloroimine.

(b) *From isonepenthol.* Isonepenthol (2.0 g.) was dissolved in cold 5*N* hydrochloric acid (10 ml.) and the solution poured into boiling water (100 ml.). Colorless needles soon began to separate, and after 2 hr. cooling these were collected. The liquors were basified with ammonia and the precipitated base was collected and recrystallized from 70% ethanol, when ψ-nepenthol (0.33 g.) was obtained as colorless needles, m.p. 313°, undepressed on mixing with material prepared by the reduction of ψ-nepenthone.

The needles that separated in the acid solution (1.05 g.) were dissolved in hot water and converted into the base by treatment with sodium carbonate solution. Recrystallization of the base afforded 0.65 g. of flavonepenthone as colorless rods, m.p. 263° alone or mixed with flavonepenthone,[2] $[\alpha]_D^{21}$ +32° ($CHCl_3$, *c* 0.41) (flavonepenthone $[\alpha]_D^{18}$ +33°).

Flavonepenthone. (a) *From ψ-nepenthol.* ψ-Nepenthol (0.5 g.) was heated with anhydrous formic acid (10 ml.) for 16 hr. on the water bath. Dilution of the mixture with water (50 ml.) and addition of ammonia solution precipitated flavonepenthone (0.2 g.), which was collected and recrystallized from ethanol, when it was obtained as colorless rods, m.p. 262°, undepressed on mixing with an authentic specimen of flavonepenthone.

The base was more conveniently obtained by heating ψ-nepenthol (1.10 g.) in glacial acetic acid (6 ml.) and concentrated hydrochloric acid (6 ml.) under reflux for 5 hr. Dilution of the mixture with water (20 ml.) resulted in the precipitation of a crystalline salt (0.80 g.). This was collected and converted into the base by treatment with hot aqueous sodium carbonate. The base was recrystallized from ethanol, when flavonepenthone (0.51 g.) was obtained as colorless rods, m.p. 262°, undepressed on mixing with an authentic specimen of flavonepenthone.

(b) *From isonepenthol.* In addition to the production of flavonepenthone during the hydrolysis of isonepenthol to ψ-nepenthol, it was prepared most conveniently from this base as follows. Isonepenthol (1.3 g.) was heated with glacial acetic acid (6 ml.) and concentrated hydrochloric acid (6 ml.) under reflux for 5 hr. Dilution of the mixture with water (20 ml.) precipitated flavonepenthone hydrochloride (0.82 g.) from which flavonepenthone (0.53 g.) was recovered as colorless rods m.p. 262°, undepressed on mixing with a specimen of flavonepenthone.

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ABERDEEN, SCOTLAND

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, M. S. UNIVERSITY]

Iodination of 7-Hydroxy-, and 5-Hydroxy-4-methylcoumarin and Their Methyl Ethers

S. S. LELE AND SURESH SETHNA

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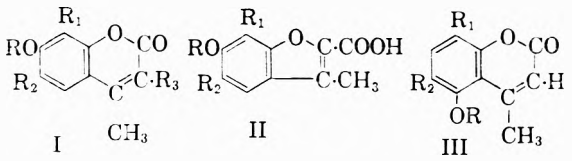
The iodination of 7-hydroxy- and 5-hydroxy-4-methylcoumarin and their methyl ethers using different molecular proportions of iodine monochloride, iodine and iodic acid, and iodine and ammonia has been studied. The results obtained are given in Table I.

In their studies on the bromination of coumarin derivatives Sethna and co-workers[1,2] found that in the case of 7-hydroxycoumarin derivatives and their methyl ethers the first bromine atom in all cases enters the pyron ring in the 3-position and the subsequent bromine atoms enter the benzene ring. In the 5-hydroxycoumarin derivatives, however, the first bromine atom was found to enter the benzene ring in the 8-position. It was thought of interest to see whether the same pattern would follow in the iodination of these coumarin derivatives.

7-Hydroxy-4-methylcoumarin(I, R,R_1,R_2,R_3 = H) on iodination with one mole of iodine monochloride gave a monoiodo derivative. The methyl ether of this did not give a coumarilic acid derivative on heating with alkali which indicated that the iodine atom had not entered the 3-position. The methyl ether when subjected to Elbs persulfate oxidation gave a good yield of the oxidation product thus indicating that the 6-position must be free, for the Elbs persulfate oxidation of 6-substituted coumarins is very difficult.[3] 7-Hydroxy-8-iodo-4-methylcoumarin (I, R,R_2,R_3 = H; R_1=I) structure has therefore been assigned to the iodination product and 6-hydroxy-7-methoxy-8-iodo-4-methylcoumarin (I, R=CH_3; R_1=I; R_2=OH; R_3=H) structure to the Elbs persulfate oxidation product. The mother liquor from the crystallization of the 8-iodo derivative left a mixture from which no other pure product could be isolated. 7-Methoxy-4-methylcoumarin (I, R=CH_3; R_1,R_3=H) on iodination with one mole of iodine monochloride gave a monoiodo derivative which was different from the methyl ether of 7-hydroxy-8-iodo-4-methylcoumarin. On hydrolysis this product gave a coumarilic acid derivative which was found, on direct comparison to be the same as 6-methoxy-3-methylcoumarilic acid (II, R,R_1,R_2 = H) obtained on hydrolysis of 7-methoxy-3-bromo-4-methylcoumarin.[4] The monoiodo product is therefore 7-methoxy-3-iodo-4-methylcoumarin (I, R=CH_3; R_1,R_2=H; R_3=I).



On iodination with two moles of iodine monochloride I (R,R_1,R_2,R_3=H) did not give a pure product. However, on iodination with 4 moles of iodine monochloride it gave two diiodo derivatives (A) m.p. 265° and (B) m.p. 248–250°. The methyl ether of (A) gave a monoiodo coumarilic acid derivative indicating that one of the two iodine atoms had entered the 3-position. Further, this methyl ether was found to be the same as the product obtained on further iodination of 7-methoxy-8-iodo-4-methylcoumarin with iodine monochloride. (A) is therefore 7-hydroxy-3,8-diiodo-4-methylcoumarin (I, R,R_2=H; R_1,R_3=I). The methyl ether of (B), also obtained by the iodination of 7-methoxy-4-methylcoumarin with excess of iodine monochloride (6 moles), also gave a monoiodo coumarilic acid derivative. It has therefore the alternate structure: 7-hydroxy-3,6-diiodo-4-methylcoumarin (I, R,R_1=H; R_2,R_3=I).

On iodination with excess of iodine monochloride I (R,R_1,R_2,R_3=II) gave a triiodo derivative, the methyl ether of which on hydrolysis gave a diiodo coumarilic acid derivative which must be 6-methoxy-5,7-diiodo-3-methylcoumarilic acid (II, R=CH_3; R_1,R_2=I). The triiodocoumarin is therefore 7-hydroxy-3,6,8-triiodo-4-methylcoumarin (I, R=II; R_1R_2,R_3=I). I (R=CH_3; R_1,R_2,R_3=H) did not give any triiodo derivative even on iodination with a large excess of iodine monochloride.

With one mole of iodine monochloride 5-hydroxy-4-methylcoumarin (III, R,R_1,R_2=H) gave a monoiodo derivative. This on methylation gave a product which was the same as the product obtained on iodination of 5-methoxy-4-methylcou-

(1) V. J. Dalvi and S. M. Sethna, *J. Indian Chem. Soc*, **26**, 359 (1949).

(2) S. S. Lele, R. J. Parikh, and S. M. Sethna, *J. Indian Chem. Soc.*, **30**, 610 (1953).

(3) V. J. Dalvi, R. B. Desai, and S. M. Sethna, *J. Indian Chem. Soc.*, **28**, 366 (1951).

(4) D. B. Limaye and N. V. Bhide, *Rasayanam*, **1**, 136 (1938) [*Chem. Abstr.*, **33**, 1699 (1939).]

marin (III, R=CH_3; R_1,R_2=H) with one mole of iodine monochloride. It did not give any coumarilic acid derivative on heating with alkali. Further, on Elbs persulfate oxidation it gave a product in good yield indicating that the 6-position was free. The products obtained on iodination are therefore the 8-iodo-derivatives: (III, R,R_2=H; R_1=I and III, R=CH_3; R_1=I; R_2=H respectively). On iodination with 4 moles of iodine monochloride III (R=CH_3; R_1,R_2=H) gave only the above monoiodo derivative. However, with a large excess of iodine monochloride (16 moles) it gave a diiodo derivative, the methyl ether of which did not give any coumarilic acid derivative. The diiodo derivative is therefore 5-hydroxy-6,8-diiodo-4-methylcoumarin (III, R=H; R_1,R_2=I). III(R,R_1,R_2=H) did not give any triiodo derivative even with a large excess of iodine monochloride.III(R=CH_3; R_1,R_2=H) did not give even the diiodo derivative with large excess of iodine monochloride.

Iodination was also carried out using iodine in the presence of iodic acid. It was assumed that the reaction took place according to the following equation:

$$5RH + 4I + HIO_3 = 5\,RI + 3H_2O$$

I (R,R_1,R_2,R_3 = H) on iodination using the above molecular proportions gave a mixture of iodo derivatives from which only the 8-iodo derivative (I, R,R_2,R_3 = H; R_1 = I) could be easily isolated. When the proportions of iodine and iodic acid were doubled the triiodo derivative (I, R = H; R_1, R_2,R_3 = I) was obtained. The diiodo derivative could not be isolated. I (R=CH_3; R_1,R_2,R_3=H) could not be iodinated by this method under similar conditions. III(R,R_1,R_2=H) on iodination using the molecular proportions given in the above equation gave 5-hydroxy-6,8-diiodo-4-methylcoumarin (III, R=H; R_1,R_2=I). The moniodo derivative could not be isolated. On iodination with double the quantity of iodine and iodic acid only the 6,8-diiodo product was obtained. The diiodo product was found to be unstable and on prolonged stirring of the reaction mixture iodine was liberated. Iodine was also liberated on crystallization from hot acetic acid. On refluxing the diiodo derivative with 10% sodium hydroxide the iodine atoms were removed and III(R,R_1,R_2=H) was obtained. III (R=CH_3; R_1,R_2=H) could not be iodinated at all under similar conditions.

Iodination of the above coumarins with iodine in potassium iodide solution in the presence of ammonia has also been studied. I (R,R_1,R_2,R_3=H) with one mole of iodine gave the 8-iodo-derivative I(R,R_2,R_3=H); R_1=I) described above. With two moles however it gave a diiodo derivative the methyl ether of which remained unchanged on boiling with alkali. Further iodination of this compound using iodine and iodic acid gave the 3,6,8-triiodocoumarin (I, R=H; R_1,R_2,R_3=I). The diiodo derivative is therefore 7-hydroxy-6,8-diiodo-4-methylcoumarin(I, R,R_3=H; R_1,R_2=I) not obtained by the above two methods. On refluxing this diiodo coumarin with 10% sodium hydroxide the pyrone ring opened up and an acid was obtained to which the β-methyl-2,4-dihydroxy-3,5-diiodocinnamic acid structure has been assigned. I(R=CH_3; R_1,R_2,R_3=H) could not be iodinated at all by this method.

III (R,R_1,R_2=H) on iodination with one mole of iodine by this method gave a mixture of a monoiodo derivative and a diiodo derivative. The monoiodo derivative was found to be different from III (R,R_2=H; R_1=I) described above and its methyl ether did not give any coumarilic acid derivative on boiling with alkali nor did it undergo Elbs persulfate oxidation. The monoiodo derivative was therefore 5-hydroxy-6-iodo-4-methylcoumarin (III, R,R_1=H; R_2=I). The diiodo derivative was found, on direct comparison, to be the 6,8-diiodo derivative (III, R=H; R_1,R_2=I). This was obtained in excellent yield by iodination with two moles of iodine. No triiodo derivative could be prepared by this method. III (R=CH_3; R_1,R_2=H) could not be iodinated at all by this method.

EXPERIMENTAL

General iodination procedures. The molecular proportions of the starting material and iodine are given in Table I. (A) *With iodine monochloride.* The coumarin derivative (2 g.) was dissolved in a minimum quantity of glacial acetic acid or alcohol and hydrochloric acid (*d* 1.11; 15 ml.) was added. The mixture was then added to a weighed amount of iodine monochloride. The reaction mixture was then kept in an oven at 50° for 24 hr. It was shaken occasionally. The separated iodo derivative was then filtered and washed with the same solvent and then crystallized from acetic acid. In the case of 7-hydroxy-4-methylcoumarin the solvent used was acetic acid and in the case of 5-hydroxy-4-methylcoumarin it was alcohol. In the case of methoxycoumarin derivatives acetic acid was used as solvent. It was found in the case of methoxycoumarins that the iodination products were not readily obtained if hydrochloric acid was used and hence it was not used.

(B) *With iodine and iodic acid.* The coumarin derivative (2 g.) was dissolved in alcohol by warming and the required quantity of iodine crystals were added. To the warm dark colored solution obtained the required amount of iodic acid dissolved in water was added with stirring. The reaction mixture was stirred for 2 hr. further and the iodo derivative which separated was filtered and washed with alcohol. It was crystallized from acetic acid.

(C) *With ammonia and iodine.* The coumarin derivative (2 g.) was dissolved in ammonium hydroxide (20%; 50 ml.) and the required amount of iodine dissolved in potassium iodide solution was added drop-wise with stirring at room temperature during 0.5 hr. The reaction mixture was stirred for a further 1–2 hr. If any product separated it was filtered and washed with ammonia. The filtrate was then poured into excess of dilute ice cold sulfuric acid. The precipitate obtained was washed with water and crystallized from acetic acid. The monoiodo derivatives remained in solution in ammonia while the diiodo derivatives separated out as ammonium salts which on crystallization from acetic acid gave the free iodo derivatives.

Preparation of the methyl ethers. The iodo derivatives of the hydroxycoumarins were methylated by refluxing their

TABLE I

Coumarin	Iodinating Agent and Proportions[a]	Product Obtained[b]	M.P., °C.[c]	Yield, %	Formula	Analysis, Iodine % Found	Required
7-Hydroxy-4-methyl- (I, R, R_1, R_2, R_3 = H)	A (1:1)	8-Iodo	268	25	$C_{10}H_7O_3I$	41.91	42.06
	B (5:2:1)	(I, R, R_2, R_3 = H; R_1 = I)		40			
	C (1:1)			82			
	A (1:4)	3,8-Diiodo- (I, R, R_2 = H; R_1, R_3 = I)	264	22	$C_{10}H_6O_3I_2$	58.75	59.34
		3,6-Diiodo- (I, R, R_1 = H; R_2, R_3 = I)	249	40	$C_{10}H_6O_3I_2$	59.12	59.34
	A (1:16)	3,6,8-Triiodo-	254	36	$C_{10}H_5O_3I_3$	68.69	68.77
	B (5:4:2)	(I, R = H; R_1, R_2, R_3 = I)		59			
	C (1:2)	6,8-Diiodo- (I, R, R_3 = H; R_1, R_2 = I)	230	66	$C_{10}H_6O_3I_2$	59.87	59.34
7-Methoxy-4-methyl- (I, R = CH_3; R_1, R_2, R_3 = H)	A (1:1)	3-Iodo- (I, R = CH_3; R_1, R_2 = H; R_3 = I)	162	42	$C_{11}H_9O_3I$	39.85	40.19
	A (1:6)	3,6-Diiodo- (I, R = CH_3; R_1 = H; R_2, R_3 = I)	248	75	$C_{11}H_8O_3I_2$	57.34	57.46
5-Hydroxy-4-methyl- (III, R, R_1, R_2 = H)	A (1:1)	8-Iodo- (III, R, R_2 = H; R_1 = I)	242	38	$C_{10}H_7O_3I$	42.41	42.06
	A (1:8)	6,8-Diiodo-	230	42[d]	$C_{10}H_6O_3I_2$	59.28	59.34
	B (5:2:1)	(III, R = H; R_1, R_2 = I)		68[d]			
	C (1:2)			73[d]			
	C (1:1)	6-Iodo- (III, R, R_1 = H; R_2 = I)	175	30	$C_{10}H_7O_3I$	41.97	42.06
5-Methoxy-4-methyl- (III, R = CH_3; R_1, R_2 = H)	A (1:1)	8-Iodo- (III, R = CH_3; R_2 = H; R_1 = I)	254	42	$C_{11}H_9O_3I$	39.98	40.19

A = Iodine monochloride; B = Iodine + Iodic acid; C = NH_4OH + Iodine.

[a] The figures in the brackets indicate molecular proportions. A (substance:iodine monochloride), B (substance:iodine:-iodic acid), C (substance:iodine). [b] All the iodo derivatives are crystallized from glacial acetic acid. [c] All melting points are uncorrected. Hydroxy iodo derivatives start decomposing about 30–40° below their melting points and finally melt at the above temperatures. Methoxy iodo derivatives are sharp melting. [d] 5-Hydroxy-6,8-diiodo derivative is unstable and starts decomposing on boiling in acetic acid. The yields given are of the crude product.

TABLE II

METHYL ETHERS OF THE HYDROXY IODOCOUMARINS MENTIONED IN TABLE I

Coumarin	M.P., °C.	Formula	C Found	C Required	H Found	H Required	I Found	I Required
7-Methoxy-8-iodo-4-methyl- (I, R = CH_3; R_1 = I; R_2, R_3 = H)	199	$C_{11}H_9O_3I$	41.85	41.77	2.69	2.84	40.46	40.19
6,7-Dimethoxy-8-iodo-4-methyl- (I, R = CH_3; R_1 = I; R_2 = OCH_3; R_3 = H)	218	$C_{12}H_{11}O_4I$	41.71	41.62	2.92	3.18	36.91	36.70
7-Methoxy-3,8-diiodo-4-methyl- (I, R = CH_3; R_2 = H; R_1, R_3 = I)	262	$C_{11}H_8O_3I_2$	29.52	29.86	2.16	1.81	58.03	57.46
7-Methoxy-3,6-diiodo-4-methyl- (I, R = CH_3; R_1 = H; R_2, R_3 = I)	248	$C_{11}H_8O_3I_2$	29.82	29.86	2.30	1.81	57.34	57.46
7-Methoxy-3,6,8-triiodo-4-methyl- (I, R = CH_3; R_1, R_2, R_3 = I)	217	$C_{11}H_7O_3I_3$	23.08	23.25	1.02	1.23	67.48	67.08
7-Methoxy-6,8-diiodo-4-methyl- (I, R = CH_3; R_1, R_2 = I; R_3 = H)	212	$C_{11}H_8O_3I_2$	29.92	29.86	1.89	1.81	57.18	57.46
5-Methoxy-8-iodo-4-methyl- (III, R = CH_3; R_1 = I; R_2 = H)	254	$C_{11}H_9O_3I$	41.80	41.77	3.24	2.84	39.98	40.19
5-Methoxy-6,8-diiodo-4-methyl- (III, R = CH_3; R_1, R_2 = I)	224	$C_{11}H_8O_3I_2$	30.20	29.86	1.59	1.81	57.31	57.46
5-Methoxy-6-iodo-4-methyl- (III, R = CH_3; R_1 = H; R_2 = I)	155	$C_{11}H_9O_3I$	41.91	41.77	2.91	2.84	39.81	40.19

acetone solutions with dimethyl sulfate in the presence of anhydrous potassium carbonate.

6-Hydroxy-7-methoxy-8-iodo-4-methylcoumarin (I, R = CH_3; R_1 = I; R_2 = OH; R_3 = H). 7-Methoxy-8-iodo-4-methylcoumarin (1 g.) was dissolved in sodium hydroxide solution (10%, 40 ml.) by warming on a steam bath. It was then oxidized with potassium persulfate (0.9 g. in 40 ml. water) according to the procedure described by Parikh and Sethna.[5] The product obtained crystallized from acetic acid in plates, m.p. 234°. It dissolved in sodium hydroxide solution to give a deep yellow solution.

Anal. Calcd. for $C_{11}H_9O_4I$: C, 39.77; H, 2.70; I, 38.30. Found: C, 40.22; H, 2.68; I, 38.03.

6-Methoxy-3-methylcoumarilic acid (II, R = CH_3; R_1, R_2 = H). 7-Methoxy-3-iodo-4-methylcoumarin (0.5 g.) was refluxed with alcoholic potassium hydroxide (10%, 30 ml.) for 2 hr. on a steam bath. The product obtained, on acidification of the diluted solution, was purified through sodium bicarbonate solution. It crystallized from dilute alcohol in needles, m.p. 186° (dec.). Mixed melting point with the compound prepared by hydrolyzing 7-methoxy-3-bromo-4-methylcoumarin[4] was not lowered.

6-Methoxy-7-iodo-3-methylcoumarilic acid (II, R = CH_3; R_1 = I; R_2 = H). 7-Methoxy-3,8-diiodo-4-methylcoumarin (0.5 g.) was refluxed with alcoholic potassium hydroxide (10%, 40 ml.). The product obtained on working up the reaction mixture as above crystallized from glacial acetic acid in needles, m.p. 222° (dec.). It gave a violet color with sulfuric acid.

Anal. Calcd. for $C_{11}H_9O_4I$: C, 39.70; H, 2.70; I, 38.30. Found: C, 40.12; H, 3.12; I, 38.31.

The methyl ester was prepared by refluxing 6-methoxy-7-iodo-3-methylcoumarilic acid (0.3 g.) in methyl alcohol (25 ml.) with concentrated sulfuric acid (5 ml.) on a steam bath for 8 hr. It crystallized from dilute alcohol in colorless needles, m.p. 180°.

Anal. Calcd. for $C_{12}H_{11}O_4I$: C, 41.62; H, 3.18; I, 36.70. Found: C, 41.72; H, 3.52; I, 36.83.

6-Methoxy-5-iodo-3-methylcoumarilic acid (II, R = CH_3; R_1 = H; R_2 = I) was obtained from 7-methoxy-3,6-diiodo-4-methylcoumarin by refluxing with alcoholic potassium hydroxide (10%, 40 ml.) as above. It crystallized from dilute acetic acid in colorless needles, m.p. 218° (dec.). It gave a violet color with sulfuric acid.

Anal. Calcd. for $C_{11}H_9O_4I$: C, 39.77; H, 2.70; I, 38.30. Found: C, 39.81; H, 2.75; I, 38.01.

(5) R. J. Parikh and S. M. Sethna, *J. Indian Chem. Soc.*, 27, 369 (1950).

The methyl ester was prepared as described before. It crystallized from petroleum ether (60–80°) in colorless needles, m.p. 160°.

Anal. Calcd. for $C_{12}H_{11}O_4I$: C, 41.62; H, 3.18; I, 36.70. Found: C, 41.99; H, 2.72; I, 36.81.

6-Methoxy-5,7-diiodo-3-methylcoumarilic acid (II, R = CH_3; R_1, R_2 = I) was prepared from 7-methoxy-3,6,8-triiodo-4-methylcoumarin (1 g.) by refluxing with alcoholic potassium hydroxide (10% in 50% alcohol) as above. It crystallized from glacial acetic acid in colorless needles, m.p. 270° (dec.).

Anal. Calcd. for $C_{11}H_8O_4I_2$: C, 28.82; H, 1.74; I, 55.46. Found: C, 28.76; H, 1.84; I, 55.91.

The methyl ester was prepared as described before. It crystallized from dilute alcohol in colorless needles, m.p. 160°.

Anal. Calcd. for $C_{12}H_{10}O_4I_2$: C, 30.52; H, 2.12; I, 53.81. Found: C, 30.20; H, 2.61; I, 53.79.

6-Hydroxy-5-methoxy-8-iodo-4-methylcoumarin (III, R = CH_3; R_1 = I; R_2 = OH). 5-Methoxy-8-iodo-4-methylcoumarin (1 g.) was dissolved in sodium hydroxide (10%, 40 ml.) by warming on a steam bath and by adding a little pyridine. It was then oxidized with potassium persulfate (0.9 g. in 40 ml. water) as described before. The product obtained crystallized from acetic acid in needles, m.p. 270°. It dissolves in sodium hydroxide solution to give a deep yellow solution.

Anal. Calcd. for $C_{11}H_9O_4I$: C, 39.77; H, 2.70; I, 38.30. Found: C, 39.81; H, 2.29; I, 38.49.

β-Methyl-2,4-dihydroxy-3,5-diiodocinnamic acid was prepared from 7-hydroxy-6,8-diiodo-4-methylcoumarin (1 g.) by refluxing with alcoholic potassium hydroxide (10%; 50 ml.) for 1 hr. It crystallized from glacial acetic acid in needles, m.p. 242° (dec.). Attempts to cyclize it to the original coumarin did not succeed as on boiling with concentrated hydrochloric acid iodine was liberated.

Anal. Calcd. for $C_{10}H_8O_4I_2$: C, 26.90; H, 1.79; I, 56.95. Found: C, 27.13; H, 1.38; I, 56.72.

Methyl β-methyl 2,4-dimethoxy-3,5-diiodocinnamate. Simultaneous methylation and esterification of the above acid was carried out by refluxing its acetone solution with excess of dimethyl sulfate in presence of anhydrous potassium carbonate. It crystallized from alcohol in needles, m.p. 169°. It decolorized dilute potassium permanganate solution and bromine in acetic acid.

Anal. Calcd. for $C_{13}H_{14}O_4I_2$: C, 31.96; H, 2.86; I, 52.04. Found: C, 31.89; H, 3.19; I, 51.63.

BARODA, INDIA

[CONTRIBUTION FROM THE ORGANIC CHEMISTRY LABORATORY, INSTITUTE OF SCIENCE, BOMBAY]

Reactions of Nitrohydroxychalcones: Synthesis of Nitrohydroxyflavones

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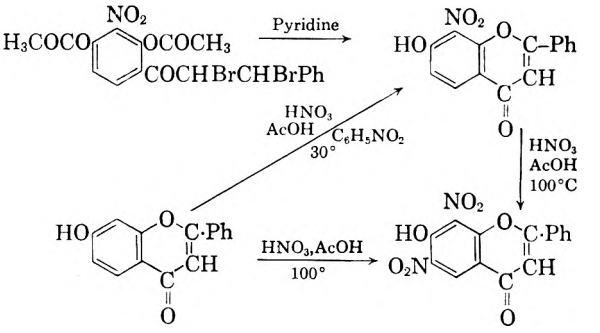
The conversion of 2′,4′-dihydroxy-3′-nitrochalcone derivatives to 7-hydroxy-8-nitroflavone derivatives is described. The formation of the 6- and 8-nitro-5-hydroxyflavone derivatives from 2′,6′-dihydroxy-3′-nitrochalcone derivatives by different routes is described and discussed. Modified procedures for the nitration of 5-hydroxyflavone and 7-hydroxyflavone are given.

In an earlier communication,[2] the preparation of several nitrohydroxychalcones and their isomerization to the flavanones was reported. The present paper deals with the conversion of the chalcones to flavones.

As already reported, the cyclization of the 2′,4′-dihydroxy-3′-nitrochalcones could not be generally effected in good yields and hence the only route to the synthesis of flavones in this case was the dehydrobromination of the corresponding chalcone dibromides. It was found desirable to protect the free hydroxyl groups by acetylation to prevent bromination of the benzene ring. The dibromides were obtained readily by the bromination of the diacetates in chloroform solution. The bromination of the chalcones with alkoxy substituents in the styryl part did not go to completion with molecular proportions of bromine. The dibromides were, however, obtained when more than molecular proportions of bromine were employed. The dehydrobromination of the dibromides was effected by boiling with pyridine, whereupon 7-hydroxy-8-nitroflavone derivatives were obtained. That both the acetyl groups are removed is shown by the positive ferric reaction as well as the instantaneous reaction with alkali. This easy deacetylation can be ascribed to the labile nature of the acetoxyl groups in a position ortho or para to a nitro group. The constitution of the flavone obtained from chalcone diacetate Ia, *viz.*, 7-hydroxy-8-nitroflavone, was confirmed by its identity with the mononitration product of 7-hydroxyflavone as well as by its nitration to the known 7-hydroxy-6,8-dinitroflavone.[3] The sequence of reactions is shown in Chart I.

Chart I



In the case of 2′,6′-dihydroxy-3′-nitrochalcones, both routes for the synthesis of flavones, *i.e.*, dehydrobromination of the 3-bromoflavanones as well as of the chalcone dibromides, were investigated. The flavanones, on bromination, gave the corresponding 3-bromoflavanones. More than molecular proportions of bromine were required to brominate the flavanones with alkoxy substituents in the 2-phenyl nucleus. The yields of pure bromoflavanones, in such cases, were poor and in one case the pure bromoflavanone could not be isolated. The crude bromination product could, however, be directly dehydrobrominated by boiling pyridine when the flavones crystallized from the reaction mixture. The flavanones obtained by the cyclization of 2′,6′-dihydroxy-3′-nitrochalcones had earlier[2] been assigned the constitution of 5-hydroxy-6-nitro flavanones, on theoretical considerations. This has now been confirmed by the formation of 5-hydroxy-6-nitroflavone from the flavanone obtained by the cyclization of 2′,6′-dihydroxy-3′-nitrochalcone. This flavone was found to be identical with the 5-hydroxy-6-nitroflavone prepared by Kostanecki-Robinson benzoylation of 2,6-dihydroxy-3-nitroacetophenone.[4] It also resisted acetylation showing the hindered nature of the 5-hydroxyl group.

The dehydrobromination of the 2′,6′-diacetoxy-3′-nitrochalcone dibromides was next investigated. 2′,6′-Dihydroxy-3′-nitro-2-methoxychalcone and 2′,6′dihydroxy -3′-nitro-3-methoxychalcone did not yield a pure acetate by any method. The other chalcone diacetates were obtained pure and were brominated in chloroform solution. The proportions of bromine required were the same as in the case of the corresponding 2′,4′-diacetoxy-3′-nitrochalcone derivatives. The dehydrobromination of the chalcone dibromides gave 5-hydroxy-8-nitroflavone derivatives. These could be acetylated to give the 5-acetoxy-8-nitroflavone derivatives, thus showing

(1) Present address: Chemistry Department, M. N. College, Visnagar, N. Gujerat, India.

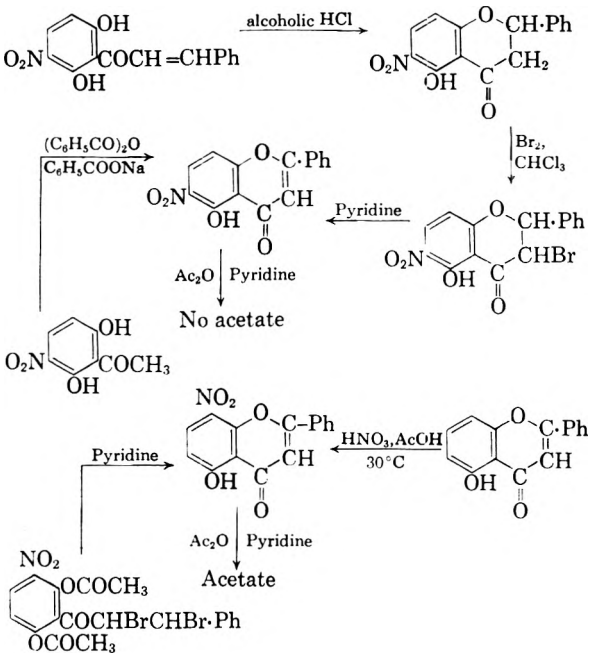
(2) S. Seshadri and P. L. Trivedi, *J. Org. Chem.*, **22**, 1633 (1957).

(3) A. M. Mehta, G. V. Jadhav, and R. C. Shah, *Proc. Indian Acad. Sci.*, **29A**, 314 (1949).

(4) R. M. Naik and V. M. Thakor, *Proc. Indian Acad. Sci.*, **37A**, 774 (1953).

that the 5-hydroxyl group is not hindered. The formation of 5-hydroxy-8-nitroflavones shows that the acetoxy group ortho to both the nitro and the carbonyl groups suffers deacetylation first and cyclization occurs preferentially at that position. 5-Hydroxy-8-nitroflavone thus obtained was found to be identical with the mononitration product of 5-hydroxyflavone. The formation of 5-hydroxy-6-nitroflavone by one method and of 5-hydroxy-8-nitroflavone by the other method is indicated in Chart II.

Chart II



The characteristic sulfuric acid colorations of the flavones are set out in Table III and show the enhanced halochromism with *o-p* alkoxy substitution in the 2-phenyl nucleus.

EXPERIMENTAL

Acetylation of the chalcones. All the chalcones were acetylated by acetic anhydride–pyridine. Some of the chalcones were heated on a water bath and some reacted at room temperature (*ca.* 30°) as shown below. Chalcones Ia, If, IIa, IId, IIe were prepared by dissolving the corresponding hydroxy chalcones (500 mg.) in hot acetic anhydride (10 cc.) and pyridine (1 cc.) and leaving overnight at room temperature. The solid obtained on treating with cold water was crystallized from alcohol. The yield was 400 mg.

Chalcones Ib, Ic, Id, Ie were prepared by dissolving the hydroxy chalcone in acetic anhydride–pyridine as before, heating on a boiling water bath for 4 hr., and leaving overnight at room temperature. The solid obtained on working up as usual was triturated with a little alcohol and filtered. The residue was then crystallized twice from alcohol. Yields were 200 to 250 mg. All the chalcone acetates were colorless or very pale yellow crystalline substances giving no color with alcoholic ferric chloride. The melting points and analyses are set out in Table I.

Bromination of the chalcone diacetates. Bromination of chalcones Ia, If, IIa. The chalcone diacetate (500 mg.) in chloroform (2 cc.) was treated with bromine in chloroform (2 cc.; 10%). The mixture was left at room temperature for 2 hr. Chloroform was removed by evaporation and petroleum ether (b.p. 40–60°) added to the residue. The solid obtained was crystallized from a mixture of benzene–petroleum ether. The yield was 400 mg. Bromination of the other chalcone diacetates was carried out similarly with the exception that 3.5 cc. of the bromine solution was employed and the yields were 200 to 250 mg. The bromides gave no color with alcoholic ferric chloride. The melting points and analyses are set out in Table I.

Bromination of the flavanones. Bromoflavanone IIA was obtained by reacting 5-hydroxy-6-nitroflavanone (500 mg.) in chloroform (2 cc.) with bromine in chloroform (2.5 cc.; 10%) at room temperature for 2 hr. Chloroform was evaporated and petroleum ether added to the residue. The solid obtained was recrystallized from a mixture of benzene–petroleum ether. The yield was 400 mg. The other bromoflavanones, IIB, IIC, IID, IIE were similarly obtained with the difference that 4 cc. of the bromine solution was employed. The pure bromoflavanones were obtained after repeated crystallizations. The yields were 80 to 100 mg. Bromoflavanone IIC could not be isolated in a pure condition and the crude reaction product was used as such for further reaction. The melting points of the bromoflavanones and their analyses are given in Table II.

Dehydrobromination of the chalcone dibromides and the bromoflavanones. The bromo derivatives (500 mg.) were refluxed in pyridine (5 cc.) for 10 min. In many cases the flavanone separated out quantitatively as a crystalline solid during the reaction or on cooling the reaction mixture. The solid was filtered and washed with alcohol and crystallized further from acetic acid (nitrobenzene was used for flavones 9 and 14). If no solid separated even on cooling, dilute hydrochloric acid was added and the solid obtained filtered and recrystallized from acetic acid. All the flavones were white or pale yellow in color and gave negative Beilstein test for halogen. The melting points and the characteristic sulfuric acid colorations are set out in Table III. The 7-hydroxy-8-nitroflavone derivatives gave pale brown color with alcoholic ferric chloride, while the 5-hydroxy flavone derivatives gave brownish red colors.

Nitration of 7-hydroxyflavone. The procedure for nitration of 7-hydroxyflavone as reported in the literature[3] was found unsuitable as it led to the formation of di- and tri-nitro derivatives. The following was the method employed; 7-hydroxyflavone (2 g.) was dissolved in acetic acid (100 cc.) and nitrobenzene (50 cc.) and treated with concd. nitric acid (d. 1.42, 5 cc.) in the cold. The mixture was left overnight at room temperature. Water was then added and the nitrobenzene layer extracted with dilute alkali solution (1%). The alkaline extract was washed with ether and acidified. The solid obtained was treated with dilute sodium bicarbonate solution (2%) in which part of it dissolved to give a yellow solution. The solution was filtered and acidified. The solid obtained was crystallized from acetic acid, melting range 185–215°, yield, 200 mg. It was purified by conversion to the acetate, m.p. 168–170° (after two crystallizations from alcohol).

Anal. Calcd. for $C_{17}H_{11}NO_6$: N, 4.31. Found: N, 4.35.

This product was hydrolyzed by dissolving in 80% sulfuric acid and keeping overnight at room temperature. The solid obtained on adding to ice was crystallized from acetic acid as fluffy white needles, m.p. 228°, mixed melting point with flavone (1) obtained through the chalcone dibromide (see Table III) was undepressed.

7-Hydroxy-6,8-dinitroflavone,[3] m.p. 289° was obtained by nitration of 7-hydroxyflavone in acetic acid at 100°. Flavone (1) on similar nitration gave the same compound, m.p. and mixed m.p. 289°.

5-Hydroxy-6-nitroflavone was obtained by the reaction of 2,6-dihydroxy-3-nitroacetophenone with sodium benzoate and benzoic anhydride.[4] The melting point of the product crystallized from acetic acid was 209° (previous shrinking at 200°). This agrees with the reported melting point. The

TABLE I

CHALCONE DIACETATES AND THEIR DIBROMIDES

No.	Chalcone	M.P., °C.	Formula	Analysis, N % Calcd.	Analysis, N % Found	Dibromide M.P., °C.	Formula	Analysis, Br % Calcd.	Analysis, Br % Found
Ia	2′,4′-(OAc)$_2$-3′-NO$_2$	133–135	$C_{19}H_{15}NO_7$	3.79	3.75	181–183	$C_{19}H_{15}Br_2NO_7$	30.24	30.60
Ib	2′,4′-(OAc)$_2$-3′-NO$_2$-2-OMe	103–105	$C_{20}H_{17}NO_8$	3.51	3.26	147–148	$C_{20}H_{17}Br_2NO_8$	28.62	28.76
Ic	2′,4′-(OAc)$_2$-3′-NO$_2$-3-OMe	105–107	$C_{20}H_{17}NO_8$	3.51	3.50	118	$C_{20}H_{17}Br_2NO_8$	28.62	29.05
Id	2′,4′-(OAc)$_2$-3′-NO$_2$-4-OMe	84–85	$C_{20}H_{17}NO_8$	3.51	3.28	141–142	$C_{20}H_{17}Br_2NO_8$	28.62	28.54
Ie	2′,4′-(OAc)$_2$-3′-NO$_2$-3,4-O$_2$CH$_2$	124–125	$C_{20}H_{15}NO_9$	3.39	3.24	148–149	$C_{20}H_{15}Br_2NO_9$	27.90	28.30
If	2′,4′-(OAc)$_2$-3′-NO$_2$-4-Me	137–139	$C_{20}H_{17}NO_7$	3.66	3.60	163–165	$C_{20}H_{17}Br_2NO_7$	29.47	28.98
IIa	2′,6′-(OAc)$_2$-3′-NO$_2$	104–105	$C_{19}H_{15}NO_7$	3.79	3.89	163	$C_{19}H_{15}Br_2NO_7$	30.24	30.70
IId	2′,6′-(OAc)$_2$-4-OMe-3′-NO$_2$	109–110	$C_{20}H_{17}NO_8$	3.51	3.59	146–148	$C_{20}H_{17}Br_2NO_8$	28.62	28.99
IIe	2′,6′-(OAc)$_2$-3′-NO$_2$-3,4-O$_2$CH$_2$	141–142	$C_{20}H_{15}NO_9$	3.39	3.40	150–151	$C_{20}H_{15}Br_2NO_9$	27.90	28.17

TABLE II

No.	Flavanone	M.P., °C.	Formula	Analysis, Br % Calcd.	Analysis, Br % Found
IIA	5-OH-6-NO$_2$-3-Br	147	$C_{15}H_{10}BrNO_5$	22.60	22.39
IIB	5-OH-6-NO$_2$-2′-OCH$_3$-3-Br	181–182	$C_{16}H_{12}BrNO_5$	20.30	20.75
IIC	5-OH-6-NO$_2$-3′-OCH$_3$-3-Br	[a]			
IID	5-OH-6-NO$_2$-4′-OCH$_3$-3-Br	179–180	$C_{16}H_{12}BrNO_5$	20.30	20.13
IIE	5-OH-6-NO$_2$-3′,4′-O$_2$CH$_2$-3-Br	270[b]	$C_{16}H_{10}BrNO_7$	19.60	19.65

[a] Could not be isolated. [b] Becomes brown at 205° and chars at 270°.

TABLE III

LIST OF FLAVONES PREPARED

No.	Flavone	M.P., °C.	H_2SO_4 Color	Formula	Analysis, N % Calcd.	Analysis, N % Found
1	7-OH-8-NO$_2$	228	Yellow	$C_{15}H_9NO_5$	4.95	4.80
2	7-OH-8-NO$_2$-2′-OCH$_3$	258–260[a]	Orange	$C_{16}H_{11}NO_6$	4.47	4.26
3	7-OH-8-NO$_2$-3′-OCH$_3$	242–243	Orange-yellow	$C_{16}H_{11}NO_6$	4.47	3.34
4	7-OH-8-NO$_2$-4′-OCH$_3$	260[a]	Orange	$C_{16}H_{11}NO_6$	4.47	4.23
5	7-OH-8-NO$_2$-3′,4′-O$_2$CH$_2$	270[a] (dec.)	Orange-red	$C_{16}H_9NO_7$	4.28	4.12
6	7-OH-8-NO$_2$-4′-CH$_3$	250	Yellow	$C_{16}H_{11}NO_5$	4.71	4.88
7	5-OH-8-NO$_2$	215[c] (190)	Yellow	$C_{15}H_9NO_5$	4.95	5.19
8	5-OH-8-NO$_2$-4′-OCH$_3$	218[c] (200)	Orange-yellow	$C_{16}H_{11}NO_6$	4.47	4.30
9	5-OH-8-NO$_2$-3′,4′-O$_2$CH$_2$	300[b]	Orange-red	$C_{16}H_9NO_7$	4.28	4.50
10	5-OH-6-NO$_2$	232	Yellow	$C_{15}H_9NO_5$	4.95	4.74
11	5-OH-6-NO$_2$-2′-OCH$_3$	208–210	Orange-yellow	$C_{16}H_{11}NO_6$	4.47	4.27
12	5-OH-6-NO$_2$-3′-OCH$_3$	216–217	Deep yellow	$C_{16}H_{11}NO_6$	4.47	4.46
13	5-OH-6-NO$_2$-4′-OCH$_3$	234–236	Orange-yellow	$C_{16}H_{11}NO_6$	4.47	4.66
14	5-OH-6-NO$_2$-3′,4′-O$_2$CH$_2$	290[b]	Orange-red	$C_{16}H_9NO_7$	4.28	4.54

[a] Melts with charring. [b] Chars but does not melt. [c] Softening occurs at the temperature indicated in brackets.

product was, however, found to be contaminated with 5-hydroxy-6-nitro-3-benzoylflavone. This impurity was removed by crystallization from chloroform, whereupon the melting point rose to 230–232°. Mixed melting point with flavone (10) was not depressed. It was recovered unreacted after boiling with acetic anhydride–pyridine.

Nitration of 5-hydroxyflavone. The nitration of 5-hydroxyflavone in sulfuric acid solution as reported in the literature[5] was found unsatisfactory. The following procedure was adopted: 5-hydroxyflavone (0.5 g.) in acetic acid (5 cc.) was treated with concd. nitric acid (5 cc.) in acetic acid (5 cc.) with cooling in running tap water. The flavone dissolved slowly and the nitroflavone started separating. After 15 min., the product was filtered, washed and crystallized from acetic acid, m.p. 215° (shrinking at 100°). Mixed melting point with flavone (7) was not depressed.

Anal. Calcd. for $C_{15}H_9NO_5$: N, 4.95. Found: N, 5.25.

Acetylation of flavones (7), (8), and (9). The flavones (200 mg.) were refluxed with acetic anhydride (5 cc.) and pyridine

(5) R. M. Naik, A. M. Mehta, G. V. Jadhav, V. M. Thakor, and R. C. Shah, *Proc. Indian Acad. Sci.*, **38A**, 31 (1953).

(0.5 cc.) for 4 hr. The solid obtained on working up as usual was ground with alcohol (10 cc.) and filtered. The residue was crystallized from a mixture of alcohol and acetic acid. They gave negative ferric reaction.

The following acetoxyflavones were thus obtained: 5-acetoxy-8-nitroflavone, m.p. 155–156°.

Anal. Calcd. for $C_{17}H_{11}NO_6$: N, 4.3. Found: N, 4.2.

5-Acetoxy-8-nitro-4′-methoxyflavone m.p. 163–165°.

Anal. Calcd. for $C_{18}H_{13}NO_7$: N, 3.94. Found: N, 4.00.

5-Acetoxy-8-nitro-3′-4′-methylenedioxyflavone, m.p. 215–217°.

Anal. Calcd. for $C_{18}H_{11}NO_8$: N, 3.79. Found: N, 3.80.

Acknowledgments. The authors wish to express their gratitude to Dr. C. V. Jadhav for his keen interest in the work.

BOMBAY, INDIA

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

Some Analogs of Toxopyrimidine and Methioprim[1]

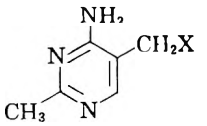
TAKUO OKUDA AND CHARLES C. PRICE

Received May 7, 1958

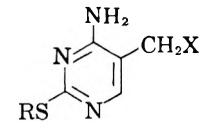
A number of new pyrimidines, related to 2-methyl-4-amino-5-hydroxymethylpyrimidine (I, toxopyrimidine) and 2-methylthio-4-amino-5-hydroxymethylpyrimidine (VIII, methioprim) have been prepared and characterized.

The antimetabolite properties of toxopyrimidine[2] (I) stimulated our earlier work leading to the discovery of interesting antimetabolite and antitumor activity in "methioprim" (VIII).[3–6] We now wish to report the syntheses and characterization of a number of additional compounds related to these substances.

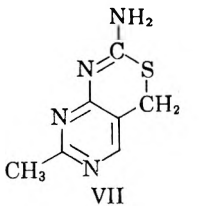
The analogs of toxopyrimidine were made by appropriate substitution reactions with the bromomethyl compound (X).[7] Reaction of X with thiourea, followed by neutralization of the crude isothiuronium salt, produced not only the disulfide III (presumably through the mercaptan) but led also to the isolation of the thiazinopyrimidine (VII), shown to be different from the isomeric thiocyanate (VI). XII, however, reacted normally with thiourea to produce the isothiuronium salt, XVII, which



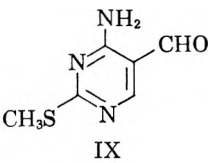
I, X = OH
II, X = SH
III, X =)$_2$S$_2$
IV, X =)$_2$S
V, X = SCH_3
VI, X = SCN
X, X = Br



VIII, R = CH_3, X = OH
XI, R = H, X = OH
XII, R = CH_3, X = Br
XIII, R = CH_3, X = OCH_3
XIV, R = CH_3, X = SCH_3
XV, R = CH_3, X = $SCOCH_3$
XVI, R = CH_3, X = SH
XVII, R = CH_3, X = $SC(NH_2)_2^+Br^-$
XVIII, R = CH_3, X =)$_2$S$_2$
XIX, R = C_2H_5, X = OH



VII

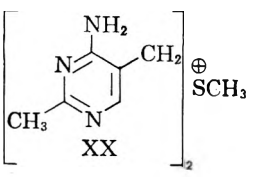


IX

was converted to disulfide, but did not give the analogous thiazinopyrimidine.

Oxidation of VIII by dichromate proceeded surprisingly smoothly to the aldehyde IX, which was also readily converted to the oxime.

When X was heated with sodium methyl mercaptide in ether, and then in dioxane, the sulfide IV instead of V was formed. This reaction may have proceeded through formation of a sulfonium salt (XX) as an intermediate.



XX

The replacement of the bromine atom of XII by methoxyl proceeded readily by solvolysis.

The reduction of 2-mercapto-4-amino-5-carbeth-

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(1) Supported in part by the U. S. Public Health Service Grant CY-2714.

(2) K. Makino, T. Kinoshita, T. Sasaki, and T. Shiei, *Nature*, **173**, 34 (1954); K. Makino, T. Kinoshita, Y. Aramaki, and S. Shintani, *Nature*, **174**, 275 (1954); K. Makino and M. Koike, *Nature*, **174**, 1056 (1954); K. Makino and T. Kinoshita, *J. Vitaminol.*, **1**, 14 (1955); S. Shintani, *J. Vitaminol.*, **8**, 185 (1956).

(3) T. L. V. Ulbricht and C. C. Price, *J. Org. Chem.*, **21**, 567 (1956); *Chem. & Ind. (London)*, 1221 (1955).

(4) T. L. V. Ulbricht and J. S. Gots, *Nature*, **178**, 913 (1956); D. B. McNair-Scott, T. L. V. Ulbricht, M. L. Rogers, E. Chu and C. Rose, *Cancer Research*, in press; D. F. Dunning, T. L. V. Ulbricht, C. C. Price, and R. Jones, Jr., unpublished results; R. Guthrie, M. E. Loebeck, and M. J. Hillman, *Proc. Soc. Exptl. Biol. Med.*, **94**, 792 (1957); R. Guthrie, J. F. Holland, E. A. Hyatt, M. Hillman, and D. T. Mount, *Proc. Am. Assoc. Cancer Research*, **2**, 113 (1956); I. J. Slotnick, R. Guthrie, J. F. Holland, and M. J. Hillman, *Proc. Am. Assoc. Cancer Research*, **3**, 251 (1957).

(5) F. Rosen, J. F. Holland, and C. A. Nichol, *Proc. Am. Assoc. Cancer Research*, **3**, 243 (1957).

(6) This name has been suggested to us by Dr. Joseph S. Gots, Univ. of Pa., and Dr. Robert Guthrie, Roswell Park Memorial Institute.

(7) Kindly supplied by Dr. Max Tishler, Merck & Co., Rahway, N. J.

thoxypyrimidine (XXI) to XI with lithium aluminum hydride was successfully carried out in *N*-ethylmorpholine.

Dr. Joseph S. Gots has found that compounds VIII, IX, XII, and XVI are antagonists for I in microorganisms requiring I for growth. Details will be reported elsewhere.

EXPERIMENTAL[8]

2-Methyl-4-amino-5-mercaptomethylpyrimidine (II) *and bis-(2-methyl-4-amino-5-pyrimidylmethyl) disulfide* (III). (I) *2-Methyl-4-amino-5-mercaptomethylpyrimidine.* 2-Methyl-4-amino-5-bromomethylpyrimidine dihydrobromide[7] (30 g., 0.082 mole) was slowly added to a solution of 6.3 g. (0.083 mole) of thioacetic acid in 150 ml. of pyridine. After the evolution of heat stopped, the mixture was stirred and refluxed gently for 7 hr. After cooling, a white precipitate was filtered and washed with ether. The precipitate was dissolved in 35 ml. of 5% hydrochloric acid and the solution was washed with ether, and then made weakly alkaline with sodium carbonate solution. The solution was quickly extracted ten times with 100-ml. portions of ether. The combined ether solutions were dried over magnesium sulfate for 1 hr. The ether was distilled *in vacuo* leaving 3.0 g. of white plates. This product was recrystallized three times from acetone, m.p. 161–163° (in vacuo). The sample was kept in a sealed tube containing nitrogen.

Anal. Calcd. for $C_6H_9N_3S$: C, 46.43; H, 5.84; S, 20.66. Found: C, 46.60; H, 5.52; S, 20.44.

(II) *Bis(2-methyl-4-amino-5-pyrimidylmethyl) disulfide.* The aqueous alkaline solution from which the 2-methyl-4-amino-5-mercaptomethylpyrimidine above was extracted was kept at room temperature for four days. A white crystalline precipitate which weighed 1.6 g. was obtained and was recrystallized from ethanol, m.p. 242–245° (dec.).

Anal. Calcd. for $C_{12}H_{16}N_6S_2$: C, 46.73; H, 5.23; N, 27.25; S, 20.79. Found: C, 47.01; H, 5.38; N, 27.00; S, 20.57.

Bis(2-methyl-4-amino-5-pyrimidylmethyl) disulfide (III), *bis(2-methyl-4-amino-5-pyrimidylmethyl) sulfide* (IV) *and 2-methyl-7-aminothiazino(6,5-e)pyrimidine* (VII). (I) *Bis-(2-methyl-4-amino-5-pyrimidylmethyl) disulfide.* 2-Methyl-4-amino-5-bromomethylpyrimidine dihydrobromide (10 g., 0.27 mole) was added to a solution of 2.08 g. (0.027 mole) of thiourea in 150 ml. of tetrahydrofuran. The mixture was refluxed with stirring for 50 min. A solid precipitate which weighed 11.6 g. was collected after cooling. The material slowly decomposed between 200° and 235°. A solution of 5 g. of this material in 50 ml. of 10% sodium hydroxide was neutralized with hydrochloric acid after standing 30 min. and then extracted five times with 100-ml. portions of ether. After the combined ether solutions were dried over magnesium sulfate for 1 hr., the ether was distilled giving *ca.* 100 mg. of pale yellow crystalline residue contaminated with viscous material. The residue was recrystallized twice from 20-ml. portions of ethanol giving colorless crystals which melted at 245°. On admixture with bis-(2-methyl-4-amino-5-pyrimidylmethyl) disulfide, no melting point depression was observed.

(II) *7-Amino-2-methyl-5(H)-metathiazino[4,5-d]pyrimidine* (VII). The neutralized solution from which ether-soluble materials were extracted in (I) was concentrated to 10 ml. *in vacuo* and cooled. A colorless precipitate was collected and recrystallized three times from ethanol, m.p. 256–258°.

Anal. Calcd. for $C_7H_8N_4S$: C, 46.65; H, 4.47; N, 31.09; S, 17.74. Found: C, 46.90; H, 4.55; N, 31.14; S, 17.76.

The condensation product (5 g.) from 2-methyl-4-amino-5-bromomethylpyrimidine dihydrobromide and thiourea was dissolved in 30 ml. of water and the solution was made weakly alkaline with sodium carbonate. The white precipitate which immediately appeared was collected, washed three times with 10-ml. portions of water, and then heated with 500 ml. of ethanol. The material slowly dissolved in ethanol with evolution of ammonia. After all the solid was dissolved in the ethanol, the solution was concentrated to 50 ml. and cooled. Colorless crystals which weighed 1.78 g. separated and were recrystallized from 80 ml. of ethanol, giving crystals which melted at 256–258°. No melting point depression was observed on admixture with the earlier sample of VII.

(III) *Bis(2-methyl-4-amino-5-pyrimidylmethyl) sulfide* (IV). The condensation product (11.6 g.) from 10 g. of 2-methyl-4-amino-5-bromomethylpyrimidine dihydrobromide and 2.08 g. of thiourea was dissolved in 15 ml. of water. The white precipitate which appeared immediately on neutralization with sodium hydroxide was collected and washed with 10 ml. of water. The material weighed 5.4 g. and melted at 154–158°. This material was dissolved in 30 ml. of boiling 10% sodium hydroxide and the solution was refluxed for 1 hr. After cooling, the precipitated crystals were recrystallized from ethanol giving 1.3 g. of colorless crystals, m.p. 284–286° (dec.).

Anal. Calcd. for $C_{12}H_{16}N_6S$: C, 52.12; H, 5.85; N, 30.42; S, 11.61. Found: C, 52.15; H, 6.07; N, 30.16; S, 11.51.

2-Methyl-4-amino-5-methylthiomethylpyrimidine (V). Methyl mercaptan (10 g., 0.208 mole) was added to a solution of 3.8 g. (0.165 mole) of sodium in 150 ml. of absolute ethanol. Then 20 g. (0.055 mole) of 2-methyl-4-amino-5-bromomethylpyrimidine dihydrobromide was added, and the mixture was stirred and refluxed for 30 min. After cooling, the precipitate (23 g.) was recrystallized from 100 ml. of 50% ethanol. A second recrystallization from 50 ml. of 50% ethanol gave 4.0 g. of colorless prisms, m.p. 176–178°. By concentration of the mother liquors, 2.5 g. more of the product was obtained.

Anal. Calcd. for $C_7H_{11}N_3S$: C, 49.68; H, 6.55; N, 24.83; S, 18.95. Found: C, 49.89; H, 6.49; N, 24.71; S, 18.76.

Bis(2-methyl-4-amino-5-pyrimidylmethyl) sulfide (IV). Sodium (2 g., 0.087 mole) was added to a solution of 5 g. (0.105 mole) of methyl mercaptan in 100 ml. of ether which was cooled in an ice salt bath. After stirring 4 hr., 10 g. (0.28 mole) of 2-methyl-4-amino-5-bromomethylpyrimidine dihydrobromide was added. Because no heat was evolved, the ether and the excess of methyl mercaptan were distilled off, and the residue was heated with 50 ml. of dioxane on a steam bath. The color of the reaction mixture suddenly changed from dark gray to pale brown when it was heated to 100°. The mixture was heated with stirring for 1 hr., and the solid was filtered off. After cooling, 10 ml. of ethanol was added to convert the remaining sodium to sodium ethoxide, and then the solvent was removed by distillation. Addition of 50 ml. of water precipitated 0.4 g. of solid which was recrystallized from 50 ml. of ethanol giving colorless crystals which melted at 277–280° (dec.). On admixture with the authentic bis(2-methyl-4-amino-5-pyrimidylmethyl) sulfide, no melting point depression was observed. The infrared spectrum was also identical with that of the sulfide.

2-Methyl-4-amino-5-thiocyanomethylpyrimidine (VI). 2-Methyl-4-amino-5-bromomethylpyrimidine dihydrobromide (5 g., 0.014 mole) was added to a solution of 1.35 g. (0.014 mole) of potassium thiocyanate in 150 ml. of tetrahydrofuran. The mixture was refluxed with stirring for 2 hr., and, after cooling, the solid precipitate (3 g.) was collected. It was dissolved in 25 ml. of water and the solution was neutralized with sodium bicarbonate giving 0.9 g. of crystalline precipitate. The precipitate was recrystallized three times from benzene. The resulting white crystals showed no definite melting point, but slowly decomposed at 150–198°.

Anal. Calcd. for $C_7H_8N_4S$: C, 46.65; H, 4.47; N, 31.09. Found: C, 47.15; H, 4.68; N, 31.07.

(8) Melting points are uncorrected. Analyses are by Microtech Inc., Skokie, Ill., and Midwest Microlab, Inc., Indianapolis, Ind.

The infrared spectra clearly distinguished this material from the isomeric thiazinopyrimidine.

The filtrate from the free thiocyanate was concentrated to 10 ml. and 0.3 g. of precipitate was obtained after standing overnight. It was recrystallized from ethanol giving colorless crystals, m.p. 248–252° (dec.). On admixture with bis(2-methyl-4-amino-5-pyrimidylmethyl) disulfide, no melting point depression was observed.

2-Methylthio-4-amino-5-formylpyrimidine (IX). A solution of 2-methylthio-4-amino-5-hydroxymethylpyrimidine (5 g., 0.027 mole) in 13 ml. of acetic acid was added with stirring to a solution of 2.9 g. (0.1 mole) of sodium dichromate dihydrate in 15 ml. of acetic acid. Colorless crystals slowly precipitated and, after 2 hr., were collected and washed with 30 ml. of water. The precipitate weighed 3.4 g. The cooled filtrate was neutralized with ammonia, and then kept at 0° overnight. An additional 0.7 g. of white precipitate was combined with the first crop. The combined product was dissolved in 300 ml. of chloroform and the green solution was washed twice with 20-ml. portions of water, which removed the color. The decolorized chloroform solution was dried with magnesium sulfate and concentrated to 100 ml. On cooling and filtering, 2.50 g. of colorless crystals, m.p. 183–184°, were obtained. The filtrate was further concentrated to 20 ml. giving another 0.50 g. of crystals, m.p. 182–183°.

Anal. Calcd. for $C_6H_7N_3OS$: C, 42.59; H, 4.17; N, 24.84; S, 18.95. Found: C, 42.53; H, 4.23; N, 24.89; S, 18.92.

2-Methylthio-4-amino-5-pyrimidylaldoxime. A solution of 1.5 g. of 2-methylthio-4-amino-5-formylpyrimidine in 50 ml. of hot ethanol was added to a solution of 5 g. of hydroxylamine hydrochloride in 10 ml. of water made basic with 20 ml. of 10% sodium hydroxide. The mixed solution was heated on a steam bath for 30 min. and concentrated to 40 ml. A crystalline precipitate, which weighed 1.5 g., was recrystallized twice from a mixture of benzene and ethanol (10:1) to yield colorless crystals, m.p. 201–202°.

Anal. Calcd. for $C_6H_8N_4OS$: C, 39.12; H, 4.37; N, 30.42; S, 17.41. Found: C, 39.19; H, 4.50; N, 30.60; S, 17.50.

2-Mercapto-4-amino-5-hydroxymethylpyrimidine (XI). To a solution of lithium aluminum hydride (5 g., 0.132 mole) in 50 ml. of anhydrous ether and 300 ml. of *N*-ethylmorpholine, 10 g. (0.050 mole) of 2-mercapto-4-amino-5-carbethoxypyrimidine was slowly added as a fine powder. After the evolution of heat ceased, the reaction mixture was stirred and heated at 80° for 2.5 hr. After cooling, 20 ml. of ethyl acetate was added with stirring, and then 10 ml. of water. The precipitate was filtered after standing overnight. The filtrate gave no crystalline residue when the solvent was distilled. The solid was extracted (Soxhlet) with boiling ethanol. The extract was concentrated to 20 ml. and neutralized with acetic acid, giving 3.8 g. of crystalline precipitate. Further extractions with methanol gave no solid product. The combined extracts were recrystallized four times from ethanol, giving pale yellow crystals, m.p. 229–232° (dec.).

Anal. Calcd. for $C_5H_7N_3OS$: C, 38.20; H, 4.49; S, 20.40. Found: C, 38.42; H, 4.69; S, 20.22.

2-Methylthio-4-amino-5-bromomethylpyrimidine hydrobromide (XII). Glacial acetic acid (175 ml.) was saturated with anhydrous hydrogen bromide at 0°, and added to a solution of 12 g. of 2-methylthio-4-amino-5-hydroxymethylpyrimidine in 100 ml. of acetic acid. After heating on a steam bath for 2 hr. and cooling, 27.5 g. of white precipitate was collected. The product was recrystallized from 650 ml. of acetic acid, giving 18.5 g. of colorless needles which began to decompose above 280°.

Anal. Calcd. for $C_6H_9Br_2N_3S$: C, 22.87; H, 2.88; Br, 50.74; N, 13.34; S, 10.18. Found: C, 23.39; H, 3.08; Br, 50.81; N, 13.11; S, 9.84.

2-Methylthio-4-amino-5-methoxymethylpyrimidine (XIII). 2-Methylthio-4-amino-5-bromomethylpyrimidine hydrobromide (2 g.) was refluxed with 20 ml. of methanol for 1 hr., and then the solvent was distilled leaving an oily residue. Aqueous ammonia was added to the residue until the solution became weakly alkaline, and after cooling, 0.7 g. of colorless crystals precipitated. Recrystallization from water followed by recrystallization from a mixture of benzene and ligroin gave colorless prisms, m.p. 104–106°.

Anal. Calcd. for $C_7H_{11}N_3OS$: C, 45.39; H, 5.98; S, 17.31. Found: C, 45.60; H, 5.70; S, 17.91.

2-Methylthio-4-amino-5-methylthiomethylpyrimidine (XIV). Methyl mercaptan (1 g., 0.02 mole) was added to a solution of 0.5 g. (0.02 mole) of sodium in 100 ml. of absolute ethanol and 3 g. (0.01 mole) of 2-methylthio-4-amino-5-bromomethylpyrimidine hydrobromide was added with stirring. After the evolution of heat stopped, the mixture was heated on a steam bath for 30 min. with stirring. The solvent was distilled off, 40 ml. of water was added to the residue and the mixture stirred and heated for 10 min. The crystalline precipitate was filtered after cooling and recrystallized twice from 30% ethanol, giving 1.4 g. of colorless prisms, m.p. 139–140°.

Anal. Calcd. for $C_7H_{11}N_3S_2$: C, 41.76; H, 5.51; N, 20.88; S, 31.86. Found: C, 41.87; H, 5.49; N, 20.62; S, 31.74.

2-Methylthio-4-amino-5-acetylthiomethylpyrimidine (XV). 2-Methylthio-4-amino-5-bromomethylpyrimidine hydrobromide (4 g., 0.013 mole) was added to a solution of 2 g. (0.026 mole) of thioacetic acid in 25 ml. of pyridine. The mixture was stirred and heated on a steam bath for 1 hr., and the solvent was distilled *in vacuo*. The hygroscopic crystalline residue was dissolved in 20 ml. of water and then 2% sodium hydroxide was added making the solution weakly alkaline. Brown viscous material separated from the solution and slowly solidified. The solid was filtered and recrystallized from ethanol, giving 1.8 g. of pale yellow crystals which melted at 148–151°. Recrystallizing once more from ethanol and then from a mixture of ligroin and benzene (2:1), yielded almost colorless crystals, m.p. 161–163°.

Anal. Calcd. for $C_8H_{11}N_3OS_2$: C, 41.92; H, 4.84; N, 18.34; S, 27.98. Found: C, 41.95; H, 4.74; N, 18.25; S, 28.15.

2-Methylthio-4-amino-5-mercaptomethylpyrimidine (XVI). 2-Methylthio-4-amino-5-bromomethylpyrimidine hydrobromide (5.4 g., 0.017 mole) was added to a solution of 2.7 g. (0.035 mole) of thioacetic acid in 25 ml. of pyridine. The mixture was heated on a steam bath for 1 hr. After cooling, crystals of pyridine hydrobromide were filtered off, and the solvent was distilled from the filtrate *in vacuo*, leaving a brown viscous residue. The residue was heated on a steam bath with 30 ml. of 2% hydrochloric acid for 1 hr. The resulting solution was neutralized with sodium carbonate after cooling, giving a brown viscous precipitate which slowly solidified. The solid gave no crystalline product after repeated attempts of recrystallization from ethanol, acetone, and benzene. The filtrate was extracted six times with 50-ml. portions of ether. The combined extracts were dried over magnesium sulfate for 1.5 hr. After the ether was distilled at atmospheric pressure, pyridine was removed *in vacuo*, leaving 99.6 mg. of white plates. These were recrystallized from benzene, m.p. 138–139° (*in vacuo*).

Anal. Calcd. for $C_6H_9N_3S_2$: C, 38.47; H, 4.84; S, 34.24. Found: C, 37.96; H, 4.89; S, 34.05.

2-Methylthio-4-amino-5-pyrimidylmethylisothiourea dihydrobromide (XVII). 2-Methylthio-4-amino-5-bromomethylpyrimidine hydrobromide (5 g., 0.016 mole) was added to a solution of 1.3 g. (0.017 mole) of thiourea in 100 ml. of acetone. The mixture was refluxed with stirring for 2 hr. After cooling, a white solid which weighed 4.5 g. was collected and recrystallized from ethanol, m.p. 240–241°.

Anal. Calcd. for $C_7H_{13}Br_2N_3S_2$: C, 21.49; H, 3.35; N, 17.90; S, 16.39. Found: C, 21.80; H, 3.37; N, 17.76; S, 16.86.

Bis(2-methylthio-4-amino-5-pyrimidylmethyl) disulfide (XVIII). 2-Methylthio-4-amino-5-pyrimidylmethylisothiourea dihydrobromide (3 g.) was dissolved in 40 ml. of water, and to this solution ammonium hydroxide was added until the solution was shown to be weakly alkaline (*p*H 8). White crystals immediately precipitated and were collected. The precipitate weighed 1.25 g. and melted at 103–105°. A 0.2-g. sample of the precipitate was dissolved in 20 ml. of boiling ethanol and the solution was concentrated to 2 ml. and

cooled overnight. The resulting precipitate was recrystallized from ethanol giving colorless crystals which melted at 213–215°, indicating formation of disulfide.

Anal. Calcd. for $C_{12}H_{16}N_6S_4$: C, 38.69; H, 4.29; N, 22.57; S, 34.43. Found: C, 39.01; H, 4.60; N, 22.47; S, 34.13.

The alkaline filtrate gave a further 0.15 g. of white precipitate after standing five days at room temperature. The precipitate was recrystallized from ethanol giving a crystalline product which was found identical with the disulfide from ethanol recrystallization of the main crop.

2-Ethylthio-4-amino-5-hydroxymethylpyrimidine (XIX) was prepared from 2-mercapto-4-amino-5-carbethoxypyrimidine *via* 2-ethylthio-4-amino-5-carbethoxypyrimidine. 2-Mercapto-4-amino-5-carbethoxypyrimidine was synthesized by condensation of ethyl ethoxymethylenecyanoacetate with thiourea by the method of Ulbricht and Price,[3] and the yield of 2-ethylthio-4-amino-5-hydroxymethylpyrimidine from ethyl ethoxymethylenecyanoacetate was 48%. This was a considerable improvement over the yields obtained by other workers.[9]

2-Mercapto-4-amino-5-carbethoxypyrimidine (10 g., 0.05 mole) was dissolved in a solution of 3.1 g. (0.055 mole) of potassium hydroxide in 50 ml. of water and 8 g. (0.052 mole) of diethyl sulfate was gradually added with shaking. After stirring 3 hr., the crystals were collected, washed and dried to yield 9.4 g. (83%) of 2-ethylthio-4-amino-5-carbethoxypyrimidine. This may be recrystallized from ethanol to give pale yellow plates, m.p. 100–102°.

This material was placed in a Soxhlet extractor mounted on a flask containing a solution of 3 g. (0.079 mole) of lithium aluminum hydride in 350 ml. of dry ether. The ether was refluxed with stirring for 3 hr. After cooling, 20 ml. of ethyl acetate was added with stirring, and then 10 ml. of water. The solid precipitate was filtered after standing overnight, and then extracted three times with 100-ml. portions of boiling acetone. The acetone solutions were combined and the solvent was distilled yielding white crystalline residue. The ether was distilled from the filtrate giving pale yellow crystalline residue which was combined with the acetone extracts. The crude products were washed with acetone and benzene leaving 7.5 g. of white crystals. After recrystallizing from ethanol, 5.9 g. (74%) of crystals which melted at 154–155.5° (lit.[8] m.p. 170° and 151–152° were obtained.

Anal. Calcd. for $C_7H_{11}N_3OS$: C, 45.38; H, 5.99; N, 22.68; S, 17.31. Found: C, 45.56; H, 6.15; N, 22.59; S, 17.49.

Infrared spectra (in potassium bromide, wavelength, and % absorption): IV; 2.98 (66), 3.15 (71), 6.06 (82), 6.29 (83), 6.43 (79), 6.76 (62), 7.02 (78), 7.33 (52), 7.78 (48), 8.12 (53), 10.00 (35), 10.30 (57), 12.64 (45), 12.89 (46).

VI; 2.90 (82), 3.22 (85), 4.61 (79), 6.00 (90), 6.29 (88), 6.38 (90), 6.75 (83), 7.01 (88), 7.80 (75), 8.13 (80), 9.63 (63), 10.35 (72), 11.38 (58), 12.65 (78), 12.97 (84), 13.27 (77), 14.50 (60).

VII; 2.90 (39), 3.34 (53), 6.57 (72), 7.04 (78), 7.31 (58), 7.60 (64), 8.33 (34), 8.70 (36), 8.82 (34), 10.41 (36), 12.27 (39), 12.47 (44), 12.85 (41), 14.54 (29).

PHILADELPHIA 4, Pa.

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[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1]]

Steroidal Sapogenins. XLIX. C-Ring Oxygenated Derivatives of Correllogenin[2]

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In the course of conversion of natural mixtures of the 25D and 25L isomeric sapogenins gentrogenin (25D) and correllogenin (25L) to 11-keto diosgenin and 11-keto yamogenin, it was found possible to separate and characterize several intermediates which were sterically pure 25L compounds, *viz.* 3β,12β-dihydroxy-20α,22β,25L-spirost-5-en-11-one, Ia, and its diacetate, Ib; 20α,22β,25L-spirost-5-en-3β,11α-diol, IIa, and its diacetate, IIb. These new correllogenin derivatives have previously evaded isolation because of the difficulties in separating the pure parent compound. It was found that 3β,12β-diacetoxy-20α,22β,25D-spirost-5-en-11-one on treatment with calcium in liquid ammonia solution gave, in the presence of water, a high yield of 20α,22β,25D-spirost-5-en-3β,11α-diol (11α-hydroxy diosgenin).

In earlier papers of this series[3,4] we have described the isolation of gentrogenin[3] (3β-hydroxy-20α,22β,25D-spirost-5-en-12-one[5]), its 25L-diastereoisomer, correllogenin,[3] and the conversion of the former to 11-keto diosgenin.[4] In the latter paper were described the properties and reactions of a number of C-11 and C-12 oxygenated derivatives of gentrogenin. Because of the unavailability of pure correllogenin,[6] we were unable to prepare the corresponding 25L- derivatives. During the large scale conversion of a gentrogenin-correllogenin mixture to 3β-hydroxy-5,16-pregnadiene-11,20-dione,[7] we were able to isolate and characterize

(1) Eastern Utilization Research and Development Division, Agricultural Research Service, United States Department of Agriculture.

(2) Paper XLVIII, E. S. Rothman and M. E. Wall, submitted to *J. Am. Chem. Soc.*

(3) H. A. Walens, S. Serota, and M. E. Wall, *J. Org. Chem.*, **22**, 182 (1957).

(4) E. S. Rothman and M. E. Wall, *J. Am. Chem. Soc.*, **79**, 3228 (1957).

(5) For basis of formal nomenclature, particularly at C_{22}, *cf. Tentative Rules for Steroid Nomenclature*, Comptes Rendus de la Dix-Huitieme Conference, Zurich, 20-28 July, 1955, pp. 190–198.

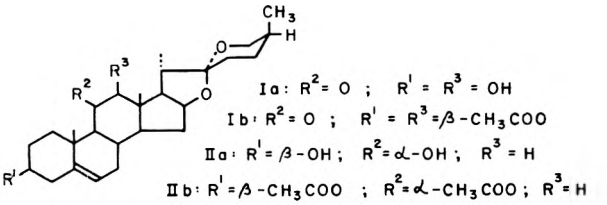
(6) Although correllogenin may constitute twenty per cent of the total ketonic fraction isolated from *D. spiculiflora*, it is difficult to separate this sapogenin from the isomeric gentrogenin[3] and consequently only minute quantities of the sterically pure 25L- form have ever been obtained.

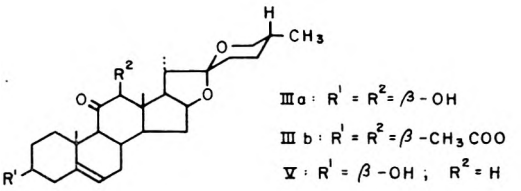
(7) Since pseudomerization followed by oxidative cleavage and alkaline hydrolysis converts the 25D- and 25L-sapogenins to the same 16-dehydro-20-keto-pregnene it is often convenient to work directly with the mixture.

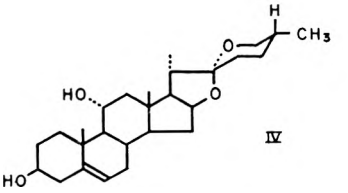
several sterically pure correllogenin derivatives. In this paper we wish to record the properties of these compounds as well as those of the corresponding 25D- series.

In the manner described previously,[4] bromination of a gentrogenin-correllogenin mixture gave the 5α,6β,11α,23-tetrabromo sapogenins which, on treatment with sodium iodide, gave the 11α,23-dibromo sapogenins of the 25D- and 25L- mixture. Alkaline equilibration in aqueous tertiary butyl alcohol[8] gave a mixture of the isomeric 25D- and 25L- derivatives of 3β,12β-diacetoxy-20α, 22β-spirosten-5-en-11-one. In experiments in the hecogenin series,[8] the English workers found that alkaline equilibration of 11α,23-dibromohecogenin acetate in methanol or ethanol gave, in addition to the desired 12β-hydroxy-11-one, some of the undesirable 11-hydroxy-12-ones. In contrast, similar equilibration in hot aqueous *t*-butyl alcohol gave only the desired 12β-hydroxy-11-one. We also[4] had previously established the absence of 12 ketone in the equilibrium mixture (by testing with Girard's reagent) when the hydrolysis step was carried out in the case of the sterically pure, brominated gentrogenin derivative. We then saponified and equilibrated a mixture of brominated sapogenins derived from a natural gentrogenin-correllogenin mixture in the tertiary-butanol system and, reasoning by analogy, felt that such treatment would lead to the desired 12β-hydroxy-11-one. After a series of crystallizations and treatment with carbon (*cf.* Experimental section) a residual fraction was saponified, resulting in the isolation of a small quantity of the very insoluble, sterically pure 3β,12β-dihydroxy-20α,22β,25L-spirost-5-en-11-one (Ia). Acetylation in hot acetic anhydride–pyridine gave 3β,12β-diacetoxy-20α,22β,25L-spirost-5-en-11-one (Ib). Because the yield of Ia was less than one per cent of the total starting material it was necessary to prove its structure. The infrared spectra of Ia and Ib showed the typical "normal" (25L) series of bands in the 800–1000 cm.$^{-1}$ region.[9] The spectrum of Ib showed the same acetate band shift from 1735 cm.$^{-1}$ to 1750 cm.$^{-1}$ observed in 11,12-ketol derivatives in the hecogenin series.[8] The carbon and hydrogen analysis of Ib confirmed the tentative structural assignments. Compound Ia did not react with Girard's reagent T eliminating from consideration ketols with the 11-hydroxy-12-one moiety. That the structure of Ia and Ib was indeed that of a 12β-hydroxy-11-one and the corresponding acetate, respectively, was shown in a clear-cut manner by the molecular rotation contribution of the 12-acetoxy group. It was shown in the hecogenin series that the Δ-M_D for a 12β-acetoxy-11-one was −237° and for the corresponding 12α-acetoxy-11-one, +212.[8] The corresponding value for Ib was −226° ± 50.[10] Hence the structure of Ia and Ib is indeed in accord with our predictions based on analogy.

The remaining crystalline fractions (after removal of sterically pure Ia) were combined, reacetylated, and reduced with calcium-ammonia[11] as described previously.[4] Chromatography of the saponified product on Florisil[12] gave first the expected mixture of 11-keto diosgenin and 11-keto yamogenin. A more tenaciously adsorbed fraction was then eluted from which, after reacetylation followed by several recrystallizations, we obtained an appreciable quantity of 3β,11α-diacetoxy-20α,22β,25L-spirost-5-ene (IIb). Saponification gave 20α,22β,25L-spirost-5-ene-3β,11α-diol (IIa).







The structure proof of IIa and IIb is based on the following considerations. The infrared spectrum of IIa shows the typical "normal" (25L) sapogenin fingerprint bands[9] and absence of carbonyl. Carbon and hydrogen analyses of IIa and IIb are in

(8) J. Elks, G. H. Phillipps, T. Walker, and L. J. Wyman, *J. Chem. Soc.*, 4330 (1956).

(9) M. E. Wall, C. R. Eddy, M. L. McClennan, and M. E. Klumpp, *Anal. Chem.*, 24, 1337 (1952).

(10) In order to calculate the MD contribution of the 12 acetoxy group in Ib it was necessary that the MD of the corresponding 12-desoxy steroid, 11-keto yamogenin acetate be known. Since the latter has not been prepared it was necessary to assign a hypothetical value based on the follow-known specific rotations:

12-keto diosgenin acetate (25D) = −56°
12-keto yamogenin acetate (25L) = −60°
11-keto diosgenin acetate (25D) = −86°

hence 11-keto yamogenin acetate (25L) = −90° ± 10°

The ±10° factor is well within the differences between all known pairs of 25D and 25L diastereoisomers.

(11) J. H. Chapman, J. Elks, G. H. Phillips, and L. J. Wyman, *J. Chem. Soc.*, 4344 (1956).

(12) Mention of commercial products does not imply endorsement by the U. S. Department of Agriculture over similar products not mentioned.

accord with the formulation of a dihydroxy or diacetoxy-sapogenin, respectively. From the method of preparation the compounds must have a 3β,11-dihydroxy function. Since IIb is a diacetate produced under mild acetylation conditions IIa and IIb must have, respectively, the 3β,11α-dihydroxy and 3β,11α-diacetoxy functions. The hitherto unknown 3β,12β-dihydroxy 20α,22β,25D-spirost-5-en-11-one (IIIa) was prepared by saponification of the known[4] 3β,12β-diacetate (IIIb).

Previously,[5] we had prepared 20α,22β,25D-spirost-5-ene-3β,11α-diol (IV) in low yield by reduction of 3β,12β-diacetoxy-20α,22β,25D-spirost-5-en-11-one (IIIb) with calcium-anhydrous liquid ammonia, the chief product being the corresponding 11-ketone (V). Reduction of IIIb with calcium–liquid ammonia in the presence of water gave IV as the sole product in good yield.

The reductive deacetoxylation of a non-olefinic 12β-acetoxy-11-ketone with calcium in ammonia *to the point of disappearance* of the blue calcium solution color *followed by* the addition of methanol was reported by Chapman, Elks, Phillipps, and Wyman.[11] Their product was 11α-hydroxy tigogenin. The behavior of a Δ^5-3β-hydroxy system toward such a reactive reagent is not predictable. Birch[13] has noted that the presence of protonic substances, for example water, profoundly affects the course of such reductions. In such systems benzene forms 1,4-dihydrobenzene and allyl alcohols are converted to hydrocarbons. While Δ^5-3β-ols are not true allyl alcohols, they have many properties that suggest a close interrelationship between the olefin and alcohol groups. For example, 3,5-cyclo systems form under appropriate conditions. When we reduced compound IIIb with blue calcium–liquid ammonia–water systems we did not observe any attack on the Δ^5-3β-hydroxy system and obtained compound IV directly in high yield.

EXPERIMENTAL

3β,12β-Dihydroxy-20α,22β,25L-spirost-5-en-11-one (Ia). The isolation of Ia was fortuitous. We had been working up mother liquors from a debromination experiment leading to 160 g. of the isomeric mixture of 3β,12β-diacetoxy-20α,22β-spirost-5-en-11-one compounds.[4] The first crop from 300 ml. of ethanol was 69 g. of 25D and 25L mixed product. The filtrate was diluted with 300 ml. of benzene and then with 1700 ml. of petroleum ether, b.p. 89–98°. The clear supernatant liquor was decanted from 64 g. of a tarry residue (which later yielded an additional 21 g. of crystalline mixed product) and the solution was boiled to expel benzene. The cooled filtrate was treated with 100 g. of Darco G-60 carbon which was well washed with petroleum ether. These washings were concentrated to a small volume whereupon 8.2 g. of crystalline mixed isomers separated. Further washing of the carbon with methylene chloride and with ethanol gave, after evaporation, 17 g. of a glassy residue. Saponification of the residue gave 1.03 g. of a very insoluble crystallizate, m.p. 244–247°, insoluble in methylene chloride and in ethanol but soluble in a 1:1 mixture of these solvents. The product recrystallized from this mixture in hexagonal prisms, $[\alpha]_D^{25}$ −112°, and melted from 247 to 248° with characteristic transition to smaller, bladed forms only above 240°. The infrared spectrum (KBr disk) showed a strong hydroxyl band envelope at 3400 to 3500 cm.$^{-1}$, ketone at 1716 cm.$^{-1}$ and sapogenin bands at 846, 900, 917, and 985 cm.$^{-1}$ of the type characteristic of 25L sapogenins. The fingerprint spectrum was highly complex showing forty-five well-defined bands. In chloroform solution the ketone band occurred at 1707 cm.$^{-1}$

3β,12β-Diacetoxy-20α,22β,25L-spirost-5-en-11-one (Ib). The dihydroxy ketone of the above preparation was acetylated by refluxing for 2 hr. in 1:1 acetic anhydride–pyridine mixture (forcing conditions). After cooling and diluting with water, the steroid was collected by filtration and dried. Its solution in methylene chloride was freed of brownish coloration by passing through a pad of Florisil.[12] After evaporation to dryness the colorless residue was crystallized from ethanol to give felted microneedles, $[\alpha]_D^{25}$ −120°, m.p. 194.3–196.8°, after slight sweating at 178°.

Anal. Calcd. for $C_{31}H_{44}O_7$: C, 70.43; H, 8.39. Found: C, 70.48; H, 8.66.

3β,11α-Diacetoxy-20α,22β,25L-spirost-5-en (IIb). Ninety grams of a C-25 diastereoisomeric mixture of 3β,12β-diacetoxy-20α,22β-spirost-5-en-11-one was deacetoxylated at C-12 by reduction with calcium in liquid ammonia.[4] Chromatography of the saponified reduction product on Florisil[12] gave, on elution with 20% chloroform in benzene, the expected mixture of 11-keto diosgenin and 11-keto yamogenin. Further elution with chloroform gave a dihydroxy fraction only partly soluble in benzene. The benzene suspension was filtered and the filtrate, which was richer in the 25L-component, was evaporated to dryness. The residue was crystallized from ether and acetylated to give 10 g. of the nearly sterically pure isomer 3β,11α-diacetoxy-20α,22β,25L-spirost-5-ene (IIb). A single recrystallization from methanol gave a sterically pure sample. Five recrystallizations from methanol did not alter the melting point, *viz.* 190–191.5°, $[\alpha]_D^{25}$ −123°, feathery, felted microneedles.

Anal. Calcd. for $C_{31}H_{46}O_6$: C, 72.34; H, 9.01. Found: C, 72.62; H, 9.07.

20α,22β,25L-Spirost-5-en-3β,11α-diol (IIa). A sample of the diacetate of the preceding preparation was saponified in methanolic 5% potassium hydroxide. Crystallization from methylene chloride–hexane gave hexagonal prisms with pyramidal caps $[\alpha]_D^{25}$ −123°, m.p. 247.2–248.2° after transition over 243° to wedges.

Anal. Calcd. for $C_{27}H_{42}O_4$: C, 75.31; H, 9.83. Found: C, 75.05; H, 9.91.

3β,12β-Dihydroxy-20α,22β,25D-spirost-5-en-11-one (IIIa). A sample of the diacetate[4] was saponified by refluxing in methanolic 5% potassium hydroxide for 4 hr. The mixture was poured into water and the steroid collected. The dried product was dissolved in ether, diluted with hexane, and the solution was freed of ether by volume reduction to yield a crystalline residue which was further recrystallized from acetone to give short, hexagonal microprisms, $[\alpha]_D^{25}$ −95°, melting from 236–240° and giving a pink melt. Incomplete transition to branched filaments was observed beyond 223°.

Reduction of IIIb to 20α,22β,25D-spirost-5-en-3β,11α-diol (11α-hydroxydiosgenin) (IV). A sample of 3β,12β-diacetoxy-20α,22β,25D-spirost-5-en-11-one, 85 g., in 900 ml. of toluene was added to a solution of 67 g. of calcium metal in 4 liters of liquid ammonia during an addition time of 20 min. The mixture was mechanically stirred during the addition and during the subsequent reaction time of 10 min. Water was added cautiously in a thin stream until the blue color of the reaction mixture was discharged, an excess of water doing no harm. The mixture was evaporated in an open vessel to a white solid residue. This residue was shaken with ether and dilute aqueous hydrochloric acid until all solids were in solution. The organic layer was separated, washed with water and with saturated saline solution, and evaporated to dryness. To insure complete saponification of the 3-acetate it

(13) A. J. Birch, *Quart. Revs.* (*London*), **4**, 69 (1950).

was occasionally necessary to carry out a saponification step with 5% methanolic caustic. The product, m.p. 228–233°, was very soluble in hexane and ether but gave thick, hexagonal prism-like forms on recrystallization. The analytical sample thus obtained melted from 233–235° after undergoing crystal transition above 228° to whips, $[\alpha]_D^{25}$ −116° ($CHCl_3$). This compound is 11α hydroxy diosgenin.

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PHILADELPHIA 18, PA.

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

Steroids. XCVIII.[1] Synthesis of Some 10β-Hydroxy-19-norsteroids

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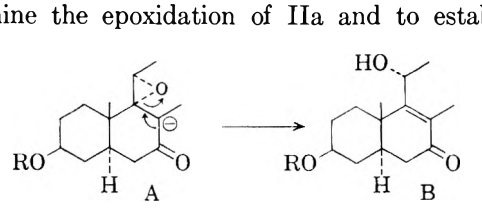
The direction and stereochemistry of the acid- and base-catalyzed opening of 5,10-epoxides of certain 19-norsteroids is discussed and the synthesis of several 10β-hydroxy-19-norsteroids is reported.

The removal of the angular methyl group at C-10 of certain steroids such as progesterone[2,3] or 17α-ethinyltestosterone[4] has led to a marked increase in biological activity. This is particularly noteworthy in the latter compound, 19-nor-17α-ethinyltestosterone (Ib)[4] whose high hormonal activity[1,4] by the oral route has led to the introduction of this compound (Norlutin) into medical practice. It was felt that it might be of interest to examine the effect of other angular substituents upon biological potency and the present paper is concerned with certain 10β-hydroxy-19-norsteroids.

Pederson and collaborators[5] reported recently that microbiological hydroxylation of 19-nortestosterone (Ia)[6] led in poor yield to a 10-hydroxy derivative, whose structure was confirmed by osmium tetroxide hydroxylation[7] of the β,γ-unsaturated precursor IIa[8] of 19-nortestosterone (Ia) followed by dehydration of the intermediate glycol. The stereochemistry of the introduced 10-hydroxyl group was not established by the Upjohn group[5] but conclusive evidence in favor of the 10β-orientation could be provided[9] by noting the coincidence of the rotatory dispersion curve of 10-hydroxy-19-nortestosterone (IVa) with that[10] of 19-nortestosterone (Ia), where the 10β-orientation is established. If the hydroxylation product had been the 10α-isomer VIa, then the rotatory dispersion curve would have been of an antipodal type.[11] Consequently, 10β-hydroxy-19-nortestosterone (IVa) can now be employed as the key reference compound for stereochemical considerations in this series.

Since we were interested in preparing 10β-hydroxy-19-norsteroids which might also bear substituents at C-5 (*vide infra*), the most attractive synthesis of 10β-hydroxy-19-norsteroids might well proceed *via* the 5,10-epoxide (*e.g.*, III) of a 5,10-unsaturated 19-nor-3-ketosteroid (II). In fact, earlier work from this laboratory[12] had demonstrated the facile conversion of the epoxy ketone A by alkaline treatment to the unsaturated hydroxy ketone B and the structural situation should be completely analogous in a 5,10-epoxy-3-ketone (III). Nevertheless, there exists a patent claim[13] that epoxidation of IIa leads to a sharp-melting epoxide (IIIa or Va) which upon exposure to alkali furnishes both C-10 epimeric hydroxy-19-nortestosterones (IVa and VIa). The mechanistic unlikeliness of such a reaction—assuming the epoxide to be homogeneous[14]—prompted us to re-examine the epoxidation of IIa and to establish



(1) Paper XCVII. D. A. McGinty and C. Djerassi, *Ann. N. Y. Acad. Sci.*, **71**, 500 (1958).

(2) C. Djerassi, L. Miramontes, and G. Rosenkranz, *J. Am. Chem. Soc.*, **75**, 4440 (1953).

(3) G. W. Barber and M. Ehrenstein, *Ann.*, **603**, 89 (1957).

(4) C. Djerassi, L. Miramontes, G. Rosenkranz, and F. Sondheimer, *J. Am. Chem. Soc.*, **76**, 4092 (1954).

(5) R. L. Pederson, J. A. Campbell, J. C. Babcock, S. H. Eppstein, H. C. Murray, A. Weintraub, R. C. Meeks, P. D. Meister, L. M. Reineke, and D. H. Peterson, *J. Am. Chem. Soc.*, **78**, 1512 (1956).

(6) A. J. Birch, *J. Chem. Soc.*, 367 (1950); A. L. Wilds and N. A. Nelson, *J. Am. Chem. Soc.*, **75**, 5366 (1953); J. A. Hartman, A. J. Tomasewski, and A. S. Dreiding, *J. Am. Chem. Soc.*, **78**, 5662 (1956).

(7) R. L. Pederson and J. C. Babcock, U.S. Patent 2,806,862.

(8) A. J. Birch and S. M. Mukherji, *J. Chem. Soc.*, 2531 (1949).

(9) C. Djerassi, R. Riniker, and B. Riniker, *J. Am. Chem. Soc.*, **78**, 6377 (1956).

(10) C. Djerassi, R. Riniker, and B. Riniker, *J. Am. Chem. Soc.*, **78**, 6362 (1956).

(11) See C. Djerassi, M. Ehrenstein, and G. W. Barber, *Ann.*, **612**, 93 (1958).

(12) C. Djerassi, O. Mancera, J. Romo, and G. Rosenkranz, *J. Am. Chem. Soc.*, **75**, 3505 (1953).

(13) F. B. Colton, U.S. Patent 2,729,654.

(14) The physical constants of this epoxide are in reasonable agreement with those found in our laboratory for a homogeneous specimen.

precisely the stereochemistry of the resulting epoxide and of its transformation products.

Treatment of $\Delta^{5(10)}$-19-norandrosten-17β-ol-3-one (IIa)[8] with monoperphthalic acid at low temperature furnished in 65% yield a pure epoxide which is assigned the 5β,10β-stereochemistry (IIIa), since upon heating with methanolic potassium hydroxide solution it was transformed smoothly into the known[5,9] 10β-hydroxy-19-nortestosterone (IVa). By the same sequence of reactions, the β,γ-unsaturated isomer IIb[15] of 19-nor-17α-ethinyltestosterone (Ib)[4] was converted into the 5β,10β-epoxide IIIb and rearranged with alkali to 10β-hydroxy-19-nor-17α-ethinyltestosterone (IVb). The 10β-orientation followed from analogy to the course of this reaction sequence in the 19-nortestosterone series (Ia, IIa, IIIa, IVa) and from the fact that its rotatory dispersion curve was nearly identical with that[10] of 19-nortestosterone (Ia).

The predominant formation of the 5β,10β-epoxide (III) is noteworthy since alpha attack is usually favored among steroids and production of the α-epoxide (V) might have been expected. However in the absence of the angular methyl group at C-10, the steric factors controlling approach of the reagent are rather subtle and in particular, it should be noted that the 5α,10α-epoxide would contain the unfavorable 9,10-*syn* backbone in contrast to the 9,10-*anti* situation existing in the β-epoxide III which may well represent the controlling factor.

As has been reported earlier,[1,4] 19-nor-17α-ethinyltestosterone (Ib) is an extremely powerful, orally effective progestational agent. In a preliminary Clauberg assay in rabbits, the 10β-hydroxy analog IVb possessed[16] only about one-fourth the oral progestational activity of Ib. We can conclude tentatively, therefore, that substitution of the C-10 angular methyl group by hydroxyl does not have the biological potentiating effect of substitution by hydrogen.

Introduction of fluorine at various positions of the steroid molecule often results in interesting biological properties[17] and this applies also to progesterone.[18] It was decided, therefore, to prepare some fluorine-containing 19-norsteroids by the boron trifluoride procedure of Henbest and Wrigley,[19] although it was appreciated that fluorohydrins have generally been obtained from trialkylated epoxides while the few tetra-substituted ones[19] led to dienes. In view of the fact that the boron trifluoride-promoted opening of epoxides is very sensitive to electronic and conformational factors[19] no secure *a priori* prediction about the course of this reaction with 3-keto-5,10-epoxides IIIa and IIIb could be made. When the reaction was performed under the conditions reported in the Experimental section, there was isolated in each case in high yield a single, homogeneous fluorohydrin which on the basis of the usual *trans* diaxial opening mechanism of epoxides[20] could only possess structures VIIa and b or VIIIa and b. Of the two alternatives, VII is favored for the reason already advanced above in a discussion of the 5β,-10β-epoxide formation, namely the presence of an *anti* 9,10-backbone[21] in the fluorohydrins VIIa and VIIb. Nevertheless, it was felt that this assignment should be subjected to more secure confirmation and for that purpose, the fluorohydrins VIIa and VIIb were treated with alkali and in each instance yielded the corresponding 10β-hydroxy-Δ^4-3-ketones IVa and IVb. This result tends to support formulations VIIa and VIIb by assuming simple base-catalyzed dehydrofluorination, but it is also possible that the reaction proceeds by initial base-promoted ring closure[22] of the fluorohydrin back to the epoxide III. Since either fluorohydrin VII or VIII would yield the same epoxide III and since the latter has already been shown above to rearrange to the 10β-hydroxy-Δ^4-3-ketone IV, this alternative course weakens the structure proof of the fluorohydrin. As a result, the epoxy ketone IIIa was treated with perchloric acid in acetone solution to yield a glycol, which was not isolated but which dehydrated directly to the 10β-hydroxy unsaturated ketone IVa. The glycol had to possess structure IX or X and since dehydration in this case would not proceed *via* an epoxide, the orientation of the surviving hydroxyl group of the dehydration product must be identical with that in the glycol. Since the dehydration product was identified as the 10β-hydroxy derivative IVa, the precursor must have been the 5α,10β-glycol IX and we feel justified in assuming the identical stereochemical arrangement for the fluorohydrin (VIIa and b).

In connection with the (perchloric) acid opening of the epoxide IIIa, there was also examined the stability of the 10β-hydroxy-Δ^4-3-keto moiety toward acidic reagents since Pederson *et al.*[5] mentioned in a preliminary communication that acid-catalyzed dehydration of 10β-hydroxy-19-nortestosterone (IVa) led to estradiol without giving any details.

(15) F. B. Colton, U.S. Patent 2,725,389.

(16) The substance exhibited anti-estrogenic activity in mice at a dose of 400γ when employing 0.4γ of estrone.

(17) See J. Fried and E. F. Sabo, *J. Am. Chem. Soc.*, **79**, 1130 (1957) and earlier references.

(18) P. Tannhauser, R. J. Pratt, and E. V. Jensen, *J. Am. Chem. Soc.*, **78**, 2658 (1956).

(19) H. B. Henbest and T. I. Wrigley, *J. Chem. Soc.*, 4596, 4765 (1957).

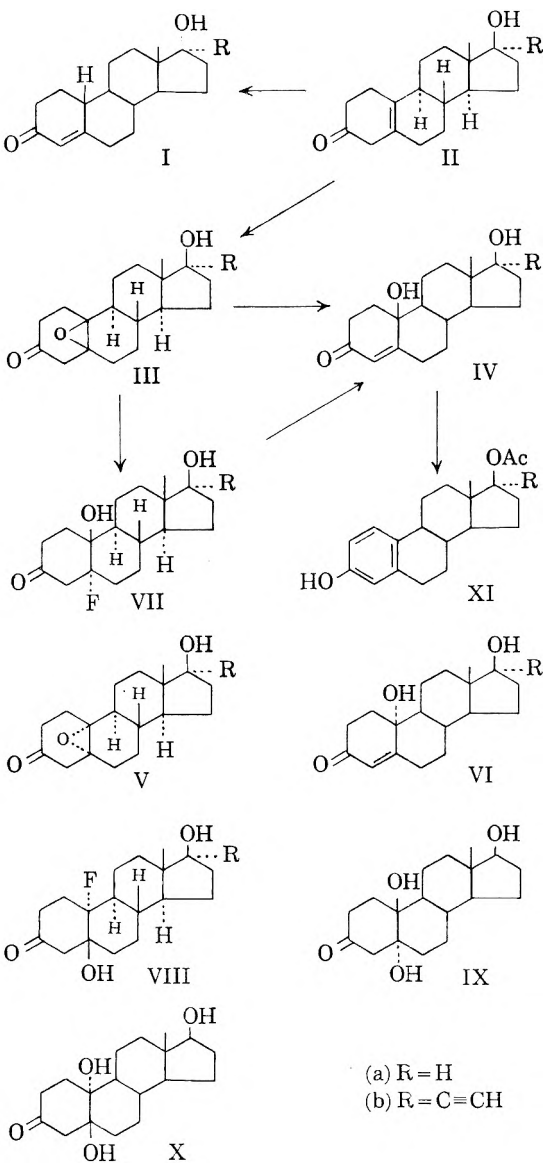
(20) A. Fürst and P. A. Plattner, 12th Internat. Congress Pure and Appl. Chem. New York, 1951, Abstracts, p. 409. For an example of abnormal epoxide opening see W. S. Knowles and Q. E. Thompson, *J. Am. Chem. Soc.*, **79**, 3212 (1957).

(21) The unfavorable *trans-syn-trans* stereochemistry (as in VIII) has already been discussed by W. S. Johnson, *Experientia*, **7**, 315 (1951).

(22) Reformation of a fluorohydrin to the epoxide by means of potassium *t*-butoxide has already been reported by Henbest and Wrigley (ref. 19).

In our hands, exposure of the 17-acetate of 10β-hydroxy-19-nortestosterone to hydrogen chloride–acetic acid at 5–10° effected the dehydration in nearly 80% yield with formation of estradiol 17-monoacetate (XI).

The fluorohydrin VIIb or the epoxy ketone IIIb showed one-fourth or less the oral progestational[23] activity of 19-norethinyltestosterone (Ib).[1,4] 10β-Hydroxy-19-nortestosterone IVa and the fluorohydrin VIIb were examined for androgenic and anabolic activity[24] in immature male rats using testosterone as standard and were found to exhibit anabolic-androgenic ratios of 1.5 and 1.7, respectively.



(23) These assays were carried out at the Endocrine Laboratories, Madison, Wis.

(24) Assays by Dr. Ralph I. Dorfman of the Worcester Foundation for Experimental Biology, Shrewsbury, Mass.

EXPERIMENTAL[25]

5β,10β-Oxido-19-norandrostan-17β-ol-3-one (IIIa). A solution of 400 mg. of $\Delta^{5(10)}$-19-norandrosten-17β-ol-3-one (IIa)[8] in 10 cc. of chloroform was left with 13.8 cc. of a 0.44*N* ethereal solution of monoperphthalic acid at −70° for 2 hr. and then for 18 hr. at 5–10° whereupon the consumption of reagent corresponded to 0.92 molar equivalents. Dilution with water, extraction with ether, washing with bicarbonate solution and water, followed by drying, evaporation, and recrystallization from acetone-benzene furnished 270 mg. of the epoxido ketone, m.p. 204–205°. The analytical sample was obtained from the same solvent pair and exhibited m.p. 208–210°, $[\alpha]_D$ −32, $\lambda_{max}^{CHCl_3}$ 2.74 and 5.83.

Anal. Calcd. for $C_{18}H_{26}O_3$: C, 74.44; H, 9.03; O, 16.53. Found: C, 74.32; H, 9.08; O, 16.47.

10β-Hydroxy-19-nortestosterone (IVa). The above 5β,10β-epoxide IIIa (100 mg.) was heated under reflux for 1 hr. with 15 cc. of a 5% methanolic potassium hydroxide solution, poured into water, extracted with ether and the ether solution washed well with water and dried. Evaporation and recrystallization from acetone-benzene led to 80 mg. of 10β-hydroxy-19-nortestosterone IVa, m.p. 208–210°, $[\alpha]_D$ + 80° (methanol), λ_{max}^{EtOH} 234–236 mμ, log ε 4.12, λ_{max}^{KBr} 3.0 and 6.02 μ. Except for some intensity differences[26] its rotatory dispersion curve (dioxane solution) was identical with that[9] of the microbiological specimen[5] (m.p. 199–205°, $[\alpha]_D$ +76°) and no depression in melting point was observed upon admixture.

Anal. Calcd. for $C_{18}H_{26}O_3$: C, 74.44; H, 9.03; O, 16.53. Found: C, 73.90; H, 8.87; O, 16.94.

Alternatively, 200 mg. of the epoxide IIIa in 20 cc. of acetone was left at room temperature for 16 hr. with 1.5 cc. of 1.5*N* aqueous perchloric acid and then poured into water. After processing in the usual manner followed by recrystallization from acetone-ether there was isolated 140 mg. of 10β-hydroxy-19-nortestosterone, m.p. 208–210°. Identity with the above sample was established by mixture melting point determination and infrared comparison.

5α-Fluoro-10β-hydroxy-19-norandrostan-17β-ol-3-one (VIIa). A mixture of 250 mg. of the epoxide IIIa, 30 cc. of dry benzene, 15 cc. of absolute ether, and 0.5 cc. of boron trifluoride etherate was kept at room temperature for 3 hr., washed with water, dried, and evaporated. Recrystallization of the residue from acetone-benzene furnished 230 mg. of colorless needles, m.p. 203–204°, raised to m.p. 215–217° upon repeated recrystallization, $[\alpha]_D$ −41°; no appreciable ultraviolet absorption, λ_{max}^{KBr} 2.98 and 5.85 μ.

Anal. Calcd. for $C_{18}H_{27}FO_3$: C, 69.65; H, 8.77; F, 6.12. Found: C, 70.01; H, 8.59; F, 5.58.

When 140 mg. of the fluorohydrin was heated under reflux with 5% methanolic potassium hydroxide solution for 1 hr., there was isolated 90 mg. of 10β-hydroxy-19-nortestosterone (IVa).

5β,10β-Oxido-17α-ethinyl-19-norandrostan-17β-ol-3-one (IIIb). The epoxidation of 400 mg. of 17α-ethinyl-$\Delta^{5(10)}$-19-norandrosten-17β-ol-3-one (IIb)[15] was performed exactly as described above for IIa and yielded 350 mg. of the epoxide IIIb, m.p. 168–170°. Further recrystallization from hexane-acetone provided the analytical sample, m.p. 185–187°, $[\alpha]_D$ −75° (methanol), λ_{max}^{KBr} 2.85, 3.05, and 5.85 μ.

Anal. Calcd. for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34; O, 15.26. Found: C, 76.63; H, 8.36; O, 15.24.

(25) Melting points are uncorrected. Unless noted otherwise rotations were measured in chloroform solution. All rotation, rotatory dispersion, ultraviolet and infrared measurements were carried out by Dr. L. Throop and staff. The microanalyses are largely due to Mr. Joseph F. Alicino, Metuchen, N. J.

(26) This is probably due to the fact that the product obtained by microbiological hydroxylation[5] was not completely pure as judged also by the melting point.

5α-Fluoro-17α-ethinyl-19-norandrostane-10β,17β-diol-3-one (VIIb). The boron trifluoride reaction of 200 mg. of the epoxide IIIb was carried out as described above for IIIa and after recrystallization from methanol-benzene there was obtained 160 mg. of the fluorohydrin VIIb, m.p. 247–249°, $[\alpha]_D$ −39° (methanol).

Anal. Calcd. for $C_{20}H_{27}FO_3$: C, 71.83; H, 8.14; F, 5.68. Found: C, 71.71; H, 7.99; F, 5.47.

10β-Hydroxy-17α-ethinyl-19-nortestosterone (IVb). This substance was obtained in about 80% yield when the epoxide IIIb or the fluorohydrin VIIb was heated under reflux for 1 hr. with 5% methanolic potassium hydroxide solution. The analytical sample crystallized from acetone or ethyl acetate and exhibited m.p. 263–264°, $[\alpha]_D$ + 4.5° (methanol), λ_{max}^{EtOH} 236 mμ, log ε 4.16, λ_{max}^{KBr} 2.95, 3.05, and 6.04 μ. The rotatory dispersion curve measured in dioxane solution (c, 0.059) was typical[9] of a Δ^4-3-ketosteroid with troughs[27] at $[\alpha]_{370}$ −556° and $[\alpha]_{365}$ −665° and a peak at $[\alpha]_{360}$ −604°.

Anal. Calcd. for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34; O, 15.26. Found: C, 76.22; H, 8.35; O, 15.06.

Dehydration of 10β-hydroxy-19-nortestosterone acetate to estradiol 17-acetate (XI). A current of dry hydrogen chloride was passed for 2 hr. at 5–10° through a solution of 200 mg. of 10β-hydroxy-19-nortestosterone 17-acetate[5] (m.p. 182–183°, $[\alpha]_D$ +70°) in 10 cc. of glacial acetic acid. After diluting with water, extracting with ether, washing until neutral, drying, and evaporating there was left a solid residue which was recrystallized from acetone-hexane to give 145 mg. of estradiol 17-acetate (XI), m.p. 217–218.5°. Identity with an authentic specimen[28] was established by mixture melting point determination and infrared comparison.

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(27) For nomenclature see C. Djerassi and W. Klyne, *Proc. Chem. Soc.*, 55 (1957).

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

[CONTRIBUTION FROM THE DEPARTMENT OF OBSTETRICS AND GYNECOLOGY, UNIVERSITY OF KANSAS MEDICAL CENTER]

Synthesis of Some 17-Methyl Phenolic Steroids

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17α-Methylestradiol was dehydrated with acid to give a product to which the structure 17-methyl-1,3,5(10),16-estratetraen-3-ol was assigned. The position of the double bond was not establlshed unequivocally. Pd-on-charcoal reduction of the tetraene gave two 17-methyl-1,3,5(10)-estratriene isomers. Neither of the three new compounds was estrogenically active at 5-micrograms in preliminary testing.

Myers *et al.*[1] have stated that "it would be of practical as well as theoretical interest if compounds could be discovered which possess little or no primary hormonal activity, but which still have the ability to modify or regulate endocrine balance." With this general objective in mind several 17-methyl phenolic steroids of the estrane series were prepared; in preliminary testing the substances were estrogenically inactive at a 5 microgram level. One of the compounds has been mentioned in the early literature, but was never properly characterized.

The starting material for their preparation was 17α-methyl estradiol, which has been adequately characterized and tested;[2–4] it is about equal in estrogenic activity to 17β-estradiol. It has been reported[5] that dehydration of 17α-methylestradiol in boiling acetic acid, followed by high vacuum sublimation gives rise to a substance, m.p. 157–159°, having the structure shown in either IIa or III. In our hands treatment of 17α-methylestradiol (I) with either hot acetic acid or hydrochloric acid gave a crystalline mixture which could not be resolved by fractional crystallization. Chromatography on Celite–Mg trisilicate afforded a quantitative separation of unreacted I and a second crystalline substance. The latter when purified melted at 162–162.5°. Julia and Heusser[6] in a somewhat analogous procedure in the androstane series, dehydrated 17-methyl-5-androstene-3β, 17β-diol-3-acetate by mild treatment with phosphorus oxychloride–pyridine and (as the diacetate) by treatment with acetic anhydride–pyridine. In both cases a mixture of 17-methyl and 17-methylene dehydration products were obtained, the latter identified by its characteristic methylene absorption in the infrared at 11.36μ and 6.03μ. Only one product (besides a small amount of unreacted starting material) was found on dehydrating 17α-

(1) T. C. Myers, R. J. Pratt, R. L. Morgan, J. O'Donnell, and E. V. Jensen, *J. Am. Chem. Soc.*, **77**, 5655 (1955).

(2) Elsevier's *Encyclopedia of Organic Chemistry*, Series III, Vol. 14, Supplement, Elsevier Publishing Company, New York, N. Y., 1956, p. 1988s. Several foreign patents are mentioned in this reference. Only the melting point of the free compound is given for characterization.

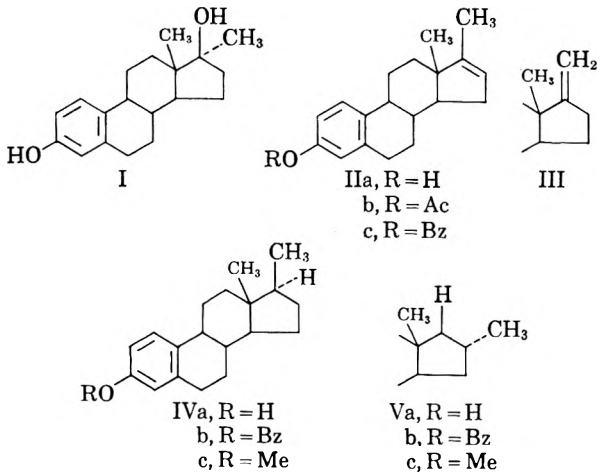
(3) H. H. Inhoffen and G. Zuhlsdorff, *Ber.*, **74**, 604 (1941).

(4) B. C. Bocklage, H. J. Nicholas, E. A. Doisy, Jr., W. H. Elliott, S. A. Thayer, and E. A. Doisy, *J. Biol. Chem.*, **202**, 27 (1953).

(5) Elsevier's *Encyclopedia of Organic Chemistry*, Series III, Vol. 14, Supplement, Elsevier Publishing Company, New York, N. Y., 1954, p. 1514s. Several foreign patents herein cited give only the m.p. of the free compound. Possible preparation of the compound is mentioned in Ref. 4.

(6) S. A. Julia and H. Heusser, *Helv. Chim. Acta*, **35**, 2080 (1952).

methylestradiol with alcoholic HCl. Barring methyl migration such as occurred in the more vigorous experiments of Cohen, Cook, and Hewitt,[7] or unexpected double bond migration (which does not seem very likely), the structure of the dehydration product would appear to be that of IIa. There is no evidence of methylene bands at 11.36μ and 6.03μ in its infrared spectrum. Structure III is therefore ruled out. However the data do not provide unequivocal evidence for the position of the double bond in IIa; further investigation is in progress.



Hydrogenation of IIa in the presence of 5% Pd-on-charcoal gave a mixture of two isomers, resolved as their benzoates. It is a general rule that hydrogenation of steroids with unsaturation at $\Delta^{16,17}$ gives rise largely or almost exclusively to a single 17-epimeride.[8] In keeping with the discussions of Shoppee and similar hydrogenations in the androstane series[9] the dextrorotatory isomer produced in larger quantity has been called 17β-methyl-1,3,5(10), estratrien-3-ol. (IVa). The other isomer, of course, is 17α-methyl-1,3,5(10), estratrien-3-ol(Va). Both compounds exhibited the typical phenolic absorption in the ultraviolet at 280 mμ.

Bioassay. Neither of the 17-methyl steroids herein reported was estrogenically active in 5 microgram quantities when tested in adult ovariectomized mice. The compounds were administered subcutaneously in oil in one injection and assayed by the Allen-Doisy vaginal smear method. When assayed in the same manner 17α-methylestradiol and estradiol-17β produced a response in all mice tested at levels of 0.5 microgram. The compounds are therefore at least ten times less active than the naturally occurring estradiol-17β or the synthetic 17α-methylestradiol. All free compounds and several derivatives are currently being subjected to extensive biological assay.

EXPERIMENTAL

All melting points were determined on a Fisher-Johns melting point block. For the optical rotations the solvent was chloroform. The ultraviolet absorption spectra were determined in 95% ethanol with a Beckman model DU spectrophotometer. The infrared curves were prepared by the KBr disk method on a Baird Associates recording spectrophotometer.

17-Methyl-1,3,5(10),16-estratetraen-3-ol (IIa). A solution of 1.77 g. of 17α-methylestradiol (m.p. 195–196°; $[\alpha]_D^{17°}$ +32.2°), prepared according to Bocklage *et al.*[5] and 100 cc. of *N* ethanolic HCl was refluxed for 24 hr. The slightly colored solution was diluted with H_2O and extracted with ethyl ether. The latter was washed with H_2O, distilled, and the residue dried *in vacuo*. The dried semicrystalline residue could not be resolved by direct crystallization from a wide variety of solvents. It was accordingly dissolved in 15 cc. of warm benzene and transferred to a 50 g. column of 50/50 magnesium trisilicate–Celite (Johns-Manville Analytical Filter Aid) previously washed with petroleum ether (b.p. 30–60°). Eight liters of petroleum ether eluted 1.32 g. (yield about 94%) of solid which on one crystallization from aqueous methanol gave white crystals, m.p. 138–140°. A sample after nine crystallizations from aqueous methanol or acetone gave 0.84 grams of analytically pure IIa, m.p. 162–162.5° as thin micro needles; $[\alpha]_D^{18°}$ +36.6°. λ_{max} 280 mμ ($E_{1\,cm.}^{1\%}$ 80).

Anal. Calcd. for $C_{19}H_{24}O$: C, 85.02; H, 9.01. Found: C, 84.98; H, 9.25.

The infrared spectrum of IIa lacked pronounced peaks at 9.2, 9.6, and 10.28 μ present in 17α-methylestradiol (I). An additional 0.38 grams of IIa, m.p. 159–160° was obtained from the mother liquor of the above crystallizations. There was no evidence of another compound.

Continued elution of the column with 2% ethanol in petroleum ether gave 0.44 grams of product which after two crystallizations from aqueous methanol melted at 192–194°, undepressed on admixture with I.

17-Methyl-1,3,5(10),16-estratetraen-3-ol acetate (IIb). The free phenol (IIa, 0.262 g., m.p. 162°) was acetylated with 3 cc. acetic anhydride and 4 cc. of anhydrous pyridine (room temperature, 24 hr.). Work-up and repeated crystallization (aqueous acetone or methanol) gave minute, glistening needles, m.p. 70–71°; $[\alpha]_D^{19°}$ −65.8°.

Anal. Calcd. for $C_{21}H_{26}O_2$: C, 81.25; H, 8.44. Found: C, 81.27; H, 8.19.

17-Methyl-1,3,5(10),16-estratetraen-3-ol benzoate (IIc). The free phenol (IIa, 0.083 g.) was treated with 20 cc. of 10% aqueous KOH and 1 cc. of benzoyl chloride. Work-up in the usual manner and crystallization to constant melting point from methanol-acetone mixtures gave jagged needles, m.p. 149–150°; $[\alpha]_D^{19°}$ −73.8°.

Anal. Calcd. for $C_{26}H_{28}O_2$: C, 83.84; H, 7.57. Found: C, 83.84; H, 7.56.

Saponification of the acetate or benzoate gave free 17-methyl-1,3,5(10),16-estratetraen-3-ol (IIa), m.p. 162°.

Hydrogenation of 17-methyl-1,3,5(10),16-estratetraen-3-ol. Attempts to selectively hydrogenate the $\Delta^{16,17}$-bond of IIa in the presence of Pt, Ni, or Pd catalyst were unsuccessful; only oils with no characteristic phenolic absorption (280 mμ) were obtained.[10]

IIa (0.884 g.) and 0.8 g. of 5% Pd-on-charcoal in 100 cc. absolute ethanol were shaken under 60 p.s.i. hydrogen for 9

(7) A. Cohen, J. W. Cook, and C. L. Hewitt, *J. Chem. Soc.*, 445 (1935).

(8) C. W. Shoppee, *Nature*, **166**, 107 (1950).

(9) M. Heller and S. Bernstein, *J. Am. Chem. Soc.*, **78**, 1161 (1956).

(10) Probably the "17-methyl octahydrofollicular hormone" (no constants given) of German Patent **643,979** (1937); Schering-Kahlbaum A.-G. According to this reference the substance shows weak androgenic activity in the capon test.

hr. Removal of catalyst and solvent gave an oil from which no crystalline product could be obtained. Elution from a magnesium trisilicate (50/50) column with petroleum ether gave 0.905 g. of light colored oil which likewise could not be crystallized.

Isolation of 17β-methyl-1,3,5(10)-estratrien-3-ol benzoate (IVb). The above oil was treated with 25 cc. 10% aqueous KOH and 5 cc. benzoyl chloride. Work-up gave a light oil which crystallized from methanol as a good crop of jagged needles, m.p. 134–135°. Several crystallizations from acetone gave white rods, m.p. 160–161.5°, unchanged by an additional crystallization from methanol-benzene; $[\alpha]_D^{17°}$ +43.5°.

Anal. Calcd. for $C_{26}H_{30}O_2$: C, 83.38; H, 8.07. Found: C, 83.20; H, 8.01.

17β-Methyl-1,3,5(10)-estratrien-3-ol (IVa). The previous benzoate (IVb, 0.271 g.) was refluxed in 20 cc. of 5% alc. KOH for 1 hr. Work-up and crystallization to constant melting point from aqueous methanol gave micro needles, m.p. 133–135°, not raised by an additional crystallization from aqueous acetone: $[\alpha]_D^{17°}$ +92.5°. λ_{max} 280 mμ ($E^{1\%}_{1\ cm.}$ 80).

Anal. Calcd. for $C_{19}H_{26}O$: C, 84.39; H, 9.68. Found: C, 84.20; H, 9.49.

17β-Methyl-1,3,5(10)-estratrien-3-methyl ether (IVc). The free phenol (IVa, 0.125 g.) was treated with 1 cc. of dimethyl sulfate and 20 cc. of 10% aqueous KOH. Work-up gave a colorless oil which could not be crystallized. Sublimation at 70° on a cold finger at 2.5×10^{-3} mm. pressure gave a colorless oil; $[\alpha]_D^{18°}$ +53.1°. λ_{max} 280 mμ.

Anal. Calcd. for $C_{20}H_{28}O$: C, 84.45; H, 9.92. Found: C, 84.36; H, 9.70.

Acetylation of IVa gave an oil which could not be crystallized and was not analyzed. Saponification of this oil gave IVa, m.p. 130°.

Isolation of 17α-methyl-1,3,5(10)-estratrien-3-ol benzoate (Vb). Following the removal of as much IVb as possible by crystallization from methanol, the mother liquor was freed of solvent, leaving an oily deposit. This was saponified, but the resulting oil could not be crystallized, even after chromatography on alumina. It was rebenzoylated (benzoyl chloride in aqueous alkali) and the crude product in methanol gave a small deposit which was filtered and discarded. The filtrate was free of solvent and the residue was dissolved in aqueous acetone. Eventually 0.243 g. of needles deposited. Crystallization to constant melting point from aqueous acetone-methanol gave brilliant needles, m.p. 118–120°; $[\alpha]_D^{17°}$ −50.7°.

Anal. Calcd. for $C_{26}H_{30}O_2$: C, 83.38; H, 8.07. Found: C, 83.37; H, 8.07.

17α-Methyl-1,3,5(10)-estratrien-3-ol (Va). Saponification of the benzoate Vb (0.130 g.) gave small, pearly scales. Crystallization to constant melting point gave white crystals, m.p. 129–129.5°; $[\alpha]_D^{17°}$ −79.1°. λ_{max} 280 mμ ($E^{1\%}_{1\ cm.}$ 81).

Anal. Calcd. for $C_{19}H_{26}O$: C, 84.39; H, 9.68. Found: C, 84.49; H, 9.51.

17α-Methyl-1,3,5(10)-estratrien-3-methyl ether (Vc). The free phenol Va (0.020 g.) was treated with 20 cc. 10% aqueous KOH and 1 cc. dimethyl sulfate. Work-up gave an oil which could not be crystallized. Sublimation at 70° under 2.5×10^{-3} mm. Hg (cold finger apparatus) gave 0.015 g. of colorless oil which could not be crystallized.

Anal. Calcd. for $C_{20}H_{28}O$: C, 84.45; H, 9.92. Found: C, 84.40; H, 9.96.

Acetylation of Va (pyridine, acetic anhydride, room temp.) gave a non-crystallizable oil which was not analyzed. This oil on saponification gave free V, m.p. 126–128°.

Acknowledgment. The author wishes to express to Dr. James Leathem of Rutgers University his appreciation for providing the preliminary bioassays and to the Central Research Department, Anheuser-Busch, Inc., for permission to publish that portion of the work performed in their laboratories.

KANSAS CITY, KANSAS

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

Synthesis of Potential Anticancer Agents. I. Nitrogen Mustards Derived from *p*-[*N*,*N*-Bis(2-chloroethyl)amino]benzaldehyde[1]

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Received June 23, 1958

An improved synthesis of *p*-[*N*,*N*-bis(2-chloroethyl)amino]benzaldehyde (benzaldehyde mustard) is described. Nitrogen mustard derivatives of cinchophen and barbituric acid have been prepared. Condensation products of benzaldehyde mustard and active methyl derivatives of selected heterocyclic compounds have been prepared. Representative benzylidene acyl hydrazides have been prepared from benzaldehyde mustard.

Compounds containing the β,β′-bischloroethylamino grouping, otherwise known as nitrogen mustards, have frequently displayed selective action against neoplastic cells as compared to normal cells.[2] The concept of a pharmacologically active substance being composed of an active moeity and a carrier moeity was first put forward by Ing.[3] The genesis of the present study was based on this concept.

Considerable information is at hand concerning the absorption and fate of the drug, cinchophen (2-phenylquinoline-4-carboxylic acid)[4] so that it seemed reasonable to expect that cinchophen might act as a carrier molecule to direct a mustard grouping to some effective locus of action. A logical

(1) This work was supported by Research Grant CY-2961 from the National Cancer Institute of the Public Health Service.

(2) The entire field has been reviewed in the monograph *Comparative Clinical and Biological Effects of Alkylating Agents*, Annals of the New York Academy of Sciences, Vol. 68, Art. 3 (April 24, 1958).

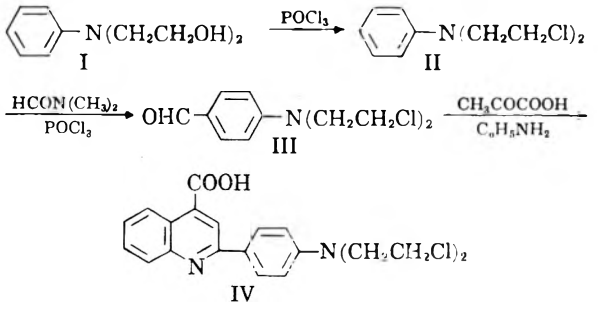
(3) H. R. Ing, *Trans. Faraday Soc.*, 39, 372 (1943); see also ref. 2, p. 1238.

(4) L. S. Goodman and A. Gilman, *The Pharmacological Basis of Therapeutics*, 2nd ed., The Macmillan Co., New York, 1955, p. 301.

position for incorporation of such a group appeared to be the *para* position of the 2-phenyl group.

For the preparation of 2-[4′-[*N*,*N*-bis(2-chloroethyl)amino]phenyl]quinoline-4-carboxylic acid (IV) initial investigations were directed toward finding suitable methods for alkylating 2-(4′-aminophenyl)quinoline-4-carboxylic acid. Either ethylene oxide or ethylene chlorohydrin would be expected to produce the *N*,*N*-bis(2-hydroxyethyl)-amino compound,[5] the hydroxyl groups of which could then be replaced by chlorine by standard methods for the preparation of nitrogen mustards. However, quantitative dialkylation was difficult, and the extreme and closely similar insolubilities of the starting material, monoalkylated product, and the desired dialkylated product in most solvents made fractional crystallization at best tedious and wasteful. Attention was therefore directed to an alternate synthesis.

The Doebner quinoline synthesis proceeds normally with *p*-aminobenzaldehydes,[6] the conditions of this synthesis appear to be sufficiently mild to apply in the presence of the solvolytically active nitrogen mustard grouping, and the intermediate *p*-[*N*,*N*-bis(2-chloroethyl)aminobenzaldehyde has been described.[7] This approach was accordingly adopted.



Chlorination of *N*-phenyldiethanolamine (I) has been reported by Ross[5] and the subsequent introduction of the *p*-formyl group to yield III has been described by Anker and Cook.[7] Chlorination of I with phosphorus oxychloride proceeded well, but the ease of isolation of the product (II) was greatly facilitated by modification of Ross' procedure as given in the experimental part. The formylation step leading to III was done following the procedure of Campaigne and Archer,[8] which substitutes dimethylformamide for *N*-methylformanilide as used by Anker and Cook.[7] Excellent yields of III were thus obtained.

Under the standard Doebner conditions, III reacted smoothly with aniline and pyruvic acid. Slightly less than one equivalent of aniline was used to minimize the possibility of piperazine formation by reaction of the mustard group with any excess aniline. No difficulty from this source was encountered.

Cinchophen mustard (IV) showed no tendency to undergo solvolysis with ethanol. It is slightly soluble in 10% hydrochloric acid and soluble in concentrated hydrochloric acid forming a red solution typical of the 4′-aminocinchophen derivatives. It was soluble in 10% sodium carbonate solution forming a yellow solution likewise characteristic of these compounds. In sodium hydroxide some tar formation occurred. These solubility data indicate that the Doebner reaction proceeded as formulated to give IV and not the annoying by-product sometimes obtained, which in this case would be 1-phenyl-5-{*p*-[*N*,*N*-bis(2-chloroethyl)amino]phenyl}-2,3-pyrrolidinedione-3-anil. Further, IV gives a precipitate slowly with cold alcoholic silver nitrate and instantly when hot. This is highly suggestive that the mustard function is intact and not in the form of the cyclized ethylenimmonium salt which would be expected to react instantly with silver ion even in the cold.

With benzaldehyde mustard (III) readily available, attention was next directed to its incorporation into other molecules which may be expected to show tumor inhibitory properties. For this purpose advantage was taken of the reactivity of the aldehyde group in III in various condensation reactions involving active methylene groups and hydrazides. Condensation of III with 3-methyl-1-phenyl-5-pyrazolone,[7] with 6-ethoxythioindoxyl[7] and with oxindole[9] has been reported. Anker and Cook[7] prepared a number of cyanine dyes by condensation of III with various quaternized heterocyclic systems containing activated methyl groups. In view of the sensitivity of the mustard grouping in III the choice of a condensing agent is rather severely limited.

2-[*p*-(Dimethylamino)styryl]quinoline has been mentioned as a tumor growth inhibitor[10] and considerable literature exists on 4-(*p*-(dimethylamino)-styryl]quinoline.[11] It therefore seemed advisable to investigate condensation of III with representative methylquinolines. Since 2,4-dimethylquinoline (V) presented the possibility of the introduction of two mustard groups, this was selected for investigation. A series of experiments involving condensation of III with V in the presence of catalysts such as acetic anhydride, zinc chloride, and hydrochloric acid was carried out. With the latter two only intractable tars were obtained. However, when acetic anhydride was the catalyst, a monostyryl derivative was obtained as the hydro-

(5) W. C. J. Ross, *J. Chem. Soc.*, 183 (1949).

(6) R. Cuisa, *Gazz. chim. ital.*, **46**, I, 135 (1916); R. F. Brown *et al.*, *J. Am. Chem. Soc.*, **68**, 2705 (1946).

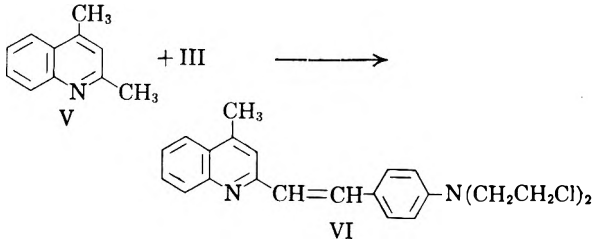
(7) R. M. Anker and J. H. Cook, *J. Chem. Soc.*, 489 (1944).

(8) E. Campaigne and W. L. Archer, *Org. Syntheses*, **33**, 27 (1953).

(9) Brit. Patent **595,571**, Dec. 9, 1947.

(10) W. J. P. Neish, *Rec. trav. chim.*, **67**, 374 (1948).

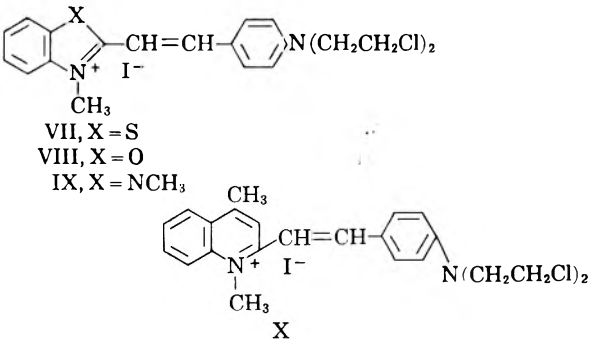
(11) See C. T. Bahner and R. Neely, *J. Org. Chem.*, **22**, 1109 (1957), and references contained therein.



chloride. We believe that this substance is the hydrochloride of 2-[4′-[*N*,*N*-bis(2-chloroethyl)]-amino)styryl-4-methylquinoline (VI) for the following reasons. In general, the reactivity of a 4-methyl group in quinoline is less than that of a 2-methyl group. In order to secure condensation of lepidine with benzaldehyde, use of zinc chloride and relatively high temperatures is necessary.[12,13] Further, Kaslow and Stayner report that whereas 2-styrylquinoline can be prepared with acetic anhydride, zinc chloride is necessary for the preparation of 4-styrylquinoline.

Attempted condensation of III with 2-methylbenzimidazole in the presence of acetic anhydride or piperidine and hydrochloric acid resulted either in tar formation or in recovery of starting materials. The stability of III under these conditions is noteworthy. It appears that the aldehyde group of III is much less reactive in these condensations than the aldehyde group of benzaldehyde.

In view of the successful preparation of a series of cyanine dyes from III,[7] attention was turned to condensation of III with quaternized heterocycles. 2,3-Dimethylbenzothiazolium iodide, 2,3-dimethylbenzoxazolium iodide, and 1,2,3-trimethylbenzimidazolium iodide condensed easily with III in refluxing ethanol with piperidine as catalyst to give VII, VIII, and IX, respectively. The products crystallized directly in pure form, but some decomposition occurred on recrystallization. It is interesting that the benzothiazolium salt was considerably more reactive than the benzimidazolium salt which required a much longer time for reaction to go to completion.[14]

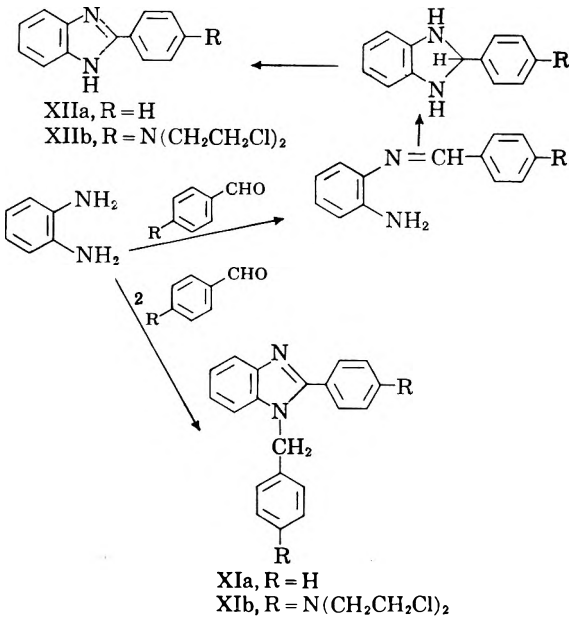


In contrast to these facile condensations, when condensation of 1,2,4-trimethylquinolinium iodide with III was attempted with piperidine as a catalyst no product could be isolated. However, when the reactants were boiled in acetic anhydride X was readily obtained. The structure of X is based on arguments similar to those used for VI.

Condensation of III with barbituric acid was almost instantaneous without a catalyst and gave a substantially quantitative yield of 5-(4′-[*N*,*N*-bis(2-chloroethyl)amino]benzylidene)barbituric acid.

Cinchophen hydrazide condenses with benzaldehyde in refluxing ethanol to give the benzylidene derivative in high yield.[15] Under the same conditions the *p*-(*N*,*N*-bis(2-chloroethyl)amino]-benzylidene hydrazide was formed from III. The analogous hydrazide mustards from *p*-aminobenzoic acid hydrazide and isonicotinic acid hydrazide were formed even more easily.

Finally, direct condensation of III with *o*-phenylenediamine was investigated. Depending on conditions, *o*-phenylenediamine can cyclize with benzaldehyde in two ways to give either XI*a* or XII*a*. Compounds of the type of XI are formed when salts of aromatic *o*-diamines are treated with aldehydes.[16] Compounds of the type of XII are formed when *o*-phenylenediamine and the aldehyde are refluxed in benzene solution in the presence of palladium on charcoal catalyst or alone in nitrobenzene.[17]



When III was refluxed with *o*-phenylenediamine in nitrobenzene for ten minutes, a greenish gray solid, m.p. 283°, was formed. No solvent could be

(12) O. Fischer, G. Scheibe, P. Merkel, and R. Muller, *J. prakt. Chem.*, [2] **100**, 86 (1920).

(13) C. E. Kaslow and R. D. Stayner, *J. Am. Chem. Soc.*, **67**, 1716 (1945).

(14) *Cf.* J. B. L. Smith, *J. Chem. Soc.*, **123**, 2288 (1923).

(15) H. John. *Ber.*, **59**, 1447 (1926).

(16) A. Ladenburg, *Ber.*, **11**, 590, 600, 1648 (1878); A. Ladenburg and T. Engelbrecht, *Ber.*, **11**, 1653 (1878).

(17) D. Jerchel, M. Kracht, and K. Krucker, *Ann.*, **590**, 232 (1954).

found for recrystallization. However, when III and *o*-phenylenediamine were refluxed in benzene in the presence of palladium on charcoal with a stream of air crystalline material which could be recrystallized from methanol was obtained. The infrared spectra of the two substances showed marked differences. Analytical data for the crystalline substance agreed with those demanded by structure XIIb.

Results of tests of these compounds against experimental tumors will be reported elsewhere.

EXPERIMENTAL[18,19]

N,N-bis(2-chloroethyl)aniline (II). The procedure was a modification of that of Ross.[5] To 170 g. (102 ml., 1.1 mole) of phosphorus oxychloride chilled in an ice bath 100 g. (0.55 mole) of *N*-phenyldiethanolamine (Tennessee Eastman Co. technical grade) was slowly added. After the addition was complete, the mixture was warmed on the steam bath for 1 hr. and then taken up in 500 ml. of benzene. The benzene solution was poured onto 500 g. of ice and the layers were separated. The aqueous layer was washed with three 50-ml. portions of benzene and the combined benzene solutions were dried over anhydrous magnesium sulfate. Removal of the benzene left an oil which was taken up in the minimum amount of hot absolute methanol. On chilling with stirring 98 g. (82%) of product, m.p. 41–45°, separated (reported m.p. 49°). By use of this inverse quenching of the reaction mixture no difficulty in inducing the crude material to crystallize was encountered, even when the alumina chromatography step included in the procedure of Ross was omitted.

p-[N,N-bis(2-chloroethyl)amino]benzaldehyde (III). A method similar to that described by Campaigne and Archer[8] for the formylation of dimethylaniline was used. To an ice cold solution of 70 g. (42 ml., 0.46 mole) of phosphorus oxychloride in 340 ml. of dimethylformamide was added slowly with stirring and cooling in ice a solution of 98 g. (0.45 mole) of *N,N*-bis(2-chloroethyl)aniline in 340 ml. of dimethylformamide. After the addition was complete, the solution was held at 5° for 15 min. and then warmed to 40° for 2 hr. The mixture was poured into one kilogram of ice and water and the purple solid which precipitated rapidly was filtered off at once. This was starting material. The filtrate rapidly deposited a copious precipitate of the desired aldehyde as long tan needles, m.p. 85–88°. After one recrystallization from ethanol 81 g. (73%) of white product, m.p. 85–88°, was obtained. Reported m.p. 88.5°.[7]

In larger scale runs complete removal of the purple contaminant was not accomplished in the initial workup. In order to remove this a solution of the crude product in benzene–petroleum ether was passed over a column of alumina which retained the pigment. Also the amount of dimethylformamide used could be halved.

2-{4-[N,N-(bis-2-chloroethyl)amino]phenyl}quinoline-4-carboxylic acid (IV). To a refluxing solution of 65 g. (0.264 mole) of III and 24 g. (0.272 mole) of pyruvic acid in 750 ml. of ethanol was added dropwise a solution of 24 g. (0.258 mole) of aniline in 250 ml. of ethanol. After the addition was complete, the solution was refluxed for 2 hr. and cooled to room temperature with stirring. The orange solid, 50 g. (50% based on aniline), was collected. After several recrystallizations from dimethylformamide-methanol (70% recovery) the material as a rule melted at 200–202° with decomposition although this was somewhat variable.

Anal. Calcd. for $C_{20}H_{18}Cl_2N_2O_2$: C, 61.7; H, 4.7; Cl, 18.2; N, 7.2. Found: C, 61.8, 61.6; H, 5.1, 5.0; Cl, 18.3, 18.3; N, 7.4, 7.1.

The compound is slightly soluble in 10% hydrochloric acid, soluble in concentrated hydrochloric acid, and soluble in 10% sodium carbonate. It is insoluble in water and slightly-soluble in ethanol, dioxane, acetonitrile, and propylene glycol. It gives a slow precipitate with alcoholic silver nitrate in the cold and a rapid precipitate when hot.

2-{4-[N,N-bis(2-chloroethyl)amino]styryl}-3-methylbenzothiazolium iodide (VII). A mixture of 4.0 g. (0.014 mole) of 2,3-dimethylbenzothiazolium iodide,[20] 4.0 g. (0.016 mole) of III, 125 ml. of absolute ethanol and 6 drops of piperidine was heated under reflux with stirring. The solution became dark red and after 2 hr. a dark solid separated. After cooling with stirring, the reddish brown crystals were collected and washed with ethanol. The yield of material, m.p. 205.5° (dec.), which was analytically pure, was 5.0 g. (71%). The substance could be recrystallized from methanol or from acetic acid. However, the melting point of the material from either of these solvents was lowered.

Anal. Calcd. for $C_{20}H_{21}Cl_2INS$: C, 46.3; H, 4.1, N, 5.4. Found: C, 46.2; H, 4.1; N, 5.4.

2-{4'-[N,N-bis(2-chloroethyl)amino]styryl}-3-methylbenzoxazolium iodide (VIII) was prepared by the above procedure from 2,3-dimethylbenzoxazolium iodide[21] except that 50 ml. of absolute ethanol were used. The yield of lustrous magenta crystals, m.p. 202.5–203.5° (dec.), was 59%. Recrystallization from 1:1 ethanol–methanol lowered the melting point.

Anal. Calcd. for $C_{20}H_{21}Cl_2IN_2O$: C, 47.7; H, 4.2; N, 5.6. Found: C, 47.6; H, 4.1; N, 5.5.

2-{4'-[N,N-bis(2-chloroethyl)amino]styryl}-1,3-dimethylbenzimidazolium iodide (IX). The above procedure was applied to 1,2,3-trimethylbenzimidazolium iodide[22] using 75 ml. of absolute ethanol and 1 ml. of piperidine. The reflux period was 6 hr. The yield of fine yellow crystals, m.p. 219° (dec.), was 54%.

Anal. Calcd. for $C_{21}H_{24}Cl_2IN_3$: C, 48.8; H, 4.7; N, 8.1. Found: C, 48.5; H, 4.5; N, 7.9.

2-{4'-[N,N-bis(2-chloroethyl)amino]styryl}-1,4-dimethylquinolinium iodide (X). A mixture of 3.0 g. (0.01 mole) of 1,2,4-trimethylquinolinium iodide, 2.46 g. (0.01 mole) of III, and 30 ml. of acetic anhydride was refluxed for 1 hr. The dark solution was cooled and poured into 200 ml. of ether. The solid was collected, washed with 200 ml. of ether, ground in a mortar, and triturated with 100 ml. of ether. The dark red microcrystalline powder did not react with 2,4-dinitrophenylhydrazine. It was suspended in ether, left overnight with occasional shaking, and collected. After three such treatments the m.p. was 87–93° (dec.). Yield 76%.

Anal. Calcd. for $C_{23}H_{25}Cl_2IN_2$: C, 52.4; H, 4.8; N, 5.3. Found: C, 52.4; H, 4.9; N, 5.4.

2-{4'-[N,N-bis-(2-chloroethyl)amino]styryl}-4-methylquinoline hydrochloride (VI). A mixture of 2.5 g. (0.02 mole) of III, 3.1 g. (0.02 mole) of 2,4-dimethylquinoline, and 1.0 g. (0.01 mole) of acetic anhydride was refluxed at 135–140° for 4 hr. The dark, oily material which formed was taken up in ethanol and an ethereal solution of hydrogen chloride was added. Crystallization of the hydrochloride was initiated by vigorous scratching and gradual cooling. After several recrystallizations from ethanol-ether red crystals, m.p. 220–222°, were obtained.

Anal. Calcd. for $C_{22}H_{23}Cl_3N_2$: C, 62.6; H, 5.5. Found: C, 62.6; H, 5.4.

2-{4'-[N,N-bis(2-chloroethyl)amino]phenyl}benzimidazole XIIb. A solution of 3.24 g. (0.03 mole) of *o*-phenylenediamine and 7.4 g. (0.03 mole) of III in 500 ml. of benzene was refluxed with 2 g. of 5% palladium on charcoal for 18

(18) All melting points are corrected.

(19) Microanalyses by Spang Microanalytical Laboratory, Ann Arbor, Mich.

(20) W. H. Mills, *J. Chem. Soc.*, **121**, 455 (1922).

(21) L. M. Clark, *J. Chem. Soc.*, 234 (1926).

(22) O. Fischer, *Ber.*, **25**, 2838 (1892).

hr. during which air was passed through the mixture. After filtering the hot solution, almost colorless needles, m.p. 139–140°, deposited on cooling. The yield was 7.3 g. (73%). Recrystallization from methanol resulted in lowering of the melting point.

Anal. Calcd. for $C_{17}H_{17}Cl_2N_3$: C, 61.1; H, 5.1; N, 12.6. Found: C, 61.5; H, 5.1; N, 12.7.

2-Phenylquinoline-4-carbox-[4′-bis(2-chloroethyl)amino]-benzylidenehydrazide. A mixture of 5.0 g. (0.019 mole) of 2-phenylquinoline-4-carboxhydrazide.[23,24] 4.7 g. (0.019 mole) of III and 350 ml. of absolute ethanol was heated under reflux. After 1 hr. yellow needles began to separate. After heating for 5 hr. and cooling 9.2 g. (99%) of the hydrazide, m.p. 208.5–210.5° with darkening at 180°, separated. Recrystallization from 30 ml. of dimethylformamide and 200 ml. of ethanol gave clusters of fine yellow needles, m.p. 214.5–215.5° (dec.). The infrared spectrum showed bands at 3160 and 1650 cm.

Anal. Calcd. for $C_{27}H_{24}Cl_2N_4O_2$: C, 66.0; H, 4.9; Cl, 14.4; N, 11.4. Found: C, 66.1; H, 4.9; Cl, 14.6; N, 11.5.

4-Aminobenz[4′-bis(2-chloroethyl)amino]benzylidenehydrazide. This was prepared as in the above case from 4-aminobenzhydrazide.[25] The hydrazide separated after 10 min. and refluxing was continued for 20 min. The yield of crude material, m.p. 183.5–184.5°, was quantitative. Recrystallization from 1:5 dimethylformamide–absolute ethanol gave pale yellow needles, m.p. 185.5°. The infrared spectrum showed bands at 3350, 3200, and 1620 cm.$^{-1}$

Anal. Calcd. for $C_{18}H_{20}Cl_2N_4O$: C, 57.0; H, 5.3; Cl, 18.7; N, 14.8. Found: C, 57.1; H, 5.2; Cl, 18.6; N, 14.7.

4-Aminopyridinecarbox[4′-bis(2-chloroethyl)amino]benzylidenehydrazide. The procedure was the same as in the above cases starting from isonicotinic acid hydrazide.[26] After refluxing for 20 min., the deep yellow solution was filtered hot. On cooling the hydrazide, m.p. 202.5–204.5° (dec.) with darkening at 195°, crystallized. Recrystallization from 1:6 dimethylformamide–absolute ethanol raised the m.p. to 203–205.5° (dec.). The infrared spectrum showed bands at 3160 and 1650 cm.$^{-1}$

Anal. Calcd. for $C_{17}H_{18}Cl_2N_4O$: C, 55.9; H, 5.0; Cl, 19.4; N, 15.3. Found: C, 56.2; H, 4.9; Cl, 19.3; N, 15.6.

5-{4′-[N,N-bis(2-chloroethyl)amino]benzylidene}barbituric acid. A warm solution of 1.23 g. (0.005 mole) of III in 25 ml. of ethanol was added to a warm solution of 0.64 g. (0.005 mole) of barbituric acid in 6 ml. of water. After heating on the steam bath for 2 min., 1.1 g. of orange crystals, m.p. 268° (dec.) separated. From the mother liquor another 570 mg. was obtained, making the total yield 94%. No further purification was necessary. The compound is sparingly soluble in most solvents and quite soluble in dimethylformamide.

Anal. Calcd. for $C_{15}H_{15}Cl_2N_3O_3$: C, 50.6; H, 4.2; N, 11.7. Found: C, 50.7; H, 4.2; N, 11.9.

Acknowledgment. We acknowledge the assistance of James Hudson and Karl Lindfors in the preparation of certain intermediates.

ANN ARBOR, MICH.

(23) H. John, *Ber.*, 59B, 1447 (1926).

(24) R. I. Meltzer, *et al.*, *J. Am. Pharm. Assoc.*, 42, 594 (1953).

(25) T. Curtius, *J. prakt. Chem.*, [2] 95, 335 (1917).

(26) Supplied by the Cancer Chemotherapy National Service Center.

[CONTRIBUTION FROM THE DEPARTMENT OF BIOLOGICAL SCIENCES, STANFORD RESEARCH INSTITUTE]

Potential Anticancer Agents.[1] X. Synthesis of Nucleosides Derived from 6-Deoxy-D-glucofuranose

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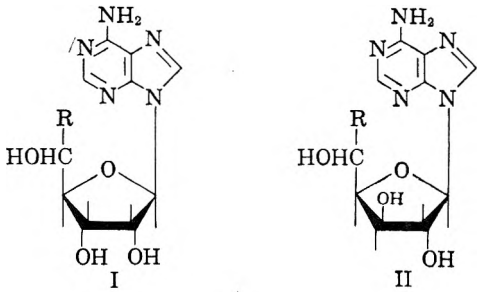
6-Amino- and 2,6-diamino-9-(6′-deoxy-β-D-glucofuranosyl)purine (XV and XVI) have been synthesized from D-glucose *via* the key intermediates 6-deoxy-1,2-*O*-isopropylidene-D-glucofuranose (VII) and 1,2-di-*O*-acetyl-3,5-di-*O*-benzoyl-6-deoxy-D-glucofuranose (IX).

Synthesis of 5′-*C*-alkylpentofuranosyl nucleosides as possible inhibitors of cellular synthesis or utilization of nucleosides (I, R = H) and nucleotides has been the subject of several previous papers of this series. 9-α-L-Rhamnofuranosyladenine[2] was synthesized from rhamnose. Similarly, the two possible 5-*C*-methyl-D-ribose nucleosides (I, R = CH_3), namely, 9-(6′-deoxy-β-D-allofuranosyl) adenine[3] and 9-(6′-deoxy-α-L-talofuranosyl)adenine,[4] have been described. Since 9-β-D-xylofuranosyladenine (II, R = H)[2] has shown weak anticancer activity against Carcinoma 755,[5] the synthesis and



(1) This program is under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, and is in collaboration with the Sloan-Kettering Institute of Cancer Research. For the preceding paper of this series *cf.* R. Koehler, L. Goodman, J. DeGraw, and B. R. Baker, *J. Am. Chem. Soc.*, in press.

(2) B. R. Baker and K. Hewson, *J. Org. Chem.*, 22, 966 (1957).

(3) E. J. Reist, R. R. Spencer, L. Goodman, and B. R. Baker, *J. Am. Chem. Soc.*, 80, 3692 (1958).

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(5) Dr. F. M. Schabel, Jr., Southern Research Institute, Birmingham, Ala., unpublished results.

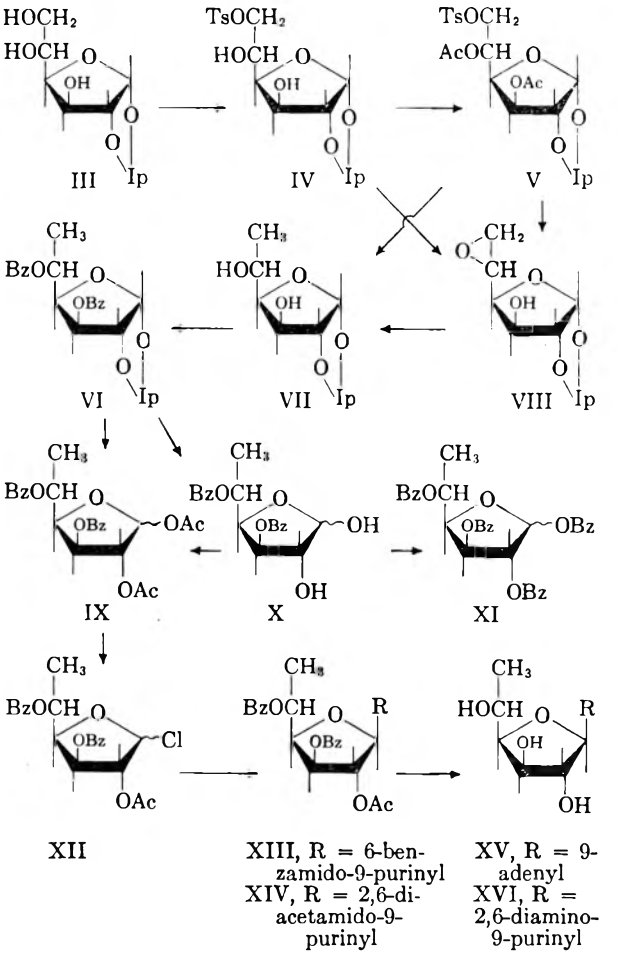
testing of its two 5′-*C*-methyl derivatives (II, R = CH_3) was considered to be of interest in this general program. Introduction of the 5′-C-methyl group in II gives an additional asymmetric center at the 5′-position, thus leading to two isomers of II. The synthesis of the nucleosides derived from one isomer, 6′-deoxy-D-glucofuranose, is the subject of this paper. The synthesis of nucleosides derived from the second isomer, 6′-deoxy-L-idofuranose, is the subject of a following paper.

The first key intermediate in the projected synthesis is 6-deoxy-1,2-*O*-isopropylidene-D-glucofuranose (VII), which has been previously synthesized by hydrogenation of 5,6-anhydro-1,2-*O*-isopropylidene-D-glucofuranose (VIII) using a palladium[6] or Raney nickel catalyst.[7] It has now been found that lithium aluminum hydride is a convenient reagent for this reduction. Preparatively, the sequence was considerably shortened by tosylation, then acetylation of 1,2-*O*-isopropylidene-D-glucofuranose (III) in the same solution to give the crude diacetate V. Reduction of V with lithium aluminum hydride proceeded through the 5,6-anhydro sugar VIII, giving a considerably better over-all yield of 6-deoxy-1,2-*O*-isopropylidene-D-glucofuranose (VII) than could be obtained by isolation of the various intermediates.

Benzoylation of VII afforded the dibenzoate VI as a crystalline solid with good crystallizing powers. It was found that the dibenzoate VI was more easily purified than VII; thus better over-all yields of the dibenzoate VI were obtained when VII was not purified. By not isolating each intermediate, the over all yield of VI from III was increased about threefold.

Although the diacetate of VII has been previously described,[6] the benzoyl blocking groups are considered superior to acetyl for further transformations[8] necessary to synthesize the required nucleosides.

Hydrolysis of the isopropylidene group of VI with a mixture of acetic acid and hydrochloric acid gave a 75% yield of 3,5-di-*O*-benzoyl-6-deoxy-D-glucofuranose (X) as a glass that was homogeneous when chromatographed on acetylated paper[14] and was free of starting material (VI). Conversion of X to the tetrabenzoate XI or to the 1,2-diacetate IX proceeded smoothly, but neither anomeric mixture could be crystallized. The second key intermediate, 1,2-di-*O*-acetyl-3,5-di-*O*-benzoyl-6-deoxy-D-glucofuranose (IX), was also prepared, in 93% yield, by acetolysis[9] of the isopropylidene derivative VI, a procedure considered to be more convenient and giving higher yields than the sequence *via* X.



Reaction of the amorphous diacetate (IX) with ethereal hydrogen chloride[10] containing acetyl chloride[11] gave the crude chloro derivative (XII). The conversion of the 1-*O*-acetyl group in IX to the halogen in XII could be readily followed by examination of the infrared absorption spectra of aliquots. The starting diacetate (IX) has acetate C—O—C bands at 8.10 and 8.20 μ. The reaction was run until the decrease in absorption in that region ceased, when conversion to XII was complete. Condensation of XII with chloromercuri-6-benzamidopurine afforded the crude blocked nucleoside (XIII). Deacylation with methanolic sodium methoxide gave the nucleoside (XV), isolated *via* its picrate. Regeneration of the base (XV) with Dowex 2 (CO_3) in the usual manner[3,12] gave the

(6) K. Freudenberg, H. Eich, C. Knoevenagel, and W. Westphal, *Ber.*, **73**, 441 (1940).

(7) E. Vischer and T. Reichstein, *Helv. Chim. Acta*, **27**, 1332 (1944).

(8) B. R. Baker, K. Hewson, H. J. Thomas, and J. A. Johnson, Jr., *J. Org. Chem.*, 22, 954 (1957).

(9) A. T. Ness, R. M. Hann, and C. S. Hudson, *J. Am. Chem. Soc.*, **65**, 2215 (1943).

(10) J. Davoll, B. Lythgoe, and A. R. Todd, *J. Chem. Soc.*, 967 (1948).

(11) B. R. Baker and R. E. Schaub, *J. Am. Chem. Soc.*, **77**, 5900 (1955), have used acetyl chloride in this type of reaction to maintain anhydrous conditions.

(12) B. R. Baker and K. Hewson, *J. Org. Chem.*, **22**, 959 (1957).

pure nucleoside, 9-(6′-deoxy-β-D-glucofuranosyl) adenine (XV),[13] in 32% yield based on IX.

Similarly, condensation of 2-*O*-acetyl-3,5-di-*O*-benzoyl-6-deoxy-D-glucofuranosyl chloride (XII) with chloromercuri-2,6-diacetamidopurine[12] to the blocked nucleoside (XIV) followed by deacylation gave 2,6-diamino-9-(6′-deoxy-β-D-glucofuranosyl)-purine (XVI)[13] in 16% yield based on IX.

EXPERIMENTAL[14-16]

3,5-Di-O-acetyl-1,2-O-isopropylidene-6-O-tosyl-D-glucofuranose (V). To a solution of 5.0 g. (23 mmoles) of 1,2-*O*-isopropylidene-D-glucofuranose (III)[18] in 55 ml. of reagent pyridine was added dropwise a solution of 4.28 g. (22.5 mmoles) of tosyl chloride in 70 ml. of methylene chloride over a period of 30 min. with vigorous stirring. After standing at room temperature for 24 hr. protected from moisture, the mixture was treated with 10 ml. (0.11 mole) of acetic anhydride with stirring, then allowed to stand an additional 24 hr. The mixture was poured into 300 g. of ice water and extracted with chloroform (3 × 30 ml.). The combined extracts were washed with excess aqueous sodium bicarbonate, then water. Dried with magnesium sulfate, the organic solution was evaporated to dryness *in vacuo*. The last traces of pyridine were removed by addition and evaporation of two 20-ml. portions of toluene, leaving 10.2 g. (97%) of an oil that only partially solidified on standing, but was suitable for reduction to VII. Recrystallization of a similar preparation from 83% aqueous methanol gave 4.82 g. (46%) of white crystals, m.p. 89–90°; λ_{max}^{KBr} 5.71 μ (C=O), 8.08 μ (acetate C—O—C), 8.50 μ (sulfonate).

Vischer and Reichstein[7] have recorded m.p. 90° for V and stated that the yield was quantitative starting with 1,2-*O*-isopropylidene-6-*O*-tosyl-D-glucofuranose (IV). The latter has been prepared in 56% yield,[19,20] and in 48% yield in this laboratory, from III. Compound IV was considerably more difficult to purify than was V.

5,6-Anhydro-1,2-O-isopropylidene-D-glucofuranose (VIII). A solution of 1.00 g. (2.1 mmoles) of pure V in 4.2 ml. of reagent chloroform was added to a solution of 0.38 g. of sodium methoxide in 6 ml. of reagent methanol cooled in an ice bath. After 30 min. at 0°, the gel-like mass was diluted with 5 ml. of water and the separated aqueous layer extracted with chloroform (4 × 5 ml.). The chloroform extracts were each washed with 10 ml. of water, then combined, dried with magnesium sulfate, and evaporated to dryness *in vacuo;* yield, 0.42 g. (96%) of white crystals, m.p. 116–122°. Recrystallization from 10 ml. of benzene gave 0.25 g. (57%) of pure product, m.p. 130–132°, $[\alpha]_D^{27}$ −26.6° (2.0% in $CHCl_3$); λ_{max}^{KBr} 2.97 μ (OH), 3.28 μ (epoxide CH), 7.21 μ (gem dimethyl), 9.00, 9.20, 9.36, 9.55, 9.85 μ (C—OH and ether C—O—C).

The same over-all yield (from III) of recrystallized product (VIII) was obtained starting with crude diacetate (V). Ohle and Vargha[21] have prepared this compound in 80% yield from IV and have given m.p. 133.5°, $[\alpha]_D^{20}$ −26.5° (4% in H_2O).

6-Deoxy-1,2-O-isopropylidene-D-glucofuranose (VII). To a mixture of 5.12 g. (0.183 mole) of lithium aluminum hydride and 130 ml. of reagent ether was added 2.22 g. (11.0 mmoles) of pure VIII over a period of about 4 min. The mixture, protected from moisture, was refluxed with stirring for 3 hr., then the excess hydride was decomposed by the dropwise addition of 21 ml. of ethyl acetate, then 21 ml. of water. After 47 ml. of 10% aqueous sodium hydroxide was added, the organic layer was decanted from the sludge. The latter was extracted with ethyl acetate (3 × 30 ml.). The combined organic extracts dried with magnesium sulfate, were evaporated to dryness *in vacuo*, leaving 1.32 g. (60%) of a yellow sirup. Distillation gave 1.23 g. (55%) of colorless oil, b.p. 76–79° (5 μ), that solidified in the receiver, m.p. 87–88°, $[\alpha]_D^{25}$ −21.3° (2.0% in $CHCl_3$); λ_{max}^{KBr} 2.90 μ (OH), 9.20, 9.84 μ (ether C—O—C), and no epoxide CH at 3.28 μ.

This compound (VII) has been prepared by catalytic hydrogenolysis of VIII in "good yield," m.p. 92°, $[\alpha]_D^{25}$ −26.3% (1% in $CHCl_3$).[6,7]

3,5-Di-O-benzoyl-6-deoxy-1,2-O-isopropylidene-D-glucofuranose (VI). To a mixture of 1.32 g. (0.035 mole) of lithium aluminum hydride in 40 ml. of anhydrous ether was added a solution of 8.0 g. (0.017 mole) of crude 3,5-di-*O*-acetyl-1,2-*O*-isopropylidene-6-*O*-tosyl-D-glucofuranose (V) in 20 ml. of dry benzene over a period of 40 min. The mixture, protected from moisture, was refluxed with stirring for 3 hr. The excess hydride was decomposed by the dropwise addition of 30 ml. of ethyl acetate, then 27 ml. of water followed by 65 ml. of 10% aqueous sodium hydroxide. The mixture was filtered through a Celite filter cake. The filter cake was washed with ethyl acetate (2 × 20 ml.), then continuously extracted with 100 ml. of chloroform for 3 hr. The combined chloroform and ethyl acetate extracts were dried with magnesium sulfate, then evaporated to dryness *in vacuo*, leaving 2.12 g. (60%) of crude VII as a yellow sirup.

To a solution of 1.82 g. (8.9 mmoles) of the preceding crude 6-deoxy-1,2-*O*-isopropylidene-D-glucofuranose (VII) in 12 ml. of reagent pyridine was added dropwise 3.6 ml. (31 mmoles) of benzoyl chloride over a period of 30 min., the temperature being maintained below 5°. The reaction mixture was stirred at 0° for 1 hr., then for 1 hr. at room temperature. After standing overnight at room temperature protected from moisture, the reaction mixture was added dropwise to a mixture of ice and excess aqueous saturated sodium bicarbonate solution. The organic layer was separated and the aqueous layer was extracted with three 10-ml. portions of chloroform. The combined extracts were washed with excess aqueous sodium bicarbonate, then water, dried with magnesium sulfate, and taken to dryness *in vacuo*. The last traces of pyridine were removed by the addition of toluene (2 × 10 ml.) and removal *in vacuo* to give 3.46 g.

(13) That this nucleoside has a C_1-C_2-*trans*-configuration, in this case β, is highly probable in view of the rule postulated for the stereochemistry of nucleoside formation. For a summary of reactions illustrating this point see B. R. Baker on *Stereochemistry of Nucleoside Synthesis*, Ciba Foundation Symposium on the Chemistry and Biology of Purines, J. and A. Churchill, Ltd., London, 1957, pp. 120–130.

(14) The paper chromatograms on the blocked sugars were run on Schleicher and Schull acetylated paper No. 2043B by the descending technique using methanol-water-benzene (6:1:2) as the solvent (solvent A), the spots being detected by visual examination with ultraviolet light; *cf.* T. Wieland and W. Kracht, *Angew. Chem.*, 69, 172 (1957).

(15) The paper chromatograms on the nucleosides were run by the descending technique on Whatman No. 1 paper using 5% disodium phosphate (solvent B) or water-saturated butanol (solvent C) as solvents. Adenine was used as a standard and R_{AD} values are recorded with R_{AD} 1.00 being assigned to adenine.

(16) Melting points were taken on a Fisher-Johns apparatus and are uncorrected. Optical rotations were determined with a Standard Polarimeter Model D attachment to the Beckman DU spectrophotometer calibrated with standard sucrose solutions.[17]

(17) A. S. Keston, Abstracts of 127th Meeting, American Chemical Society, 18C (1955).

(18) Prepared in 74% yield, m.p. 159–160°, from 1,2:5,6-di-*O*-isopropylidene-D-glucofuranose according to the procedure of S. G. Laland, *Acta Chem. Scand.*, 8, 866 (1954).

(19) A. S. Meyer and T. Reichstein, *Helv. Chim. Acta*, 29, 139 (1946).

(20) H. Ohle and E. Dickhauser, *Ber.*, **58B**, 2593 (1925).

(21) H. Ohle and L. Vargha, *Ber.*, **62B**, 2435 (1929).

(94%) of a dark sirup. The crude product was recrystallized from methanol, giving 1.47 g. (40%) of VI in two crops, m.p. 108–110°. The over-all yield from III was 23%. On a large scale the over-all yield from III was 140 g. (26%).

In a pilot run, the benzoylation of pure 6-deoxy-1,2-*O*-isopropylidene-D-glucofuranose (VII) gave 0.90 g. (59%) of VI, m.p. 111–113°. Two recrystallizations from methanol afforded white crystals, m.p. 113–113.5°, $[\alpha]_D^{25}$ −112.6° (2.0% in $CHCl_3$); λ_{max}^{KBr} 5.82 μ (benzoate C=O), 7.90, 8.92 μ (benzoate C—O—C), 9.11, 9.32, 9.72 μ (ether C—O—C).

Anal. Calcd. for $C_{23}H_{24}O_7$: C, 67.0; H, 5.87. Found: C, 66.9; H, 6.03.

Paper chromatography on acetylated paper in solvent A[14] showed only one spot with R_f 0.28.

*3,5-Di-O-benzoyl-6-deoxy-*D*-glucofuranose* (X). A solution of 0.45 g. (1.1 mmoles) of VI in 5.5 ml. of warm acetic acid was rapidly cooled to 15°, then treated with 3.0 ml. of 12*N* hydrochloric acid. After standing at room temperature for 30 min., the mixture was poured into 10 ml. of ice water and extracted with chloroform (3 × 10 ml.). The combined extracts were washed with water, excess aqueous sodium bicarbonate, and water. After being dried over magnesium sulfate, the solution was evaporated *in vacuo*, leaving 0.31 g. (75%) of product, probably an anomeric mixture, as a sirup that could not be crystallized; λ_{max}^{film} 2.93 μ (OH), 5.80 μ (C=O), 7.87, 8.98 μ (ester C—O—C). Chromatography on acetylated paper[14] with solvent A showed only one spot with R_f 0.66 and the absence of starting material with R_f 0.28.

Anal. Calcd. for $C_{20}H_{20}O_7$: C, 64.5; H, 5.41. Found: C, 64.8; H, 5.61.

Treatment of X with benzoyl chloride and pyridine, as described for the preparation of VI, gave the tetrabenzoate XI as an anomeric mixture that failed to crystallize but had R_f 0.09 when chromatographed on acetylated paper[14] with solvent A.

*1,2-Di-O-acetyl-3,5-di-O-benzoyl-6-deoxy-*D*-glucofuranose* (IX). To a stirred solution of 2.25 g. (5.46 mmoles) of crystalline VI in 27 ml. of acetic acid and 3 ml. of acetic anhydride was added dropwise with cooling 1.65 ml. of 96% sulfuric acid at such a rate that the temperature was 10–20°. After standing in a stoppered flask for 24 hr., the solution was poured into 200 ml. of ice water, then stirred for 30 min. The mixture was extracted with chloroform (3 × 25 ml.). The chloroform extracts were washed with 25 ml. of saturated aqueous sodium bicarbonate, then 25 ml. of water. The extracts were combined, dried with magnesium sulfate, and evaporated to dryness *in vacuo*; yield, 2.33 g. (93%) of a nearly colorless sirup; λ_{max}^{film} 5.68 μ (acetate C=O), 5.77 μ (benzoate C=O), 7.84 μ (benzoate C—O—C), 8.10 μ (acetate C—O—C). This compound, which failed to crystallize and was probably an anomeric mixture, traveled as a single spot on acetylated paper[14] in solvent A at R_f 0.28 and had $[\alpha]_D^{25}$ −67.0° (2.1% in $CHCl_3$).

Anal. Calcd. for $C_{24}H_{24}O_9$: C, 63.2; H, 5.30. Found: C, 62.9; H, 5.40.

Acetylation of X in acetic anhydride–pyridine gave IX as a sirup that had an R_f in solvent A[14] and an infrared spectrum essentially identical with that of the above preparation.

*9-(2′-O-Acetyl-3′,5′-di-O-benzoyl-6′-deoxy-β-*D*-glucofuranosyl)-6-benzamidopurine* (XIII). A solution of 2.33 g. (5.1 mmoles) of IX in 5 ml. of acetyl chloride[11] was added to 55 ml. of reagent ether that had been previously saturated with hydrogen chloride.[10] After standing at −5° for 3 days in a stoppered container, the mixture was evaporated to dryness *in vacuo* with protection from moisture. Acetic acid was removed by addition of benzene (2 × 5 ml.) and evaporation *in vacuo*. The pale yellow, sirupy XII was dissolved in xylene and coupled with 2.64 g. of chloromercuri-6-benzamidopurine[22] in the usual manner.[3] Evaporation of the chloroform solution gave 2.72 g. of a gum that was dissolved in 50 ml. of hot benzene. The solution deposited 0.20 g. of 6-benzamidopurine,[23] m.p. 239–242°, that had an infrared spectrum identical with that of an authentic sample. Evaporation of the filtrate afforded 2.04 g. of crude, blocked nucleoside (XIII); λ_{max}^{film} 3.00 μ (NH), 5.68 μ (acetate C=O), 5.78 μ (benzoate C=O), 5.89 μ (amide C=O), 6.20, 6.28 μ (purine ring), 9.10, 9.31, 9.70 (C—O—C).

*9-(6′-Deoxy-β-*D*-glucofuranosyl)adenine* (XV). A solution of 2.04 g. of crude XIII in 50 ml. of reagent methanol and 6 ml. of 1*N* methanolic sodium methoxide was refluxed for 1.5 hr. The solution was neutralized with acetic acid, then evaporated to dryness *in vacuo*. The residue was partitioned between 20 ml. of water and 20 ml. of chloroform. The aqueous solution, washed once more with chloroform, was evaporated to dryness *in vacuo*. A solution of the residue in 20 ml. of water was treated with 30 ml. of 10% methanolic picric acid. After several hours at 0°, the mixture was filtered and the precipitate washed with methanol. Recrystallization from 20 ml. of water gave 0.65 g. of the picrate of XV as yellow crystals, m.p. 204–208° dec. The free nucleoside was regenerated from the picrate with 3.1 g. of Dowex 2 (CO_3) and 20 ml. of water in the usual fashion.[3,12] Evaporation of the aqueous solution to dryness *in vacuo* gave 0.29 g. (32%) of white solid, m.p. 118–120°. Recrystallization from ethanol afforded white crystals, m.p. 118–118.5°, $[\alpha]_D^{25}$ −59.9° (2% in H_2O); λ_{max}^{KBr} 2.95, 3.11 μ (OH, NH), 6.12, 6.25, 6.75 μ (NH and purine ring), 7.28 μ (CH_3), 9.21, 9.32, 9.62 μ (C—O—C and C—O—H). Both the crude and recrystallized products were chromatographically homogeneous and traveled at R_{AD} 1.53 in solvent B and at R_{AD} 0.91 in solvent C.[15] That the recrystallized nucleoside was an ethanol solvate was demonstrated by the ethoxyl determination.

Anal. Calcd. for $C_{11}H_{15}N_5O_4 \cdot C_2H_5OH$: C, 47.7; H, 6.47; N, 21.4; one ethoxyl, 1.0. Found: C, 47.5; H, 6.54; N, 21.9; ethoxyl, 0.90.

This nucleoside, as expected for structure XV, consumed 0.90 mole-equivalents of periodate in 96 hr.; the rate curve was then approaching 1.0 mole-equivalents asymptotically.

*2,6-Diacetamido-9-(2′-O-acetyl-3′,5′-di-O-benzoyl-6′-deoxy-β-*D*-glucofuranosyl)purine* (XIV). Condensation of XII, prepared from 2.60 g. (5.7 mmoles) of the diacetate (IX) with 2.88 g. (6.1 mmoles) of chloromercuri-2,6-diacetamidopurine[12] in the usual manner[3,12] gave 2.49 g. (70%) of crude, blocked nucleoside; λ_{max}^{film} 5.70 μ (acetate C=O), 5.80 μ (benzoate C=O), 6.18, 6.25 μ (NH and purine ring), 9.12, 9.28, 9.72 μ (C—O—C).

*2,6-Diamino-9-(6′-deoxy-β-*D*-glucofuranosyl)purine* (XVI). A solution of 2.49 g. of crude XIV in 20 ml. of reagent methanol and 3 ml. of *N* methanolic sodium methoxide was refluxed for 3 hr. The solution was neutralized with acetic acid, then processed through the picrate (0.53 g.) as described for XV. The free nucleoside was regenerated from the picrate with 2.09 g. of Dowex 2 (CO_3) and 20 ml. of water in the usual fashion.[3,12] Evaporation of the aqueous solution to dryness *in vacuo* gave 0.26 g. of a white solid, m.p. 129–132°. Recrystallization from ethanol-ether afforded white crystals, m.p. 172–175°, $[\alpha]_D^{25}$ −27.7° (0.37% in H_2O); λ_{max}^{KBr} 3.00, 3.12 μ (NH, OH), 6.10, 6.25, 6.75 μ (NH and purine ring), 7.25 μ (CH_3), 9.22, 9.48, 9.82 μ (C—O—C and C—O—H). Both the crude and the recrystallized products were chromatographically homogeneous[15] and traveled at R_{AD} 0.90 in solvents B and R_{AD} 0.51 in solvent C.

Anal. Calcd. for $C_{11}H_{16}N_6O_4.H_2O$: C, 42.0; H, 5.77; N, 26.7. Found: C, 42.5; H, 5.70; N, 26.6.

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(22) Prepared from 6-benzamidopurine as described for the preparation of chloromercuri-2,6-diacetamidopurine.[12]

(23) This procedure effectively avoids the presence of adenine in a final deblocked nucleoside and is particularly useful if the blocked nucleoside cannot be crystallized.

Acknowledgments. The authors are indebted to Dr. Peter Lim for interpretation of the infrared spectra as well as for discussions, to O. P. Crews, Jr., and staff for large-scale preparation of intermediates, and to Dr. L. K. Moss and staff for the chromatograms and optical rotations.

MENLO PARK, CALIF.

[CONTRIBUTION FROM THE DEPARTMENT OF BIOLOGICAL SCIENCES, STANFORD RESEARCH INSTITUTE]

Potential Anticancer Agents.[1] XI. Synthesis of Nucleosides Derived from 6-Deoxy-L-idofuranose

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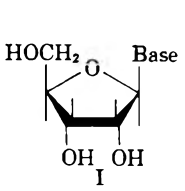
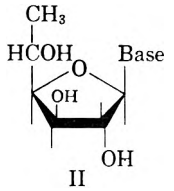
Lithium aluminum hydride reduction of 6-*O*-benzoyl-1,2-*O*-isopropylidene-5-*O*-tosyl-D-glucofuranose (IV) has led to a new and useful synthesis of 6-deoxy-1,2-*O*-isopropylidene-L-idofuranose (IX). The latter was converted to 9-(6′-deoxy-α-L-idofuranosyl)adenine (XV) and to 2,6-diamino-9-(6′-deoxy-α-L-idofuranosyl)purine (XIV) *via* the key intermediate 1,2-di-*O*-acetyl-3,5-di-*O*-benzoyl-6-deoxy-L-idofuranose (VII).

In a preceding paper of this series,[2] the rationale for synthesizing 6-deoxy-L-idofuranosyl nucleosides (II) was presented. This paper describes the synthesis of 9-(6′-deoxy-α-L-idofuranosyl)adenine (XV) and 2,6-diamino-9-(6′-deoxy-α-L-idofuranosyl)purine (XIV), compounds that might be antagonists of natural D-ribofuranosyl nucleosides (I).



I



II

The key intermediate in the projected synthesis of the nucleosides XIV and XV is 6-deoxy-1,2-*O*-isopropylidene-L-idofuranose (IX), which has been synthesized by the hydrogenation of 5,6-anhydro-3-*O*-benzyl-1,2-*O*-isopropylidene-L-idofuranose (VI)[3] and by hydrogenation of the glucosene (XII).[4] A new synthesis of this key intermediate (IX) that is considered to be shorter and more convenient has now been developed.

Ohle and Dickhauser[5] have claimed that tosylation of 6-*O*-benzoyl-1,2-*O*-isopropylidene-D-glucofuranose (III) in pyridine-chloroform at 37° for 4 days gave the 5-*O*-tosyl derivative (IV) in 34% yield, but Meyer and Reichstein[3] obtained a yield of only 20% by this procedure. It was observed in this laboratory that the infrared absorption spectrum of 6-*O*-benzoyl-1,2-*O*-isopropylidene-D-glucofuranose (III) contained the benzoate carbonyl stretching band at 5.90 μ instead of at the normal position of 5.80 μ. Tosylation of III to give the 5-*O*-tosyl derivative (IV) caused this carbonyl stretching band to shift back to the normal 5.80 μ position, presumably because the 5-tosylate destroyed hydrogen bonding between an available hydroxyl and the 6-benzoate carbonyl of III. This shift in the position of the carbonyl band made it possible to determine the degree of completion of the reaction by the gradual disappearance of the band at 5.90 μ. Thus, the most optimum conditions found involved the use of pyridine–methylene chloride at 40–50° for 4 days, which gave IV in 43% yield; a shorter reaction time, a lower temperature, or chloroform as a solvent[5] gave less complete conversion.

Meyer and Reichstein[3] have converted the 5-tosyl derivative (IV) with methanolic sodium methoxide to 5,6-anhydro-1,2-*O*-isopropylidene-L-idofuranose (V) in 61% yield. In this laboratory, their procedure gave a 64% yield of partially crystalline product (V) that was difficult to purify since it readily decomposed. It has now been found that lithium aluminum hydride reduction of the tosylate (IV) gave a 78% yield of the desired 6-deoxy-1,2-*O*-isopropylidene-L-idofuranose (IX), the reaction presumably proceeding *via* the anhydro L-idose derivative (V). The 6-deoxy-L-idose derivative (IX) agreed in melting point (90–92°) with that given by Meyer and Reichstein[3,4] and gave a large depression in melting point when mixed with the isomeric 6-deoxy-1,2-*O*-isopropylidene-D-glucofuranose,[2] a possible, though theoretically unlikely, product.

Treatment of 6-deoxy-1,2-*O*-isopropylidene-L-idofuranose (IX) with benzoyl chloride in pyridine gave the dibenzoate (VIII) in quantitative yield as an oil that could not be crystallized. Acetolysis of

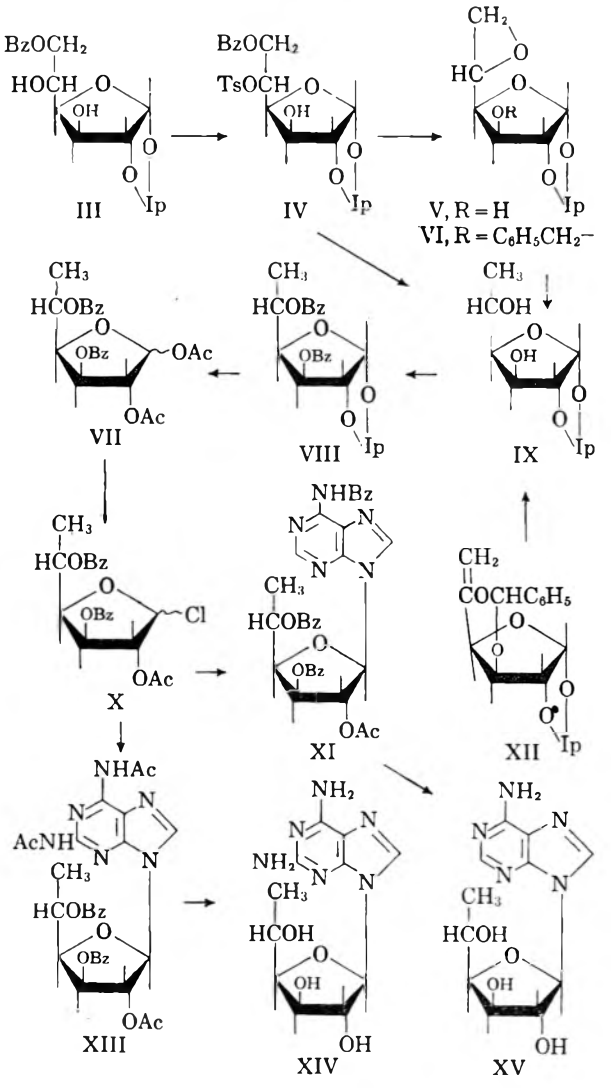
(1) This program is under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, and is in collaboration with the Sloan-Kettering Institute for Cancer Research.

(2) E. J. Reist, R. R. Spencer, and B. R. Baker, Paper X of this series, *J. Org. Chem.*, **23**, 1753 (1958).

(3) A. S. Meyer and T. Reichstein, *Helv. Chim. Acta*, **29**, 152 (1946).

(4) A. S. Meyer and T. Reichstein, *Helv. Chim. Acta*, **29**, 139 (1946).

(5) H. Ohle and E. Dickhauser, *Ber.*, **58B**, 2593 (1925).



VIII with acetic acid, acetic anhydride, and sulfuric acid gave a 72% yield of an anomeric mixture of diacetates (VII) that also failed to crystallize. However, crystalline nucleosides (XIV and XV) were obtained by the standard coupling procedure.[6,7]

Conversion of the diacetate (VII) to the chloro sugar (X) with ethereal hydrogen chloride[8] containing acetyl chloride,[9] followed by coupling with chloromercuri-6-benzamidopurine, gave the crude blocked nucleoside (XI). Deacylation of XI with methanolic sodium methoxide afforded a 15% yield (based on VII) of crystalline 9-(6′-deoxy-α-L-idofuranosyl)adenine (XV),[10] isolated *via* its picrate and regenerated with Dowex 2 (CO_3).[6,11] This nucleoside, when chromatographed on paper,[12] gave a single spot with R_{Ad} 1.44 in solvent A and R_{Ad} 0.76 in solvent B.

Similarly, condensation of X with chloromercuri-2,6-diacetamidopurine followed by deacylation gave a 6.5% yield (based on VII) of crystalline 2,6-diamino-9-(6′-deoxy-α-L-idofuranosyl)-purine (XIV).[10] This nucleoside, when chromatographed on paper,[12] also gave a single spot with R_{Ad} 0.88 in solvent A and R_{Ad} 0.36 in solvent B.

EXPERIMENTAL[12,13]

6-O-Benzoyl-1,2-O-isopropylidene-D-glucofuranose (III). A solution of 4.41 g. (12 mmoles) of 3-*O*-benzoyl-1,2:5,6-di-*O*-isopropylidene-D-glucofuranose[15] in 20 ml. of 60% ethanol was adjusted to *p*H 2 with 6*N* hydrochloric acid, then heated at 50° for 4.5 hr. At the end of this time a 5-ml. aliquot was removed and extracted with chloroform (3 × 10 ml.). The combined extracts, dried with magnesium sulfate and evaporated to dryness *in vacuo*, left 0.71 g. of 3-*O*-benzoyl-1,2-*O*-isopropylidene-D-glucofuranose: λ_{max}^{film} 2.90 μ (OH), 5.80 μ (C=O), 7.87 μ (benzoate C—O—C). This material consumed 0.64 mole-equivalents of periodate in 1 hr.

The remaining 15 ml. of hydrolysis solution was carefully adjusted to *p*H 8 with 2*N* potassium hydroxide, then allowed to stand at about 3° overnight. The 6-benzoate (III) was collected on a filter and washed with cold 60% ethanol; yield, 2.56 g. (87%), m.p. 182–184°. Recrystallization from 60% ethanol gave 1.70 g. (58%) of white crystals, m.p. 193–195°, $[\alpha]_D^{25}$ +6.0° ± 2.5° (0.5% in ethanol); λ_{max}^{KBr} 2.85 μ (OH), 5.92 μ (benzoate C=O), 7.25 μ (CH_3), 7.77 μ (benzoate C—O—C). This compound did not react with periodate.

Ohle[16] has recorded a melting point of 191–192° and a rotation of +7.4° in ethanol for this product. The above periodate data give unambiguous support to Ohle's hypothesis that acid removes the 5,6-*O*-isopropylidene group only and that base isomerizes the 3-benzoate to the 6-benzoate. The *p*H 2 and *p*H 8 required for the two steps are quite critical to avoid over- or under-hydrolysis of groups.

(6) E. J. Reist, L. Goodman, R. R. Spencer, and B. R. Baker, Paper IV of this series, *J. Am. Chem. Soc.*, **80**, 3962 (1958).

(7) B. R. Baker and K. Hewson, *J. Org. Chem.*, **22**, 966 (1957).

(8) J. Davoll, B. Lythgoe, and A. R. Todd, *J. Chem. Soc.*, 967 (1948).

(9) B. R. Baker and R. E. Schaub, *J. Am. Chem. Soc.*, **77**, 5900 (1955).

(10) That this nucleoside has the α-configuration is reasonably certain since formation of nucleosides by this process normally gives a product with a C_1-C_2-*trans*-configuration in the sugar moiety. For a summary of reactions illustrating this point *cf.* B. R. Baker on Stereochemistry of Nucleoside Synthesis, Ciba Foundation Symposium on the Chemistry and Biology of Purines, J. and A. Churchill, Ltd., London, 1957, pp. 120.

(11) B. R. Baker and K. Hewson, *J. Org. Chem.*, **22**, 959 (1957).

(12) Paper chromatograms of the nucleosides were run on Whatman No. 1 paper by the descending technique in 5% disodium phosphate (solvent A) and in water-saturated butanol (solvent B). The spots were located by visual examination with an ultraviolet lamp. Adenine was used as a standard and was arbitrarily assigned a value of R_{AD} 1.00.

(13) Melting points were taken on a Fisher-Johns apparatus and are uncorrected. Optical rotations were determined with a Standard Polarimeter Model D attachment to the Beckman DU spectrophotometer calibrated with standard sucrose solutions.[14]

(14) A. S. Keston, Abstracts of 127th Meeting, American Chemical Society 18C (1955).

(15) E. Fischer and H. Noth, *Ber.*, **51**, 321 (1918).

(16) H. Ohle, *Biochem. Z.*, **131**, 611 (1912); *Ber.*, **57B**, 403 (1924).

6-O-Benzoyl-1,2-O-isopropylidene-5-O-tosyl-D-glucofuranose (IV). To a stirred solution of 11.9 g. (30.8 mmoles) of III in 79 ml. of reagent pyridine was added dropwise a solution of 6.95 g. (36.6 mmoles) of tosyl chloride in 190 ml. of methylene chloride over a period of 45 min. The solution was kept at 40–50° for 4 days protected from moisture, then poured into 500 ml. of ice water with stirring. The separated aqueous phase was extracted with chloroform (3 × 50 ml.). The organic extracts were washed with 50 ml. of saturated aqueous sodium bicarbonate and 50 ml. of water, then combined. Dried with magnesium sulfate, the organic solution was evaporated to dryness *in vacuo*. The last traces of pyridine were removed by the addition and removal of toluene (2 × 10 ml.) *in vacuo*. The gummy solid (16.2 g.) showed a benzoate band at 5.80 μ with a small shoulder at 5.90 μ, thus indicating that tosylation was essentially complete. Recrystallization from ethanol gave 7.52 g. (43%) of product, m.p. 138–140°, $[\alpha]_D^{25}$ +20.6° ± 1.4° (2.0% in $CHCl_3$);[17] λ_{max}^{KBr} 2.90 μ (OH), 5.80 μ (benzoate C=O), 7.85 μ (benzoate C—O—C), 8.50 μ (sulfonate).

Anal. Calcd. for $C_{23}H_{26}O_8S$: C, 57.7; H, 5.48; S, 6.70. Found: C, 58.0; H, 5.60; S, 6.55.

Ohle and Dickhauser[5] have recorded m.p. 142°, $[\alpha]_D^{27}$ +9.34° (2.142% in $CHCl_3$), and a yield of 34%, whereas Meyer and Reichstein[3] obtained a 20% yield by their procedure.[5]

6-Deoxy-1,2-O-isopropylidene-L-idofuranose (IX). To a mixture of 4.74 g. (0.12 mole) of lithium aluminum hydride and 300 ml. of reagent ether was added 25.0 g. (0.052 mole) of pure IV over a period of about 45 min. The mixture, protected from moisture, was refluxed with stirring for 20 hr., then the excess hydride was decomposed by the dropwise addition of 25 ml. of ethyl acetate, then 12 ml. of water. After 36 ml. of 10% aqueous sodium hydroxide was added, Celite was added to make a filterable slurry. The mixture was filtered and the filter cake was washed with chloroform (3 × 20 ml.). The filtrate and washings were combined, dried with magnesium sulfate, and evaporated to dryness *in vacuo* at 20 mm. and finally at 0.5 mm. to give 3.14 g. (30%) of a light yellow sirup that crystallized overnight. The Celite cake was placed in a Soxhlet extractor and extracted for 4 hr. with chloroform, giving an additional 5.19 g. (48%) of product; λ_{max}^{KBr} 2.95 μ (OH), 7.26 μ (CH_3), 9.25, 9.58, 9.85 μ (C—O—C, C—OH). A total yield of 8.33 g. (78%) was thus obtained that was suitable for the next step.

A sample of 0.72 g. was distilled at 3 μ (b.p. 90–95°), giving 0.51 g. of a clear sirup that crystallized overnight, m.p. 90–92°, $[\alpha]_D^{25}$ −7.1 ± 1.9° (2.2% in $CHCl_3$). A mixture with 6-deoxy-1,2-*O*-isopropylidene-D-glucofuranose melted at 65–70°.

Meyer and Reichstein[3,4] have recorded m.p. of 90–91° and $[\alpha]_D^{21}$ −12.9 ± 0.6° (3.6% in $CHCl_3$) for this compound prepared in other ways.

3,5-Di-O-benzoyl-6-deoxy-1,2-O-isopropylidene-L-idofuranose (VIII). To a solution of 5.17 g. (25.6 mmoles) of crude 6-deoxy-1,2-*O*-isopropylidene-L-idofuranose (IX) in 50 ml. of reagent pyridine, cooled to 0°, 9.3 ml. (81 mmoles) of benzoyl chloride was added dropwise with stirring, the temperature being maintained below 5°. After being stirred for an additional hour at 0°, the mixture was left at room temperature for 24 hr., protected from moisture. The reaction mixture was then added dropwise to a well-stirred mixture of ice and excess saturated aqueous sodium bicarbonate solution. The organic layer was separated and the aqueous layer was extracted with three 50-ml. portions of chloroform. The organic layer and separate extracts, washed with excess saturated aqueous sodium bicarbonate, then water, were combined and dried with magnesium sulfate and evaporated *in vacuo*. The last traces of pyridine were removed by the addition of two 20-ml. portions of toluene and removal *in vacuo* to give 11.1 g. (108%) of dark sirup which contained benzoic anhydride; λ_{max}^{film} 5.60 μ (anhydride C=O), 5.82 μ (benzoate C=O), 7.25 μ (CH_3), 7.88, 9.01 μ (benzoate C—O—C), 9.10, 9.33, 9.75 μ (C—O—C). This material was suitable for the next step.

In a pilot run, 0.20 g. (0.93 mmoles) of pure 6-deoxy-1,2-*O*-isopropylidene-L-idofuranose (IX) gave a product free of benzoic anhydride; yield, 0.30 g. (60%), $[\alpha]_D^{30}$ −12.3° (0.5% in $CHCl_3$).

Anal. Calcd. for $C_{23}H_{24}O_7$: C, 67.0; H, 5.87. Found: C, 66.9; H, 6.09.

1,2-Di-O-acetyl-3,5-di-O-benzoyl-6-deoxy-L-idofuranose (VII). To a solution of 9.14 g. (22.2 mmoles) of crude 3,5-di-*O*-benzoyl-6-deoxy-1,2-*O*-isopropylidene-L-idofuranose (VIII) in 100 ml. of glacial acetic acid and 12.2 ml. of acetic anhydride was added 7.6 ml. of 96% sulfuric acid dropwise with stirring, the temperature being maintained below 20°. After standing at room temperature overnight while protected from moisture, the mixture was poured into 300 ml. of ice water and stirred for 30 min. The organic layer was separated and the aqueous layer was extracted twice with 50-ml. portions of chloroform. The organic layer and separate extracts were washed with water, excess aqueous sodium bicarbonate solution, and water, then combined, dried over magnesium sulfate, and evaporated *in vacuo* to yield 7.13 g. (69%) of a dark yellow sirup which did not crystallize so could not be obtained analytically pure; λ_{max}^{film} 5.70 μ (acetate C=O), 5.80 μ (benzoate C=O), 7.27 μ (CH_3), 7.88, 9.00 μ (benzoate C—O—C), 8.10, 8.22 μ (acetate C—O—C), 9.10, 9.33, 9.72 μ (C—O—C); $[\alpha]_D^{27}$ +35.5 (3.4% in $CHCl_3$). 7

Anal. Calcd. for $C_{24}H_{24}O_9$: C, 63.1; H, 5.30. Found: C, 64.7; H, 5.48.

9-(2'-C-Acetyl-3',5'-di-O-benzoyl-6'-deoxy-α-L-idofuranosyl)-6-benzamidopurine (XI). A solution of 2.30 g. (5.0 mmoles) of VII in 5 ml. of acetyl chloride was added to 60 ml. of reagent ether that had been previously saturated with hydrogen chloride at 0°. After standing at −5° for 3 days in a stoppered container, the mixture was evaporated to dryness *in vacuo* with protection from moisture. Acetic acid was removed by the addition of benzene (2 × 10 ml.) and evaporation *in vacuo*. The pale yellow sirup (X) was dissolved in xylene and condensed with 2.87 g. of chloromercuri-6-benzamidopurine[18] in the usual manner.[6,7] Evaporation of the chloroform solution gave 2.46 g. of crude XI as an amber colored glass: λ_{max}^{film} 3.00 μ (NH), 5.71 μ (acetate C=O), 5.78 μ (benzoate C=O), 6.22, 6.31, 6.60, 6.68 μ (NH and aromatic rings), 7.82, 9.00 μ (benzoate C—O—C), 8.10 μ (acetate C—O—C), 9.10, 9.34, 9.72 μ (C—O—C).

9-(6'-Deoxy-α-L-idofuranosyl)adenine (XV). A solution of 2.46 g. of crude XI in 30 ml. of reagent methanol and 6 ml. of *N* methanolic sodium methoxide was refluxed for 1.5 hr. The solution was neutralized with acetic acid, then evaporated to dryness *in vacuo*. The residue was partitioned between 10 ml. of water and 10 ml. of chloroform. The aqueous layer was washed with chloroform, then evaporated to dryness *in vacuo*. A solution of the residue in 15 ml. of reagent methanol was treated with 20 ml. of 10% methanolic picric acid. After several hours at 0°, the mixture was filtered and the precipitate was washed with methanol. Recrystallization from 25 ml. of water gave 0.60 g. of the picrate of XV as yellow crystals, m.p. 200–220° (dec.). The free nucleoside was regenerated from the picrate with 2.5 g. of Dowex 2 (CO_3) and 20 ml. of water in the usual fashion.[6,11] Evaporation of the aqueous solution to dryness *in vacuo* gave 0.21 g. (15%), m.p. 205–210°. Recrystallization from ethanol afforded white crystals, m.p. 196–198°; λ_{max}^{KBr} 2.98, 3.09 μ (NH, OH), 6.07, 6.22, 6.33, 6.75 μ (NH and aromatic ring), 7.25 μ (CH_3), 9.07, 9.23, 9.46, 9.87 μ (C—O). The

(17) This value has been checked several times but it does not agree with the value reported by Ohle and Dickhauser.[5]

(18) Prepared from mercuric chloride and 6-benzamidopurine as described for chloromercuri-2,6-diacetamidopurine.[11]

crude material contained a trace of adenine which was readily removed by the one recrystallization. The nucleoside was then chromatographically homogeneous and travelled at R_{Ad} 1.44 in solvent A and R_{Ad} 0.76 in solvent B[12]; $[\alpha]_D^{28}$ −36.9° (0.4% in H_2O).

Anal. Calcd. for $C_{11}H_{15}N_5O_4$: C, 47.0; H, 5.38; N, 24.9. Found: C, 46.7; H, 5.35; N, 24.8.

The nucleoside, in agreement with structure XV, consumed 0.78 mole-equivalent of periodate in 66 hr. The rate curve was then approaching about 0.85 mole-equivalent asymptotically.

2,6-Diacetamido-9-(2′-O-acetyl-3′,5′-di-O-benzoyl-6′-deoxy-α-L-idofuranosyl)purine (XIII). Condensation of X, prepared from 2.50 g. (5.5 mmoles) of diacetate (VII), with 2.20 g. (4.69 mmoles) of chloromercuri-2,6-diacetamidopurine[11] as described for XI gave 2.47 g. (72%) of crude blocked nucleoside; λ_{max}^{film} 3.00, 3.10 μ (NH), 5.78 μ (ester C=O), 6.14, 6.22, 6.68, 6.85 μ (NH and aromatic rings), 7.80, 8.98 μ (benzoate C—O—C), 8.09 μ (acetate C—O—C), 9.10, 9.32, 9.72 μ (C—O—C).

2,6-Diamino-9-(6′-deoxy-α-L-idofuranosyl)purine (XIV). A solution of 2.47 g. (3.90 mmoles) of XIII in 20 ml. of reagent methanol was treated with 5 ml. of *N* methanolic sodium methoxide and heated at reflux for 3 hr. The solution was then processed to the picrate as described for XV. Recrystallization from 20 ml. of water gave 248 mg. of the picrate of XIV as yellow crystals, m.p. 195–205° (dec.). Regeneration to the free nucleoside with 2.0 g. of Dowex 2 (CO_3) and 10 ml. of water in the usual fashion[6,11] gave 102 mg. (6.5%) of a white solid, m.p. 184–190°. Recrystallization from ethanol afforded white crystals, m.p. 210–211°; λ_{max}^{KBr} 2.92, 3.08 μ (NH, OH), 6.10, 6.23, 6.60, 6.75 μ (NH and aromatic rings), 9.22, 9.42 μ (C—O); $[\alpha]_D^{27}$ −50.8° (1.0% in H_2O). Both the crude and recrystallized products were chromatographically homogeneous and travelled at R_{Ad} 0.88 in solvent A and R_{Ad} 0.36 in solvent B as compared with R_{Ad} 0.54 and R_{Ad} 0.39, respectively, for 2,6-diaminopurine.

Anal. Calcd. for $C_{11}H_{16}N_6O_4 \cdot {}^1/_2H_2O$: C, 43.2; H, 5.58; N, 27.5. Found: C, 43.2; H, 5.88; N, 27.6.

Acknowledgments. The authors owe thanks to Dr. Peter Lim for interpretation of the infrared spectra, to O. P. Crews, Jr., and group for large-scale preparation of intermediates, and to Dr. L. K. Moss and group for the chromatography, periodate data, and optical rotations.

MENLO PARK, CALIF.

[CONTRIBUTION OF THE FULMER CHEMICAL LABORATORY, THE STATE COLLEGE OF WASHINGTON]

Schiff Bases and Related Substances. IV. Reaction of Acyclic and Heterocyclic α-Amino Sulfides with Phenyl Isocyanate. Comparative Reactions with Phenyl Isothiocyanate[1]

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When the Schiff base–thiol adduct, *N*-[α-(*p*-tolylthio)benzyl]aniline (I), is treated with phenyl isocyanate, none of the expected phenylurea derivative is obtained. Instead, the mercaptal, α,α-bis(*p*-tolylthio)toluene (III), *N*-benzylideneaniline (IV), carbanilide (V), and *p*-tolyl phenylthiolcarbamate (VI) are isolated from the reaction mixture. On the other hand, the adduct I fails to react with phenyl isothiocyanate under similar conditions. A possible explanation for the formation of the products III–VI is suggested. Related cyclic systems containing the S—C—NH group are shown to react with phenyl isocyanate to form phenylurea derivatives and none of the unusual behavior associated with the adduct I is observed. Phenyl isothiocyanate also reacts with most of the eyclic systems which were studied (the products in these cases are the corresponding phenylthiourea derivatives). However, in the case of 2,2-pentamethylenebenzothiazoline (XII), no reaction occurs with phenyl isothiocyanate under a variety of conditions, thus paralleling the result with I.

The reaction of the Schiff base–thiol adduct, *N*-[α-(*p*-tolylthio)benzyl]aniline (I), with acetylating agents has been shown to proceed only in part to give the expected acetyl derivative.[1] To a greater extent, cleavage of I occurred to yield acetanilide and the corresponding mercaptal III or *p*-tolyl disulfide. The behavior of I with phenyl isocyanate and phenyl isothiocyanate, respectively now has also been investigated and is reported in the present paper.

Unlike the acetylation reaction,[1] none of the corresponding *N*-acyl derivative (in this case the phenylurea derivative II) was isolated when I was heated with phenyl isocyanate; instead, a cleavage reaction occurred extensively to form the mercaptal

$$C_6H_5CH(ArS)NHC_6H_5 + C_6H_5NCO \longrightarrow$$

I

$$C_6H_5CH(ArS)NCONHC_6H_5$$

C_6H_5

II

Ar = *p*-$CH_3C_6H_4$

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(1) Presented in part before the Oregon Section of the American Chemical Society, Salem, Ore., May 21, 1955, and in part before the Division of Organic Chemistry at the 132nd Meeting of the American Chemical Society, New York, N. Y., Sept. 10, 1957. Paper III. G. W. Stacy, R. I. Day, and R. J. Morath, *J. Am. Chem. Soc.*, **80**, 3475 (1958).

(2) To be presented in part as a thesis by Philip A. Craig in partial fulfillment of the requirements for the Degree of Master of Science, the State College of Washington.

(3) In part abstracted from a thesis submitted by Richard I. Day in partial fulfillment of the requirements for the degree of Doctor of Philosophy, the State College of Washington, June 1957.

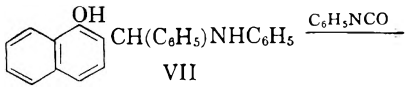
III, *N*-benzylideneaniline (IV), and carbanilide (V), all isolated in good yield. In addition, however, a small amount of *p*-tolyl phenylthiolcarbamate (VI) was isolated.

$$\mathrm{I} \xrightarrow{C_6H_5NCO} \underset{\text{III}}{C_6H_5CH(SAr)_2} + \underset{\text{IV}}{C_6H_5CH{=}NC_6H_5} + \underset{\text{V}}{(C_6H_5NH)_2CO} + \underset{\text{VI}}{C_6H_5NHCOSAr}$$

The identity of VI followed from the elemental analysis and comparison with a sample of a synthetic product prepared directly from *p*-toluenethiol. Preparation or compound VI has been reported by Gilman and King;[4] these authors found that *p*-toluenethiol did not react directly with phenyl isocyanate but that VI could be obtained by employing *p*-tolylmercaptomagnesium iodide. However, since the recent work of Dyer and Glenn[5] had demonstrated that thiols will react with phenyl isocyanate if triethylamine is employed as catalyst, this direct method was applied successfully to the present independent preparation of VI. In an additional observation of interest, it was found that phenyl isothiocyanate reacts in a similar manner with *p*-toluenethiol under the influence of triethylamine.

Because of the catalytic effect of triethylamine on the reactions of *p*-toluenethiol with phenyl isocyanate and with phenyl isothiocyanate, it was questioned as to whether a different result from that already described might be observed if I were treated with phenyl isocyanate in the presence of triethylamine. And, indeed, under these conditions, products III and V were not obtained, while IV and VI were isolated in good yield as the exclusive products.

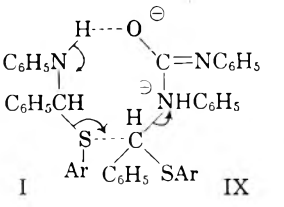
Although no previous studies of the reaction of phenyl isocyanate on Schiff base–thiol adducts, such as I, have been reported, Neri[6] observed a similar reaction with the secondary amine VII. However, this was an anomalous result in the work of this author, for he did obtain exclusively the phenylurea derivative corresponding to the 2-hydroxy-1-naphthyl isomer of VII,[6] as well as in several other instances,[6,7] whereas in no case have we been able to obtain the expected phenylurea derivatives in our work.



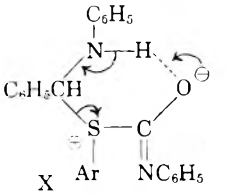
VII

$$\underset{\text{V}}{(C_6H_5NH)_2CO} + \underset{\text{VIII}}{C_6H_5CH(C_{10}H_6OH\text{-}1,2)_2} + C_6H_5CHO$$

An explanation of the formation of the products, III–V, as a result of the action of phenyl isocyanate on I, might involve the concerted interaction of the complex IX (formed from I and phenyl isocyanate) with a molecule of I.[8] The formation of VI, on the other hand, might result from complexing of phenyl isocyanate with the sulfur atom rather than the nitrogen atom of I with subsequent decomposition of the intermediate complex X into VI and *N*-benzylideneaniline (IV).



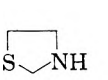
I IX



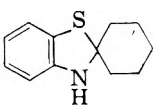
X

In order to determine if a less reactive reagent might react with I to form a derivative, rather than causing the decomposition that occurred in the case of phenyl isocyanate, I was treated with phenyl isothiocyanate. However, no reaction was observed under a variety of conditions.

Because of the unusual results obtained when I was treated with phenyl isocyanate and with phenyl isothiocyanate, it seemed desirable to study the action of these reagents on some better known systems containing the S-C-NH group. Because such known systems are cyclic, it seemed that they very likely would not decompose in the same manner as I but would tend to form phenylureas and phenylthioureas with the reagents in question.[9] Further, the possibility of obtaining some qualitative information on comparative reactivities was apparent. The two cyclic systems of primary interest were thiazolidine (XI) and the benzothiazoline derivative XII, recently reported by Kiprianov and Portnyagina;[10] the latter compound is, of course, even more closely related to I because of the attachment of S and N to a benzene ring. It was found



XI



XII

that XI reacted rapidly and smoothly with phenyl isocyanate in anhydrous ether to give in contrast to I the expected phenylurea derivative. The closely

(4) H. Gilman and W. B. King, *J. Am. Chem. Soc.*, **47**, 1136 (1925).

(5) E. Dyer and J. F. Glenn, *J. Am. Chem. Soc.*, **79**, 366 (1957).

(6) A. Neri, *Gazz. chim. ital.*, **61**, 681, 815 (1931); *Chem. Abstr.*, **26**, 1277, 1922 (1932).

(7) A. Neri, *Gazz. chim. ital.*, **64**, 420 (1934); *Chem. Abstr.*, **28**, 6436 (1934).

(8) A stepwise process, as discussed in Paper III (ref. 1), is also to be considered, and *vice versa*. The explanations presented are not necessarily intended to be proposals of reaction mechanisms but rather interpretations of product formation based on the possible interaction of logical reactive centers. A convincing case for any specific mechanism would, of course, require more extensive experimentation.

(9) With one exception, these derivatives are new compounds.

(10) A. I. Kiprianov and V. A. Portnyagina, *J. Gen. Chem.* (*U.S.S.R.*), English translation, **25**, 2223 (1955).

related thiazolidine-4-carboxylic acid did not react so smoothly, but gave a hydantoin in low yield. The benzothiazoline XII did not react in ether with phenyl isocyanate, so that it was necessary to remove the ether and heat the mixture to obtain the phenylurea derivative. The same diminished reactivity was observed in the case of the adduct I when the reaction was attempted in ether, and a substantial amount of the starting material I was recovered.

As might have been anticipated, phenyl isothiocyanate proved to be less reactive than phenyl isocyanate. Although it reacted in good yield with both thiazolidine (XI) and thiazolidine-4-carboxylic acid to give the expected products, it failed to react with either I or XII under a variety of conditions. These results raise a question concerning the influence of various factors in diminishing the nucleophilic character of the nitrogen atom in these conpounds. By a comparison of the yields of phenylurea and phenylthiourea derivatives obtained for thiazolidine and pyrrolidine, it was suggested that the α-sulfide group has an effect on the nitrogen atom. Thiazolidine forms a phenylurea derivative in 66% yield and a phenylthiourea derivative in a 73% yield, while pyrrolidine forms the same derivatives in higher yields, 85% and 95%, respectively.[11] An even more dramatic demonstration of the effect, however, was noted by the fact that *o*-methylthioaniline (XIII) reacted readily with phenyl isothiocyanate, while the benzothiazoline XII had not. Phenyl isocyanate also reacted readily with XIII; however, the difference in the reactivity of this reagent with this compound, as compared with I and XII, is not as great as in the case of phenyl isothiocyanate. For structure XIII, of course, the sulfide group is not *alpha* relative to the nitrogen atom and hence cannot exercise the same effect as with I or XII.

EXPERIMENTAL[12]

Reaction of N-[α-(p-tolylthio)benzyl]aniline (I) *with phenyl isocyanate. A. Without catalyst.*[13] A mixture of 3.05 g. (10 mmoles) of I[14] and 0.54 ml. (596 mg., 5 mmoles) of phenyl isocyanate was heated at 90° for 20 min. in an oil bath. Then 20 ml. of ligroin (b.p. 100–110°) was added, and heating was resumed for an additional 10 min. The hot ligroin solution was removed from the solid remaining in the flask by means of a filter stick. The solid was washed with two 3-ml. portions of ligroin, and these were added to the main ligroin solution. The solid which had separated proved to be *carbanilide* (V); yield 655 mg. (72%[15]), m.p. 243–243.5°, lit.[16] m.p. 238–239°, mixed m.p. 242–243.5°.

The ligroin solution which had been separated from the carbanilide was cooled, whereupon a yellow, crystalline solid, which was identified as *p-tolyl phenylthiolcarbamate* (VI), precipitated; yield 272 mg., m.p. 130–131.5°. Recrystallization from ethanol gave 192 mg. of colorless platelets (16%), m.p. 133.5–134.5°, lit.[4] m.p. 127°.

Anal. Calcd. for $C_{14}H_{13}NOS$: C, 69.10; H, 5.38; N, 5.76. Found: C, 69.40; H, 5.51; N, 5.58.

The ligroin filtrate from VI was shaken with two drops of water to convert any unreacted phenyl isocyanate to carbanilide; 13 mg. of material was obtained and discarded. Then 11 ml. of 5% ethanolic potassium hydroxide solution was added to the ligroin solution to convert unreacted adduct to mercaptide and Schiff base. This mixture was extracted with 25 ml. of water; the resulting aqueous extract was acidified with hydrochloric acid and in turn was extracted with one 20-ml. and two 10-ml. portions of ether. The ether extracts, which contained *p*-toluenethiol, were dried over Drierite, and the ether was then removed by evaporation to give a 10-ml. volume of residue. By an iodine–thiosulfate titration, 1.50 mmoles of thiol were shown to be present.

The ligroin solution remaining after the above extraction procedure was subjected to distillation to remove most of the ligroin; the residue then was steam distilled until about 300 ml. of distillate had been collected. The distillate was extracted with one 40-ml. portion and two 20-ml. portions of ether. The solvent was removed from the combined, dried extracts to give 713 mg. of a residual oil. This was crystallized from ligroin to give 476 mg. of *N-benzylideneaniline* (IV), m.p. 49–50.5°, lit.[17] m.p. 53.5°.

The material remaining in the steam distillation flask was extracted with one 20-ml. and two 10-ml. portions of ether. The combined extracts were dried, and the ether was removed by evaporation to yield 1.43 g. of the mercaptal, *α,α-bis(p-tolylthio)toluene* (III). This material was recrystallized from ethanol to yield 786 mg. (55%); m.p. 79–79.5°, lit.[18] m.p. 79°, mixed m.p. 79.5–80°.

B. In ether solution. Phenyl isocyanate (596 mg., 5 mmoles) was added dropwise to 3.05 g. (10 mmoles) of I in 50 ml. of absolute ether. When the ether was evaporated and the residue was recrystallized from 2-propanol, 1.04 g. (34%) of starting material was recovered.

C. With triethylamine as catalyst.[5] Quantities of reactants were identical as in Procedure A; however, 2–3 drops of triethylamine were added. The reaction mixture was heated for 15 min. on a steam bath; then 15 ml. of ligroin (b.p. 100–110°) was added, and heating was resumed for an additional 15 min. The hot ligroin solution was decanted from the insoluble residue, the residue was washed with two 2-ml. portions of ligroin, and the washings were added to the main portion of ligroin. The insoluble residue, 1.26 g., m.p. 119–123°, and the material which precipitated from the ligroin solution, 1.11 g., m.p. 90–110°, were combined and recrystallized twice from ethanol to give fairly pure VI; yield 1.21 g. (50%), m.p. 124–127°, mixed m.p. 128–131°.

The ligroin filtrate was seeded with a crystal of *N*-benzylideneaniline and maintained at −20°. Crude *N*-benzylidene-

(11) A comparison of the acidic and basic dissociation constants of thiazolidine-4-carboxylic acid and proline, as obtained by S. Ratner and H. T. Clarke, *J. Am. Chem. Soc.*, 59, 200 (1937), also demonstrates the effect of the α-sulfide group in lessening the nucleophilic character of the nitrogen atom.

(12) All melting points are corrected. The microanalytical work was performed by Galbraith Laboratories, Knoxville, Tenn., and by Weiler and Strauss Laboratories, Oxford, England. In most cases, experiments were carried out in duplicate and the agreement between results was good.

(13) Some preliminary aspects of this experiment were carried out by Richard J. Morath, Ph.D. received from the State College of Washington, February 1954.

(14) Prepared in yields of 85–90% by a method previously described, G. W. Stacy, R. I. Day, and R. J. Morath, *J. Am. Chem. Soc.*, 77, 3869 (1955).

(15) The percentage yield of each product is adjusted for the amount of unreacted adduct as determined by alkaline decomposition and iodine titration (subsequently described).

(16) G. Young and E. Clark, *J. Chem. Soc.*, 73, 361, 367 (1898).

(17) G. Pyl, *Ber.*, 60, 287 (1927).

(18) E. Fromm and G. Raiziss, *Ann.*, 374, 90, 101 (1910).

aniline (IV) crystallized; yield 1.23 g. (68%), m.p. 44–47°, mixed m.p. 48–49°.

p-Tolyl phenylthiolcarbamate (VI) *from p-toluenethiol.* To 1.24 g. (0.01 mole) of *p* toluenethiol and 1.19 g. (1.09 ml., 0.01 mole) of phenylisocyanate was added 2–3 drops of triethylamine.[5] A crystalline mass formed immediately with a considerable evolution of heat. Recrystallization from ethanol gave colorless crystals; yield 2.10 g. (87%), m.p. 132–132.5°. Admixture of this substance with that isolated in the preceding experiment resulted in no depression in melting point, m.p. 130–131°.

p-Tolyl phenyldithiocarbamate. To a mixture of 1.24 g. (0.01 mole) of *p*-toluenethiol and 1.35 g. (1.20 ml., 0.01 mole) of phenyl isothiocyanate was added 2–3 drops of triethylamine. The crude product, obtained in quantitative yield, was recrystallized from ethanol to give 2.54 g. (98% yield) of colorless needles, m.p. 141–141.5°.

Anal. Calcd. for $C_{14}H_{13}NS_2$: C, 64.82; H, 5.05; S, 24.73. Found: C, 64.77; H, 5.03; S, 24.74.

Attempted reaction of N-[α-(p-tolylthio)benzyl]aniline (I) *with phenyl isothiocyanate.* After preliminary experiments in anhydrous ether showed no perceptible reaction had occurred [by virtue of recovery of starting material (67%)], the following procedure, as employed above with phenyl isocyanate, was attempted. A mixture of 3.05 g. (0.01 mole) of I and 1.35 g. (1.20 ml., 0.01 mole) of phenyl isothiocyanate was heated on a steam bath for 15 min.; 15 ml. of ligroin (b.p. 100–110°) was added, and heating was continued for an additional 15 min. From the ligroin solution, 2.70 g. (89% recovery) of starting material I was obtained, m.p. 63–66°. Recrystallization of this material from 2-propanol gave 2.22 g. (73% recovery) of relatively pure I, m.p. 68–70°.

Phenylurea of thiazolidine (XI). To 890 mg. (0.78 ml., 0.01 mole) of thiazolidine[19] in 25 ml. of absolute ether was added dropwise with stirring 1.19 g. (1.09 ml., 0.01 mole) of phenyl isocyanate dissolved in 25 ml. of absolute ether. As the addition was begun, a crystalline material began to precipitate immediately. When the addition was complete, the product was removed by filtration, yield 1.37 g. (66%), m.p. 129–130.5°. Recrystallization from ethanol gave 550 mg. (26% yield) of colorless plates, m.p. 131.5–132.5°.

Anal. Calcd. for $C_{10}H_{12}N_2OS$: C, 57.66; H, 5.81; N, 13.45. Found: C, 57.88; H, 5.76; N, 13.73.

Phenylthiourea of thiazolidine (XI). To 890 mg. (10 mmoles) of thiazolidine in 25 ml. of absolute ether was added dropwise with stirring 1.35 g. (10 mmoles) of phenyl isothiocyanate dissolved in 25 ml. of absolute ether. The ensuing reaction yielded 1.66 g. (74%) of colorless plates, m.p. 161.5–162.5°. Recrystallization from ethanol gave 1.27 g. (57%), m.p. 166–167°.

Anal. Calcd. for $C_{10}H_{12}N_2S_2$: C, 53.53; H, 5.39; N, 12.49. Found: C, 53.63; H, 5.61; N, 12.56.

Phenylhydantoin derivative of thiazolidine-4-carboxylic acid. To 1.33 g. (0.01 mole) of thiazolidine-4-carboxylic acid[11] dissolved in 9.5 ml. of *N* sodium hydroxide solution was added dropwise with stirring 2.98 g. (0.025 mole) of phenyl isocyanate (sufficient *N* sodium hydroxide solution was added simultaneously to maintain an alkaline reaction mixture). The carbanilide which formed was removed by filtration, and the filtrate was acidified with *N* hydrochloric acid to a *p*H of 3. The hydantoin derivative, which crystallized from solution, was obtained in a yield of 430 mg. (18%), m.p. 152–154°. Recrystallization from 2:1 aqueous ethanol gave 300 mg. (13%), m.p. 153.5–154°.

Anal. Calcd. for $C_{11}H_{10}N_2O_2S$: C, 56.39; H, 4.30; S, 13.69. Found: C, 56.13; H, 4.20; S, 13.10.

Phenylthiohydantoin derivative of thiazolidine-4-carboxylic acid. To 1.33 g. (0.010 mole) of thiazolidine-4-carboxylic acid in 9.5 ml. of *N* sodium hydroxide solution was added slowly 1.43 g. (0.011 mole) of phenyl isothiocyanate. It was necessary to shake the reaction mixture for 60 hr. on a mechanical shaker before the reaction appeared complete. Insoluble material was removed by filtration, and the filtrate was acidified with *N* hydrochloric acid to *p*H 2–3. The resulting product was removed by filtration to give 1.73 g. (69% yield), m.p. 190.5–193.5°. Two recrystallizations from ethanol gave 1.08 g. (43%), m.p. 196–197.5°.

Anal. Calcd. for $C_{11}H_{10}N_2OS_2$: C, 52.77; H, 4.03; N, 11.19; S, 25.62. Found: C, 52.83; H, 4.05; N, 11.18; S, 25.45.

A second method, which has been employed by Edman[20] for the preparation of thiohydantoins, gave a better yield. To 1.33 g. (0.01 mole) of thiazolidine-4-carboxylic acid in a solution of 25 ml. of pyridine and 25 ml. of water was added sufficient *N* sodium hydroxide solution to adjust the *p*H to 9. The mixture was warmed to 40°, and 2.86 g. (0.021 mole) of phenyl isothiocyanate was added with stirring over a period of 1.5 hr. The resulting reaction mixture was extracted with eight 25-ml. portions of benzene to remove pyridine and excess phenyl isothiocyanate. The reaction mixture was acidified to a *p*H of 3, and the precipitated product removed by filtration; yield 2.06 g. (90%), m.p. 192.5–194.5°.

2,2-Pentamethylenebenzothiazoline (XII). This substance was obtained by heating under reflux for 1 hr. on a steam bath a mixture of 2.20 g. (0.0175 mole) of *o*-aminobenzenethiol[21] and 1.76 g. (0.018 mole) of cyclohexanone.[10] Upon cooling, the reaction mixture formed a crystalline mass; this was recrystallized from ethanol to give colorless needles; yield 2.77 g. (77%), m.p. 111–112°, lit.[10] m.p. 111–112°.

Phenylurea of XII. Initially, the reaction of 1.03 g. (5 mmoles) of XII in 25 ml. of absolute ether and 740 mg. (6.22 mmoles) of phenyl isocyanate in an equal volume of ether was attempted. Since no reaction seemed apparent because of the lack of the usual precipitate forming immediately in the solution, the ether was removed, and the reactants heated directly. Under these conditions, a crude, crystalline product formed and was recrystallized from ethanol to give 1.14 g. (70% yield) of long needles, m.p. 155.5–156.5°.

Anal. Calcd. for $C_{19}H_{20}N_2OS$: C, 70.34; H, 6.21; N, 8.64. Found: C, 70.23; H, 6.18; N, 8.90.

Attempted phenylthiourea formation from XII. Several different sets of conditions were employed using equivalent amounts of XII and phenyl isothiocyanate. In all of these attempts, reaction failed to take place, as demonstrated by a good recovery of XII: (1) Reactants stirred in ether solution, recovery 74%. (2) Reactants heated under reflux in benzene solution, recovery 65%. (3) Reactants heated on a steam bath without solvent, recovery 93%. (4) Reactants heated on a steam bath without solvent but with 2–3 drops of triethylamine added as catalyst, recovery 84%.

Phenylurea of pyrrolidine. To 1.00 g. (0.014 mole) of pyrrolidine in 50 ml. of absolute ether was added dropwise with stirring 2.08 g. (0.018 mole) of phenyl isocyanate. A colorless, crystalline precipitate formed immediately and was collected by filtration; yield 2.31 g. (85%), m.p. 134.5–135.5°, lit.[22] m.p. 133–134°.

Phenylthiourea of pyrrolidine. From 1.00 g. (0.014 mole) of pyrrolidine in 50 ml. of absolute ether and 2.38 g. (0.018 mole) of phenyl isothiocyanate was obtained an extremely pure product as fine needles (no recrystallization was required); yield 2.76 g. (95%), m.p. 123–124°. The analytical sample was dried *in vacuo* over phosphorus pentoxide for 2 hr. at room temperature.

Anal. Calcd. for $C_{16}H_{14}N_2S$: C, 64.05; H, 6.84; N, 13.58. Found: C, 64.13; H, 6.81; N, 13.50.

(19) Prepared by the method of Ratner and Clarke (ref. 11); the starting material, mercaptoethylamine hydrochloride (96%), was obtained from Evans Chemetics, Inc., 250 E. 43rd St., New York, N. Y.

(20) P. Edman, *Acta Chem. Scand.*, 4, 277 (1950).

(21) American Cyanamid Co., New York, N. Y.

(22) R. A. Henry and W. M. Dehn, *J. Am. Chem. Soc.*, 71, 2297 (1949).

Drying conditions were critical, for if the sample were dried at 95° for 14 hr., the product was converted to a different substance, m.p. 150–151°. This substance was not investigated further.

Anal. Found: C, 64.36; H, 6.95; N, 14.70.

o-Methylthioaniline (XIII). A mixture of 25.0 g. (0.21 mole) of *o*-aminobenzenethiol,[21] 28.4 g. (0.20 mole) of methyl iodide, and 10 g. of sodium hydroxide in 100 ml. of 50% ethanol was heated under reflux with stirring for 45 min. A major part of the ethanol was removed by distillation, and the resulting solution was extracted with ether. The combined ether extracts were washed with several portions of water to remove sodium iodide and then dried over Drierite. After the ether had been removed by distillation, the residual oil was distilled to give 15.7 g. (57% yield) of a light yellow, foul smelling liquid; b.p. 124° (14 mm.), n_D^{25} 1.6220, d_4^{25} 1.115, lit.[23] b.p. 234°. As the original report[23] of this compound did not include an analysis, this was carried out in respect to the present sample.

Anal. Calcd. for C_7H_9NS: C, 60.39; H, 6.52; S, 23.03. Found: C, 60.52; H, 6.38; S, 23.15.

Phenylurea of XIII. From the reaction of 1.39 g. (0.01 mole) of *o*-methylthioaniline with 1.19 g. (0.01 mole) of phenyl isocyanate, by heating the mixture on a steam bath as previously described, was obtained 2.48 g. (86% yield) of a crystalline product, m.p. 126–127°. Recrystallization from ethanol gave fine needles, yield 2.19 g. (85%), m.p. 129–131°. The analytical sample, prepared by a second recrystallization from ethanol, melted at 132.5–134°.

Anal. Calcd. for $C_{14}H_{14}N_2OS$: C, 65.09; H, 5.46; N, 10.85. Found: C, 65.13; H, 5.39; N, 10.82.

Phenylthiourea of XIII. The same procedure was followed as for the phenylurea except that 1.35 g. (0.01 mole) of phenyl isothiocyanate was used; yield 2.44 g. (89%), m.p. 168–169°. Recrystallization from ethanol gave 1.28 g. (47% yield) of fine needles, m.p. 168–168.5°.

Anal. Calcd. for $C_{14}H_{14}N_2S_2$: C, 61.28; H, 5.14; N, 10.21. Found: C, 61.23; H, 5.16; N, 9.98.

Acknowledgments. This investigation was supported by a grant (G1100) from the National Science Foundation. Appreciation is extended to the American Cyanamid Co., 30 Rockefeller Plaza, New York 20, N.Y., for a generous sample of *o*-aminobenzenethiol, which was employed in this work.

PULLMAN, WASH.

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

Benzilic Acid Rearrangement of Carbon-14 Labeled 2-Methylbenzil

JEROME F. EASTHAM, RONALD G. NATIONS, AND CLAIR J. COLLINS

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2-Methylbenzil has been synthesized specifically labeled with carbon-14 in the carbonyl group adjacent to the unsubstituted phenyl ring. Rearrangement of the labeled 2-methylbenzil produces 2-methylbenzilic acid with over 97% of the labeling in the carboxyl group, indicating that in the rearrangement the unsubstituted phenyl group migrates almost exclusively. The relationship of this finding to the mechanism of the benzilic acid rearrangement is briefly discussed.

In connection with another problem[1] it was necessary to prepare 2-methylbenzil. Because of recent interest in the rearrangement of benzils,[2] the 2-methylbenzil prepared was labeled with carbon-14 and its benzilic acid rearrangement was examined.

Labeling of 2-methylbenzil with carbon-14 adjacent to the unsubstituted ring was effected by standard reactions shown in Chart I. The 2-methyldesoxybenzoin (I) intermediate in this preparation had not been previously prepared and was characterized by its reduction to a carbinol and also by its conversion to a 2,4-dinitrophenylhydrazone. The specificity of the labeling of the 2-methylbenzil (II) was checked by addition of phenylmagnesium bromide to this compound

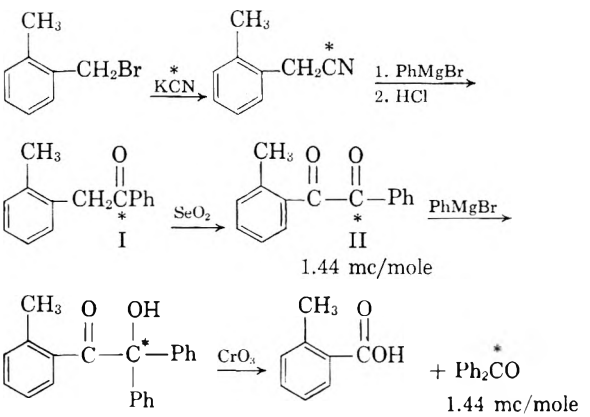


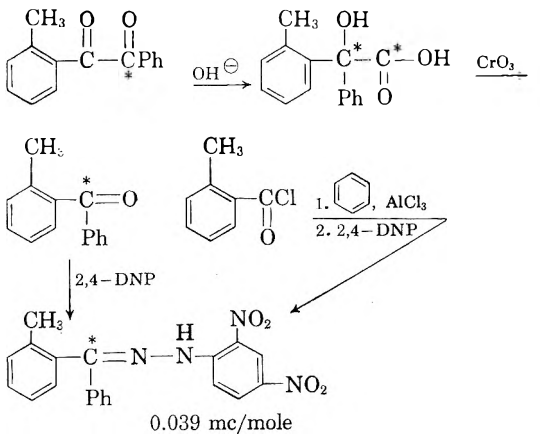
Chart I

followed by oxidation of the resulting α-phenyl-2-methylbenzoin[1] to *o*-toluic acid devoid of radioactivity and benzophenone of the same molar radioactivity as the 2-methylbenzil (II).

Rearrangement of the labeled 2-methylbenzil in the usual manner afforded in good yield 2-methylbenzilic acid (III) of the same molar radioactivity as the benzil (II). The labeled acid (III) was oxidized with chromium trioxide to 2-methyl-

(1) J. F. Eastham, J. E. Huffaker, V. F. Raaen, and C. J. Collins, *J. Am. Chem. Soc.*, 78, 4823 (1956).

(2) (a) W. von E. Doering and R. S. Urban, *J. Am. Chem. Soc.*, 78, 5938 (1956); (b) M. T. Clark, E. C. Hendley, and O. K. Neville, *J. Am. Chem. Soc.*, 77, 3280 (1955); (c) D. B. Ott and G. G. Smith, *J. Am. Chem. Soc.*, 77, 2325, 2342 (1955); (d) J. D. Roberts, D. R. Smith, and C. C. Lee, *J. Am. Chem. Soc.*, 73, 619 (1951); (e) W. von E. Doering, T. I. Taylor, and E. F. Schoenwaldt, *J. Am. Chem. Soc.*, 70, 445 (1948).



IV

Chart II

benzophenone which was converted to a 2,4-dinitrophenylhydrazone (IV) for radioassay. The molar radioactivity of the 2,4-dinitrophenylhydrazone (IV) was just 2.7% of the starting benzil (II). Since IV had not previously been characterized it was also independently synthesized. These reactions are summarized in Chart II.

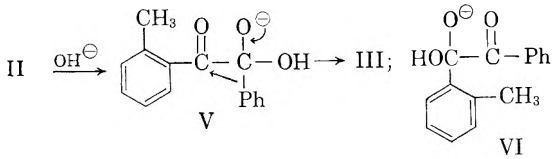
The findings shown in Chart II indicate that in the rearrangement of 2-methylbenzil the phenyl group migrates almost exclusively. In Table I this finding is compared with related results previously reported. In terms of the accepted mechanism for the benzilic acid rearrangement, the present finding shows that V, rather than VI, is the intermediate through which II is rearranged.[3]

TABLE I

MIGRATION IN THE BENZILIC ACID REARRANGEMENT

Compound	Per Cent Migration of Substituted Ring	Migration Ratio of Substituted Ring[a]
4-Methylbenzil	38.8[b]	0.63
2-Methylbenzil	2.7[c]	0.028
4-Chlorobenzil	67.2[b]	2.05
2-Chlorobenzil	31.2[d]	0.46

[a] Ratio of per cent migration of substituted ring to 100 minus this value. The ratios are not corrected for any isotope effect. [b] Ref. 2b. [c] This work. [d] Ref. 2c.

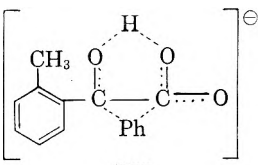


V VI

(3) The first proposal of an intermediate similar to VI for the benzilic acid rearrangement was by A. Michael [*J. Am. Chem. Soc.*, **42**, 815 (1920)]. This concept of the key intermediate in the rearrangement has been investigated and refined[2] until today it is virtually incontrovertible. The last reported work[2a] substantiates this concept by showing rearrangement to be caused also by alkoxide ion (instead of hydroxide ion) in which case the product is the corresponding alkyl ester (instead of an acid).

It is apparent that V should be much more stable than VI. Both by its electron release and by the steric compression it introduces, the *ortho* methyl group should destabilize VI. Destabilization of a similar intermediate by an *ortho* chloro (instead of methyl) group should be much less and it is therefore pertinent that the migration ratio of the substituted ring in 2-chlorobenzil is sixteen times that of the substituted ring in 2-methylbenzil (see Table I). It is also pertinent that the decrease in migration ratio of the substituted ring is much greater in going from 4- to 2-methylbenzil than it is in going from 4- to 2-chlorobenzil. These observations show the primary retarding effect of the *ortho* methyl group to be a steric one.

These observations are best explained with the assumption that the transition state for the benzilic acid rearrangement closely resembles expected intermediates such as V and VI, i.e., that the transition state lies quite close to the intermediate along a reaction coordinate leading from intermediate to product.[4] In other words we reject the proposal by Clark, Hendley, and Neville[2b] of a transition state, such as VII, with elaborately redistributed bonding electons.[5] If a transition state resembling VII were obtained, there could be little



VII

difference between the migration rate of a sterically encumbered group and an unsubstituted group; *o*-tolyl migration toward phenyl would have about the same steric requirements as phenyl migration toward *o*-tolyl.

EXPERIMENTAL[6]

2-Methylbenzyl cyanide-C^{14}. To a stirred solution of 55.5 g. of 2-methylbenzyl bromide in 200 ml. of absolute alcohol was added in one portion 22 g. of potassium cyanide (*ca.* 1.5 mc./mole) in 50 ml. of water. The reaction mixture refluxed spontaneously for a few minutes, was refluxed for 90 min., and was then allowed to stand at room temperature overnight. After the reaction mixture was treated with Norit-A and filtered through a pad of Fisher alumina, all of the alcohol was distilled at reduced pressure. The aqueous mixture remaining was extracted with ether which was in turn washed, dried, and evaporated. The residue was dis-

(4) For a discussion of the possible relationship between transition states and known intermediates in a reaction see G. S. Hammond, *J. Am. Chem. Soc.*, **77**, 334 (1955).

(5) For other reasons other authors[2a] have criticized the proposal of Clark, Hendley, and Neville. It is important to note however that the latter stressed the tentative, speculative nature of their proposal.

(6) Melting points and boiling points are uncorrected. Microanalyses were performed by Weiler and Strauss, Oxford, England. Radioassays were performed by combusting samples to CO_2 and counting this in an ionization chamber with a vibrating reed electrometer.

tilled to yield 26 g. of 2-methylbenzyl cyanide-C^{14}, b.p. 95–96°/1 mm. (lit.[7] 115–120°/10 mm.).

2-Methyldesoxybenzoin (I). To the Grignard reagent prepared from 49 g. of bromobenzene and 7.6 g. of magnesium in 200 ml. of ether, there was added 20.5 g. of the above *o*-tolyl cyanide-C^{14} in 80 ml. of ether. The addition took about 20 min. during which time the stirred reaction solution refluxed spontaneously. The reaction solution was refluxed for 3 hr. and then poured onto a stirred mixture of 300 g. of ice and 150 ml. of concentrated hydrochloric acid. The aqueous layer was separated quickly and allowed to stand at room temperature overnight. This aqueous mixture was then extracted with ether which was in turn washed, dried, and evaporated to leave 11.6 g. of a crystalline residue, m.p. 60–65°, which could be used for oxidation to 2-methylbenzil (see below) without further purification. Purification of the crude desoxybenzoin was attempted by distillation (b.p. 170–175°/8 mm.), crystallization, and sublimation. The latter process gave material with a sharp m.p., 65.5–66°, but this material did not give the proper elemental analysis for 2-methyldesoxybenzoin. For characterization the compound was reduced to 2-methylbenzylphenylcarbinol (see below) and converted to a 2,3-dinitrophenylhydrazone.

To a solution of 47 mg. of 2,4-dinitrophenylhydrazine in 0.25 ml. of concentrated sulfuric acid there was added a solution of 50 mg. of the 2-methyldesoxybenzoin (m.p. 65–66°) in 2 ml. of 95% alcohol. The mixture was refluxed 10 min., cooled, and the red needles which appeared collected. Recrystallization of this product from alcohol then from chloroform gave 57 mg. of *2-methyldesoxybenzoin 2,4-dinitrophenylhydrazone*, m.p. 182–183°.

Anal. Calcd. for $C_{22}H_{18}N_4O_4$: C, 64.60; H, 4.65; N, 14.35. Found: C, 64.54; H, 4.76; N, 14.30.

2-Methylbenzylphenylcarbinol. A solution of 40 mg. of lithium aluminum hydride and 210 mg. of 2-methyldesoxybenzoin (m.p. 65–66°) in 20 ml. of ether was refluxed for 10 min. Work up in the usual manner gave an oil which crystallized from ligroin as 2-methylbenzylphenylcarbinol, m.p. 29–30°.

Anal. Calcd. for $C_{15}H_{16}O$: C, 84.87; H, 7.60. Found: C, 84.67; H, 7.81.

2-Methylbenzil-C^{14} (II). A solution of 6 g. of crude 2-methyldesoxybenzoin-C^{14} (m.p. 60–65°), 3.2 g. of selenium dioxide, and 0.5 ml. of water in 20 ml. of dioxane was refluxed for 12 hr. The reaction mixture was filtered and the solvent was distilled. The residue was leached with ether and the resulting ethereal solution was washed, dried, and evaporated to an oil which was distilled; the fraction collected 175–185°/3 mm., 4.2 g., crystallized spontaneously. Recrystallization gave pure 2-methylbenzil, m.p. 57–57.5° (lit.[8] 57–58°), 1.442 ± 0.001 mc./mole.

α-Phenyl-2-methylbenzoin-C^{14}. A Grignard reaction between the above-labeled benzil and phenylmagnesium bromide was carried out exactly as described[1] for the unlabeled benzil. There was produced carbinol-labeled α-phenyl-2-methylbenzoin-C^{14}, m.p. 116–117°, 1.442 ± 0.003 mc./mole. Oxidation of a sample of the carbinol-labeled benzoin was carried out with chromium trioxide, again exactly as described[1] for the unlabeled benzoin. There was produced *o*-toluic acid, m.p. 104–105°, which was devoid of radioactivity, and benzophenone which was characterized as its 2,4-dinitrophenylhydrazone, m.p. 238–239°, 1.441 ± 0.002 mc./mole.

2-Methylbenzilic acid-C^{14} (III). A solution containing 130 mg. of 2-methylbenzil, 550 mg. of potassium hydroxide, 1 ml. of alcohol, and 1.5 ml. of water was heated for 10 min. on the steam cone. The solution was cooled, diluted with water, and extracted with ether. There was recovered 29 mg. of 2-methylbenzil from this ether extraction of the reaction mixture. The aqueous layer was acidified and extracted with ether. This ether extract was dried and evaporated and the residue recrystallized to give 105 mg. (96% based on unrecovered starting material) of 2-methylbenzilic acid C^{14}, m.p. 113.5–114.5° (lit.[9] 114.5°), 1.443 ± 0.001 mc./mole.

Degradation of 2-methylbenzilic acid-C^{14}. A solution of 99 mg. of 2-methylbenzilic acid and 31 mg. of chromium trioxide in 1 ml. of glacial acetic acid was heated on the steam cone for 30 min. with occasional swirling. Two milliliters of water were added and the solution was extracted with ether. The ether solution was extracted with saturated sodium bicarbonate solution and with water, dried and evaporated to give 74 mg. of a light yellow oil. A solution of this oil and 74 mg. of 2,4-dinitrophenylhydrazine in 1 ml. of concentrated sulfuric acid and 0.25 ml. of ethanol was heated for about 30 sec. on the steam cone, then the total volume was increased to 5 ml. by the addition of 95% ethanol. This solution was refluxed for 20 min., during which time red crystals began to appear. The mixture was cooled and centrifuged and the liquid decanted. The red crystals were washed with water and recrystallized five times from a mixture of equal portions by volume of chloroform and alcohol. There was obtained 86 mg. of 2-methylbenzophenone 2,4-dinitrophenylhydrazone, m.p. 176–178° (undepressed by authentic material prepared as described below), 0.039 ± 0.001 mc./mole.

2-Methylbenzophenone 2,4-dinitrophenylhydrazone (IV). A mixture of 20 g. of 2-methylbenzoyl chloride, 20 g. of anhydrous aluminum chloride, and 50 ml. of dry benzene was refluxed for 1 hr. The excess benzene was removed by distillation and the residue was distributed between water and ether. The ether layer was washed with aqueous hydrochloric acid, aqueous sodium carbonate and water, dried, filtered and the ether distilled. The residue was distilled; the fraction distilling at 121.5–122.5°/1.25 mm. amounted to 14 g. of crude 2-methylbenzophenone as a light yellow oil. A sample of this oil was treated with 2,4-dinitrophenylhydrazine in ethanolic sulfuric acid in the usual manner. 2-Methylbenzophenone 2,4-dinitrophenylhydrazone was obtained as red needles, m.p. 176–178°.

Anal. Calcd. for $C_{20}H_{16}N_4O_4$: C, 63.85; H, 4.25; N, 15.42. Found: C, 64.15; H, 4.38; N, 14.84.

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(7) P. Hill and W. F. Short, *J. Chem. Soc.*, 1123 (1935).

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(9) K. Mislow and M. Siegel, *J. Am. Chem. Soc.*, **74**, 1060 (1952).

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

Cyclic Sulfides. III. The Reaction of Some Ethylene Sulfides with Triphenylphosphine and with Triethyl Phosphite

ROBERT EARL DAVIS[1,2]

Received April 25, 1958

The products of the reaction of two ethylene sulfides with triphenylphosphine and with triethyl phosphite in ether have been examined. The most favored reaction is the elimination of the sulfur atom of the three membered ring and formation of the olefin, the sulfur being donated to the $P^{(III)}$ compound forming the thiono $P^{(V)}$ derivative.

Various ethylene sulfides were reported to react with triphenyl- and triethyl-phosphine to give the corresponding phosphine sulfide and with triethyl phosphite to produce the thionophosphate;[3] however, the remainder of the ethylene sulfide ring was not determined. The other products of this reaction are the subject of this report. Triphenylphosphine appears to be a mild and selective reagent for degradation of various types of sulfur compounds.

EXPERIMENTAL[4]

The preparation and purification of the ethylene sulfides have been reported previously.[1]

Cyclohexene sulfide with triphenyl phosphine. Freshly distilled cyclohexene sulfide (5.493 g., 0.0481 mole) was dissolved in 10 ml. of anhydrous ether and cooled in an ice bath. Triphenylphosphine (12.613 g., 0.0481 mole) was dissolved in ether and the solution quantitatively added to the sulfide solution (total volume 80 ml.). The flask was tightly stoppered and placed in a water bath at 25.0° in the dark. The solution soon became turbid and platelets separated. After three days at 25.0° the mixture was filtered giving 10.15 g. of white platelets, m.p. 159–161°, recrystallized from alcohol, m.p. 160.5–161°. The infrared spectrum, melting point and mixed melting point with an authentic sample identified the material as triphenylphosphine sulfide.[5]

The ether liquor was quantitatively transferred onto a vacuum line with the aid of a known amount of ether. The solution was frozen and then the volatile components removed and condensed in traps. The residue amounted to 3.402 g., m.p. 145–159°. Infrared analysis demonstrated the presence of some unreacted triphenyl phosphine (2 ± 1% based on the over-all reaction) and some of the polymer of cyclohexene sulfide (1 ± 0.5%). The remainder was the phosphine sulfide, from alcohol, m.p. 160–161°. The total amount of phosphine sulfide accounted for was 96 ± 2%.

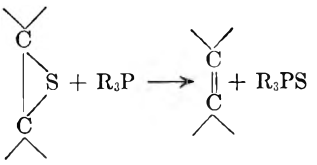
The volatile components collected in the traps were analyzed by infrared spectra and vapor-phase chromatography, which demonstrated the presence of 3.90 g., 95%, of cyclohexene, b.p. 83°, n_D^{25} 1.4441, identical with an authentic sample. Ultraviolet spectra[1] disclosed 0.5% of unreacted cyclohexene sulfide.

Cyclohexene sulfide with triethyl phosphite. Cyclohexene sulfide (3.99 g., 0.035 mole) and triethyl phosphite (5.81 g.) were reacted together in 50 ml. of anhydrous ether at 25° for three days. The turbid reaction mixture was fractionally distilled. The solvent was removed at 35–36°; cyclohexene was recovered at 83°, 2.63 g., 91%; traces of triethyl phosphite, b.p. 155° were obtained. The remainder was distilled in vacuum and triethyl thionophosphate obtained, b.p. 102–103° at 20 mm., 6.01 g., 87%. The products were identified by comparison of the physical properties and infrared spectra with authentic samples. The pot residue and chaser contained at least 5% of the polymer of cyclohexene sulfide.

Propylene sulfide with triphenyl phosphine. Propylene sulfide (2.84 g.) was dissolved in 25 ml. of anhydrous ether and quantitatively added to an ether solution of triphenyl phosphine (10.00 g. in 100 ml. ether) at room temperature. The flask was connected to an ice condenser, an ice trap, and then to a Dry Ice–acetone trap. As the reaction progressed some propylene (b.p., −48°) collected in the Dry Ice trap. The infrared spectrum was identical with an authentic sample. From the ether solution triphenylphosphine sulfide (10.5 g., 94%, m.p. 160–162°) was isolated.

DISCUSSION

The most favored reaction between ethylene sulfides and triphenylphosphine or triethyl phosphite is the removal of the sulfur atom forming the corresponding olefin and the thion phosphorus-V derivative.



The amount of polymer formation seems to be slight if the solvent is anhydrous and has low ability to solvate ions. Reactions of the ethylene sulfides in alcoholic solvents[3] sometimes lead to more polymer formation; possibly the solvent lyate ion contributes to this reaction. Polymer formation increases with increasing temperature.[3]

Other examples are available of the ability of many trivalent phosphorus compounds to remove sulfur from various sulfur compounds. Alkane thiols are desulfurized with triethyl phosphite under irradiation to form the thionophosphate and the alkane.[6,7] Certain reactive disulfides as tetramethylthiuram disulfide and aroyl disulfides readily donate

(1) Paper II, R. E. Davis, *J. Org. Chem.*, 23, 1380 (1958).

(2) National Science Foundation predoctoral fellow, 1955–1957.

(3) C. C. J. Culvenor, W. Davies, and N. S. Heath, *J. Chem. Soc.*, 282 (1949).

(4) All temperatures are corrected.

(5) P. D. Bartlett and G. Meguerian, *J. Am. Chem. Soc.*, 78, 3710 (1956).

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(7) C. Walling and R. Rabinowitz, *J. Am. Chem. Soc.*, 79, 5326 (1957).

one sulfide sulfur to triphenylphosphine forming the phosphine sulfide.[8,9] Other disulfides are reactive under conditions of photolysis or free radicals.[7]

Recently Scott[10] has observed the reaction of triethyl phosphite with epoxides forming the corresponding olefin and triethyl phosphate. The reaction conditions were much more severe (three hours at 150–175°) than those needed for the sulfur compounds (one to three days at 25°). Scott suggested a mechanism involving ring opening by the phosphite at the carbon atom and then formation of a four membered 1-oxa-2-phosphacyclobutane ring which then decomposes to the phosphate and the olefin. Wittig[11] studied the reaction of triphenylphosphine with epoxides at 160–180°. A four center transition state was postulated and the relationship to the Wittig reaction is obvious. Discussions concerning the reaction mechanism are speculative.

Phosphines and phosphites appear to be well suited as reagents in the structure determination of various sulfur compounds. The conditions are mild; polysulfides, disulfides, thiiranes, thiols, and other functional groups can be easily degraded. Investigation of other functional groups containing sulfur is continuing with phosphorus-III compounds.

CAMBRIDGE 38, MASS.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY, KALAMAZOO, MICHIGAN]

Carbonic Anhydrase Inhibitors. I. Benzothiazole Derivatives

JEROME KORMAN

Received May 21, 1958

A number of aryl-substituted benzothiazole-2-sulfonamides have been prepared, all of which are potent carbonic anhydrase inhibitors. One of these, the 6-ethoxybenzothiazole-2-sulfonamide, produces a clinically useful diuresis.

Carbonic anhydrase inhibitors have become important drugs for the treatment of conditions which are evidenced by edema.[1] The more important substances are diuretics, which produce a beneficial loss of sodium and water with concurrent body weight loss, and are characterized by a sulfonamide group in which the sulfonamide nitrogen is unsubstituted.[2] Research in this field was prompted by the experiments of Schwartz[3] with sulfanilamide in cases of congestive heart failure. Although diuresis occurred, low potency and the recognized toxic effects of sulfanilamide rendered it valueless for this purpose.

In the search for a more active replacement, Roblin and Clapp[4] prepared a large number of heterocyclic sulfonamides, many of which were indeed powerful carbonic anhydrase inhibitors. Among these, benzothiazole-2-sulfonamide, which appeared to be one of the most potent enzyme inhibitors, was subsequently reported[5] to be devoid of diuretic activity, a fact which was confirmed in these laboratories. This apparent anomaly can be reasonably explained on the basis of insolubility or an unfavorable rate of metabolism. Since diuretic activity in these compounds had been attributed to carbonic anhydrase inhibition,[3] it seemed of interest to prepare a series of substituted benzothiazole-2-sulfonamides and determine, firstly, the effect of the substituent and its position on carbonic anhydrase activity and, secondly, what effects, if any, these substituents might have upon such factors as solubility and metabolism.

Prior to the report of Roblin and Clapp, very few heterocyclic sulfonamides had been prepared. Chlorosulfonation, which works admirably with aromatic compounds to produce a sulfonyl chloride, fails generally with heterocyclic systems. Although a few such reactions have been reported,[6,7] the yields are poor, and the usual product is one in which nuclear chlorination has taken place. Similarly the reaction involving conversion of the salt of a sulfonic acid into the acid chloride results either in chlorination or replacement of the sulfonic acid

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(2) T. Mann and D. Keilin, *Nature*, **146**, 134 (1940), H. A. Krebs, *Biochem. J.*, **43**, 525 (1948).

(3) W. B. Schwartz, *New Engl. J. Med.*, **240**, 173 (1949).

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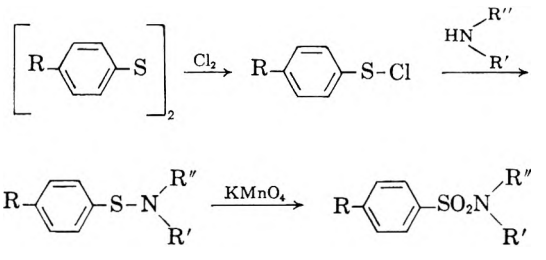
group by chlorine.[8-10] The oxidative chlorination of heterocyclic mercaptans to give the sulfonyl chloride, which was used so successfully in previous studies for the preparation of benzothiazole-2-sulfonamide, we found to be unsatisfactory with other members of this series. One experiment with 6-ethoxy-2-mercaptobenzothiazole gave a very low yield of impure sulfonamide, and another method was sought.

Among the processes reported for the preparation of N^1-substituted sulfanilamides is one involving an intermediate aryl sulfenamide, which is oxidized to a sulfonamide.[11] The sulfenamide was prepared from the sulfenyl chloride by treatment with the appropriate amine according to the scheme:



R = NO_2, CH_3CONH

This same procedure was found applicable to the preparation of benzothiazole-2-sulfenyl chloride[12] and benzothiazole-2-sulfenamides, references to which appear in the patent literature.[13] These latter compounds have found wide application as accelerators in the rubber processing industry. Alternate methods for the direct preparation of sulfenamides have also been described.[14] In these cases the sodium salt of a mercaptan is treated with a solution of chloramine, as such, or which is prepared *in situ*. Since we had found by experience that chlorine was an unsatisfactory reagent, we used the last method for the preparation of our sulfenamides. The scope of the reaction has been thoroughly covered in an excellent article by Carr, Smith, and Alliger.[15] Various substituted 2-mercaptobenzothiazoles in aqueous solution as the sodium salt were added simultaneously with a solution of sodium hydrochlorite to concentrated ammonium hydroxide. The resulting sulfenamides were oxidized to the sulfonamides with potassium permanganate in aqueous acetone solution (Table I):[16]

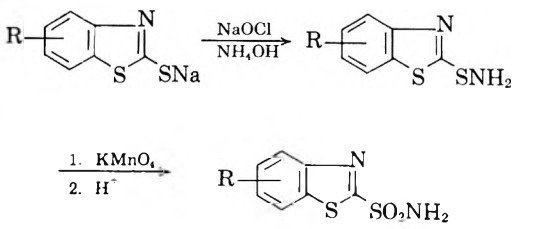


TABLE I

	Compound	M.p.	Analysis N Calcd.	N Found	S Calcd.	S Found
1.	Benzothiazole-2-sulfonamide	175.5–176°	[a]	[a]	[a]	[a]
2.	4-Methylbenzothiazole-2-sulfonamide[b]	182.5–184.5°	12.27	12.50	28.09	27.88
3.	6-Methylbenzothiazole-2-sulfonamide[b]	196–198.5°	12.27	12.64	28.09	28.13
4.	5-Chlorobenzothiazole-2-sulfonamide[c]	205.5–208°	11.27	11.94	25.78	25.68
5.	4-Methoxybenzothiazole-2-sulfonamide[d]	195–199°	11.47	11.70	26.26	26.52
6.	6-Ethoxybenzothiazole-2-sulfonamide[e]	188–190.5°	10.85	10.72	24.82	24.74
7.	6-Acetamidobenzothiazole-2-sulfonamide	233–235°	15.49	15.58	23.63	23.51

[a] Identical with that prepared by the method of Roblin and Clapp (*cf.* ref. 4). [b] The starting mercaptan was prepared by the method of L. B. Sebrell and C. E. Boord, *J. Am. Chem. Soc.*, **45**, 2390 (1923). [c] The starting mercaptan was prepared by the method of J. Teppema and L. B. Sebrell, *J. Am. Chem. Soc.*, **49**, 1748 (1927). [d] The starting mercaptan was prepared by a modification of the method of H. Erlenmeyer, H. Ueberwasser, and H. M. Weber, *Helv. Chim. Acta*, **21**, 709 (1938). [e] The starting mercaptan was obtained from duPont. It was purified by precipitation from a solution of the sodium salt with excess acid followed by recrystallization from 95% ethyl alcohol.

When one considers the number of reactions which may occur in a mixture of mercaptan, hypochlorite, and ammonium hydroxide, it is surpris-

(8) C. M. Suter, *The Organic Chemistry of Sulfur*, John Wiley and Sons, Inc., New York, N. Y., 1944, pp. 459, 500.

(9) R. Forsyth, J. A. Moore, and F. L. Pyman, *J. Chem. Soc.*, 919 (1924); G. R. Barnes and F. L. Pyman, *J. Chem. Soc.*, 2711 (1927).

(10) S. B. Greenbaum, *J. Am. Chem. Soc.*, **76**, 6052 (1954).

(11) E. H. Northey, *The Sulfonamides and Related Compounds*, Reinhold Publishing Corp., New York, N. Y., 1948, pp. 258, 309, and 310.

(12) W. E. Messer, U. S. Patent **2,257,974** (1941).

(13) W. H. Ebelke, U. S. Patents **2,343,538** (1944) and **2,351,496** (1944).

(14) Ger. Patent **586,351** (1933); R. S. Hanslick, U. S. Patent **2,304,568** (1942); R. H. Cooper, U. S. Patent (1944); **2,339,002** G. E. P. Smith, Jr., U. S. Patent **2,560,021** (1951).

(15) E. L. Carr, G. E. P. Smith, Jr., and G. Alliger, *J. Org. Chem.*, **14**, 921 (1949).

(16) Shortly after the culmination of our work the preparation of 6-Uracilsulfonamide by this procedure was reported (*cf.* ref. 10).

ing that any of the desired product can be isolated. For example, hypochlorite and ammonia may react in the following ways:[17]

(a) $NH_3 + NaOCl \longrightarrow NH_2Cl + NaOH$

(b) $2NH_3 + 3NaOCl \longrightarrow N_2 + 3H_2O + 3NaCl$

Any free chlorine in the hypochlorite may also react with excess ammonia to produce nitrogen and ammonium chloride.[17] Reaction (b) is an accepted analytical method for the quantitative determination of ammonia. In addition the hypochlorite may react with the mercaptan to produce a disulfide or the salt of a sulfonic acid:[15]

(c) $2RSNa \longrightarrow RSSR$

(d) $RSNa \longrightarrow RSO_3Na$

Despite the fact that some of these side reactions are most certainly taking place, we have been able to prepare sulfenamides of high purity in satisfactory yields. Although they appear to be stable when dry and free from alkali, it has been found advantageous to convert the crude material directly into the sulfonamide without further treatment.

The real simplicity of the process lies in the fact that the course of both oxidative steps may be followed potentiometrically. In later experiments the end-point of sulfenamide formation was determined with an antimony *vs.* standard calomel electrode system,[18] and the permanganate oxidation with a platinum *vs.* calomel system. Excellent results were obtained with a Beckman "Model G" *p*H Meter which reads in millivolts. Since the potentiometer indicates the presence of excess oxidizing agents, exact concentrations of solutions are relatively unimportant. This is a decided advantage when one works with commercial sodium hypochlorite solution, the concentration of which varies from about 9 to 16 per cent during shipment and storage.

The crude sulfonamides were usually purified by recrystallization from a suitable solvent. In some cases, however, the product was always contaminated with a second substance which could best be separated by chromatography. This was subsequently shown by its infrared absorption spectrum and elementary analysis to be an aryl substituted 2-hydroxy-benzothiazole (I), which displayed a keto-enol system: The formation of this impurity

appeared to be dependent both upon the type of aryl substituent and its position. Generally the stronger electron donating groups stabilized the sulfonamide, whereas an increased amount of cleavage was observed with the weaker donors. The substituent at position 6 tended to impart greater stability than did that in position 4 or 5. Electron attracting groups, on the other hand, contributed to extensive decomposition. For example, 6-nitrobenzothiazole-2-sulfonamide was not isolated by this procedure. The only product obtained was 2-hydroxy-6-nitrobenzothiazole. The order of stability in the series under discussion, then, appeared to be as follows: H > C_2H_5O > CH_3CONH > CH_3 > Cl > NO_2.

The acid-catalyzed nucleophilic displacement of 6-uracilsulfonic acid to give barbituric acid was recently reported by Greenbaum and Holmes.[19] Similarly Roblin and Clapp[4] described the cleavage of a number of their heterocyclic sulfonamides including benzothiazole-2-sulfonamide, which took place upon warming with 6*N* hydrochloric acid. The products obtained were the hydroxy compounds. Except for the acidification of the final solution of the potassium salt of the sulfonamide, the conditions for our procedure dictate basic solutions. We believe that a base-catalyzed nucleophilic displacement of the sulfonamide group adequately accounts for the observed results. In those cases where hydrolysis occurred a noticeable odor of sulfur dioxide was detected when the final solution was acidified. It does not seem reasonable to expect the cleavage to be instantaneous, and we conclude that the by-product is formed during the permanganate oxidation, when the *p*H increases to approximately 10.

Biological activity. (Table II). All of the compounds prepared were found to be potent carbonic anhydrase inhibitors when tested by the method of Philpot and Philpot.[20] Of the three compounds which possessed significant diuretic activity in the rat,[21] the most potent, 6-ethoxybenzothiazole-2-sulfonamide (Cardrase),[22] has received extensive clinical study in cases of congestive heart failure and glaucoma.[23] Published clinical studies showed this compound to possess two to four times the diuretic activity of 2-acetamido-1,3-4-thiadiazole-5-sulfonamide (Diamox)[24] on a milligram basis. Pharmacological activities are shown in Table II. More complete pharmacological data will be published elsewhere.

(17) C. A. Jacobson, *Encyclopedia of Chemical Reactions*, Reinhold Publishing Corp., New York, N. Y., 1955, pp. 143, 144.

(18) P. T. Paul and B. D. Hunter, U. S. Pat. 2,419,283 (1947).

(19) S. B. Greenbaum and W. L. Holmes, *J. Am. Chem. Soc.*, 76, 2899 (1954).

(20) F. J. Philpot and J. S. L. Philpot, *Biochem. J.*, **30**, 2191 (1936).

(21) The assay method is a modification of the procedure of W. L. Lipschitz, Z. Hadidian, and A. Kerpcsar, *J. Pharmacol. and Exptl. Therap.*, 79, 97 (1943).

(22) CARDRASE is the Upjohn trademark for ethoxyolamide.

(23) (a) J. Moyer, S. Kinard, and R. Serscherger, *Antibiotic Med. & Clin. Therapy*, 3, 179 (1956). (b) H. Gold, T. H. Greiner, L. Warshaw, N. T. Kwit, and A. Ganz, *J. Am. Med. Assoc.*, 167, 814 (1958).

(24) DIAMOX is the trademark for acetazolamide.

TABLE II

Compound	Carbonic Anhydrase Inhibition[a]	Diuretic Activity[b]
1	3.2×10^{-6}	Inactive
2	6.5×10^{-8}	Inactive
3	2.8×10^{-8}	Active
4	4.8×10^{-8}	Inactive
5	1.04×10^{-7}	Inactive
6	2.7×10^{-8}	Active
7	7.3×10^{-8}	Active

[a] The concentration required to produce 50% inhibition. [b] Indicates at least a 25% increased urine excretion in rats in excess of the controls, at doses of 5, 10, and 20 mg./kg.

EXPERIMENTAL[25]

The procedure used was essentially the same in all cases and is illustrated by the preparation of 6-ethoxybenzothiazole-2-sulfonamide. The apparatus consisted of a small battery jar fitted with a clear plastic (Lucite) cover. Holes were drilled in the cover to accommodate a stirrer, thermometer, two dropping funnels, and the two electrodes (calomel and either antimony or platinum). An additional small opening served as a vent. The same container was used for both reactions.

A. *6-Ethoxybenzothiazole-2-sulfenamide.* A solution of 21 g. (0.1 mole) of 6-ethoxy-2-mercaptobenzothiazole and 4 g. of sodium hydroxide in 75 ml. of water, and a solution of sodium hypochlorite (approximately 10%) were added dropwise simultaneously to 300 ml. of concentrated ammonium hydroxide which was cooled to 7–10° and vigorously stirred. The initial reading of the potentiometer was −530 mv; the final reading, indicating a slight excess of hypochlorite, was −430 mv. The material, which began to precipitate almost immediately, was filtered and thoroughly washed with ice water to remove ammonia.

B. *6-Ethoxybenzothiazole-2-sulfonamide.* The crude, damp sulfenamide was suspended in 250 ml. of acetone and 450 ml. of water. With stirring there was added 440 ml. of 5% potassium permanganate solution at such a rate that the temperature was maintained at about 35° and the potentiometer showed no great excess of oxidizing agent at any time. The initial reading was usually less that +50 mv; the final potential was +440 mv. The mixture was filtered from the precipitated manganese dioxide, and the latter washed with 100 ml. of 5% sodium hydroxide solution and then with 200 ml. of water. The combined filtrates were concentrated under reduced pressure at 40° to remove most of the acetone. Acidification with concentrated hydrochloric acid gave the sulfonamide as a light tan solid. There was obtained 17.6 g. of material which melted at 175–188°. Recrystallization from ethyl acetate–petroleum ether gave 12.3 g. of colorless product, m.p. 188–190.5°.

When it was necessary to separate the sulfonamide from the 2-hydroxybenzothiazole, the crude mixture was dissolved in methylene chloride and chromatographed over Florisil (80 g. of adsorbent for each gram of material). Elution with 5% acetone in Skellysolve B gave the cleavage product. The sulfonamide could be recovered with 20% acetone in Skellysolve B. The compounds which were identified are: (a) 5-Chloro-2-hydroxybenzothiazole, m.p. 235–237°. *Anal.* Calcd. for C_7H_4ClNOS: N, 7.55; S, 17.27; Cl, 19.10. Found: N, 7.88; S, 17.36; Cl, 19.24.

(b) 6-Nitro-2-hydroxybenzothiazole, m.p. 252–256°. *Anal.* Calcd. for $C_7H_4N_2O_3S$: N, 14.28; S, 16.34. Found: N, 14.44; S, 16.88.

Acknowledgment. We wish to acknowledge the encouragement and support given by Dr. Robert H. Levin and Dr. Richard V. Heinzelman. The determinations of carbonic anhydrase inhibition were made by Dr. Margaret Greig and Miss Anna Gibbons. The diuretic and electrolyte studies were performed by Mr. Boyd E. Graham and associates. Microanalyses were prepared by Mr. William A. Struck and members of the Analytical Section of the Upjohn Company.

KALAMAZOO, MICH.

(25) Melting points are uncorrected.

Notes

A department for short papers of immediate interest.

Preparation and Properties of Tertiary Alkyl Formates

DAVID W. YOUNG AND EILEEN M. PARÉ

Received January 2, 1958

Although Cottle[1] has reported the use of ion exchange resins as catalysts in the preparation of alkyl esters, he utilized special dry resins and limited his work to the acetate esters. In this work tertiary alkyl esters of formic acid have been prepared using ion exchange resins containing as much as 53% moisture.

Five tertiary alkyl formates were prepared by Barkenbus.[2] He made *tert*-butyl formate by the reaction of aluminum *tert*-butoxide with *n*-butyl formate and also, using sulfuric acid as the catalyst in the reaction of formic acid with isobutylene. The use of sulfuric acid as a catalyst in the addition of acids other than formic to alkenes has been reported.[3–5]

Earlier workers[6,7] have prepared tertiary alkyl formates but their yields have been poor and the esters impure.

The cationic exchange resins tested in this study were of the polystyrene divinylbenzene sulfonic acid type, the most effective resin being Dowex 50-X8 (200–400 mesh). Reactions were run using the resin as obtained from the supplier, that is, "wet" containing as much as 53% moisture. Other reactions were run using resins which had been dried at 100° for 24 hr. In addition both types of resin were reused several times without losing their effectiveness. The best yields of the ester were obtained when between 1–1.5% wet catalyst (based on the weight of formic acid) was used at a reaction temperature below 65°. Below this catalyst concentration the reaction rate was too slow to be efficient while above this concentration and temperature the formation of polymer by-product became appreciable.

It is of interest to note that no reaction took place when diisobutylene was treated with formic acid in the presence of Dowex 50-X8. This would seem to indicate that, although diisobutylene type material is a by-product in the formation of *tert*-butyl formate, the ion exchange resin is not a catalyst for the addition of acids to the higher polymers of isobutylene.

EXPERIMENTAL

tert-Butyl formate. A typical preparation is given. Formic acid (208 g., 4.5 moles) and "wet" Dowex 50-X8, 200–400 mesh (2.5 g., 1.2% by weight of formic acid) were placed in a gas washing bottle and isobutylene gas was bubbled through the system at the approximate rate of one mole per hour. After 4 hr. the gas flow was discontinued and the resin filtered off. The reaction mixture was washed with eight portions of ice water and then dried over anhydrous magnesium sulfate. Vacuum distillation of the product gave *tert*-butyl formate (43.6% yield): b.p. 83°/760 mm., n_D^{25} 1.3790, d_4^{25} 0.8717 (reported,[2] n_D^{25} 1.3783, d_4^{25} 0.8718, b.p. 82.8/760 mm.).

Anal. Calcd. for $C_5H_{10}O_2$: C, 58.9; H, 9.8. Found: C, 59.2; H, 9.7.

tert-Amyl formate. Anhydrous formic acid (50 g., 1.09 moles) and 2 methyl butene-2 (72 g., 1.03 moles) were agitated occasionally for two days at room temperature in a 4-oz. glass stoppered bottle using "wet" Dowex 50-X8, 200–400 mesh (0.3 g., 0.6% by weight of formic acid) as the catalyst. The resin was filtered off and the filtrate was washed six times with ice water. After drying over anhydrous magnesium sulfate the sample was distilled. There were obtained 2-methyl-2-butene boiling at 41° and *tert*-amyl formate (23.8%) b.p. 112.1°, n_D^{25} 1.3952, d_4^{25} 0.8821 (reported[2] n_D^{25} 1.3951, d_4^{25} 0.8853, b.p. 112.9°).

Anal. Calcd. for $C_6H_{12}O_2$: C, 62.0; H, 10.7. Found: C, 62.1; H, 10.4.

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(1) D. Cottle, U. S. Patent 2,678,332 (1954).
(2) C. Barkenbus, M. Naff, and K. Rapp, *J. Org. Chem.*, 19, 1316 (1954).
(3) G. Timofejev and L. Andreasov, *Chem. Zentr.*, 96, (II), 1652 (1925).
(4) W. Scovill, R. E. Burk, and H. Lankelma, *J. Am. Chem. Soc.*, 66, 1039 (1944).
(5) R. Altschul, *J. Am. Chem. Soc.*, 68, 2605 (1946).
(6) W. Taylor, *J. Chem. Soc.*, 1852 (1937).
(7) E. Sucharda and T. Mazonski, *Brit. Chem. Abstracts*, B 497 (1933).

Reduction of Fluorenonecarboxylic Acids to Fluorenecarboxylic Acids[1]

D. C. MORRISON

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Many of the syntheses in the fluorene series are rendered difficult by the inaccessibility of the fluorenecarboxylic acids. The reduction of the fluorenonecarboxylic acids to the corresponding fluorene acids is the step which seems to give the poorest yields. Several processes have been described for this reduction but the Clemmensen and

(1) The work described in this paper was carried out under a research grant (No. C-327 and CY-2915) to Prof. D. M. Greenberg, from the National Cancer Institute, United States Public Health Service.

Wolff-Kishner methods have been used most often. Thus, Gutmann and Albrecht[2] described a modified Clemmensen reduction of fluorenone-1-carboxylic acid during 40 hours reflux, and British workers[3,4] have used a shorter heating period. Sawicki and Chastain[5] report unsatisfactory yields or mixtures resulted from three different procedures for reduction of the fluorenone-1 acid.

Schiessler and Eldred[6] obtained 43% of fluorene-2-carboxylic acid by a Wolff-Kishner type reduction of fluorenone-2-carboxylic acid. It has also been prepared by a Grignard carbonation in 20% yield,[7] and by a 2-step processs, the last step of which involves iodine and phosphorus reduction.[6,8]

The method of Suzuki[9] was tried in the present work, employing some variations. This worker reduced fluorenone-4-carboxylic acid to fluorene-4-carboxylic acid using hydriodic acid and phosphorus in acetic acid during 10 hr. heating at 130–140°. This work was repeated in refluxing acetic or propionic acids as solvents, and was extended to the other fluorenonecarboxylic acids. In each case, the corresponding fluorenecarboxylic acids were formed in good yields in the refluxing solvent, and the process is adaptable to large scale work. Propionic acid is advantageous in that the fluorenonecarboxylic acids are more soluble in it at the boiling point, and a higher reaction temperature may be realized, but the use of acetic acid is more economical.

Enough solvent was employed to keep the fluorenonecarboxylic acids in solution throughout the reaction. As the other isomeric fluorenonecarboxylic acids are less soluble than fluorenone-4-carboxylic acid, a greater volume of solvent was required for their solution. The solubility of the fluorenone-2-carboxylic acid was so low that it was found to be more convenient to reduce its ethyl ester. During the course of the reduction, the ester was hydrolyzed by the hydriodic acid and fluorene-2-carboxylic acid was isolated. The methyl ester of fluorenone-3-carboxylic acid was employed for reduction in the 3 series. In all of the reductions, no unchanged fluorenonecarboxylic acids were detected in the products under the conditions used.

EXPERIMENTAL

Melting points are uncorrected and were taken on a Fisher-Johns melting point block.

In view of the results of Suzuki, it is probable that the reflux time may be shortened but this was not done in order to ensure completeness of the reaction. Descriptions of the reduction of fluorenone-1-carboxylic acid and fluorenone-2-carboxylic ethyl ester are given as representative examples of the process. Yields ranged from 83% to nearly theoretical.

Fluorene-1-carboxylic acid. A solution of 3.44 g. of fluorenone-1-carboxylic acid in 250 ml. of glacial acetic acid was mixed with 5.5 g. of red phosphorus and 6 ml. of 47–50% hydriodic acid. This mixture was refluxed for 46 hr. and then most of the solvent distilled. The residue was diluted to 350 ml. with cold water and after several hours standing was filtered and the product was washed. It was stirred with an excess of warm dilute potassium carbonate solution and filtered from phosphorus. The filtrate was acidified with hydrochloric acid and left overnight. The acid was filtered, washed, and dried. It weighed 3.18 g. or 99%. After several recrystallizations from acetone–petroleum ether at low temperatures, it had a melting point of 242–247° with previous sintering (Lit. 245–247° Corr.[2]). A run which was refluxed 70 hr. gave a nearly theoretical yield of slightly better quality acid. The reduction was also carried out in propionic acid as solvent with a 40-hr. reflux period.

Fluorene-2-carboxylic acid. The ethyl ester of fluorenone-2-carboxylic acid was prepared by overnight refluxing of the acid in ethanol containing a little sulfuric acid. This ester (10.96 g.) was dissolved in 250 ml. of hot acetic acid and treated with 15 g. of red phosphorus and 17 ml. of 47–50% hydriodic acid. The mixture was refluxed 30 hr. and worked up as with the 1 isomer. Decolorization with a little Norit was carried out in potassium carbonate solution and the acid precipitated with hydrochloric acid. A yield of 8 g. or 88% of air-dried acid was obtained. It sintered about 200° and discolored above 220° with melting 255–272°. One recrystallization from ethanol gave a product sintering at 235° and m.p. 265–275°. The literature melting points vary from 265–277°.[6,7] A reduction in propionic acid as solvent gave a crude yield of 97%.

If the free fluorenone-2-carboxylic acid is reduced in acetic acid, 300–350 ml. of boiling solvent is required for solution of 2 g. The fluorenone-2-carboxylic acid should be finely ground and refluxed for complete solution in excess acetic acid before adding the other reagents, which are best introduced near the boiling point. Though this is wasteful of acetic acid, a nearly theoretical yield of fluorene-2-carboxylic acid was obtained of good melting point without recrystallization. Propionic acid is slightly better as a solvent for the acid.

Fluorene-2-carboxylic acid was esterified by refluxing its solution in an excess of absolute ethanol containing some sulfuric acid for 16 hr. and isolating as usual. A nearly quantitative yield of ethyl ester was obtained which was recrystallized from ether–petroleum ether and acetone-water. It had m.p. 81–82°. The ethyl ester does not seem to have been prepared previously.

Anal. Calcd. for $C_{16}H_{14}O_2$: C, 80.67 H, 5.88. Found: C, 80.63 H, 5.61.

Fluorene-3-carboxylic acid. The reduction of the methyl ester of fluorenone-3-carboxylic acid has already been described.[10] In general it was similar to the method employed with the 2 isomer and fluorene-3-carboxylic acid was obtained in 96% yield.

Fluorene-4-carboxylic acid. In two experiments, fluorenone-4-carboxylic acid was reduced in propionic acid solution using 24 and 42 hr. reflux time. In both cases, 87% of fluorene-4-carboxylic acid was obtained. After recrystallization from

(2) H. R. Gutmann and P. Albrecht, *J. Am. Chem. Soc.*, **77**, 175 (1955).

(3) J. Forrest and S. H. Tucker, *J. Chem. Soc.*, 1137 (1948).

(4) N. Campbell and W. H. Stafford, *J. Chem. Soc.*, 299 (1952).

(5) E. Sawicki and B. Chastain, *J. Org. Chem.*, **21**, 1028 (1956).

(6) R. W. Schiessler and N. Eldred, *J. Am. Chem. Soc.*, **70**, 3958 (1948).

(7) D. C. Morrison, *J. Am. Chem. Soc.*, **74**, 3430 (1952).

(8) F. E. Ray and G. Rieveschl, *J. Am. Chem. Soc.*, **65**, 836 (1943).

(9) K. Suzuki, *Technol. Repts. Tôhoku Univ.*, **19**, 63 (1954). *Chem. Abstr.*, **50**, 905 (1956).

(10) D. C. Morrison, *J. Org. Chem.*, **23**, 1371 (1958).

aqueous acetone, this acid had m.p. 191–193° (Lit.[9] 189–191°).

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Synthesis of Some β-Phenethylamine Derivatives. I

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β-Phenethylamines are well known for their sympathomimetic activity, which is modified by the presence of substituents both in the side chain as well in the aromatic nucleus.[1] With a view to studying the effects on the physiological activity of different substituent groups like alkyl, alkoxyl, and halogen in various positions in the nucleus a number of β-phenethylamines were synthesized.

These amines were synthesized by the condensation of aromatic aldehydes with nitromethanes in acetic acid solution,[2] to yield the corresponding β-nitrosytrenes. The latter were then reduced with lithium aluminum hydride[3] to the β-phenethylamine derivatives, which were characterized as their picrates and wherever possible as their hydrochlorides.

2,3,5- (XIII) and 2,3,6- (XIV) -Trimethoxy-β-phenethylamines are hitherto unknown analogs of Mescaline. The starting material for the synthesis of XIII was 2,3,5-trimethoxybenzaldehyde.[4] The latter was prepared[5] by the Elb's persulfate oxidation of *o*-vanillin to 2,5-dihydroxy-3-methoxybenzaldehyde and subsequent methylation.

For the synthesis of 2,3,6-trimethoxy-β-phenethylamine, the starting material was 2,3,6-trimethoxybenzaldehyde,[5] whose synthesis was attempted by different routes. The easiest approach to its synthesis appeared to be through 2-hydroxy-6-methoxybenzaldehyde,[6] which on Elb's persulfate oxidation and subsequent methylation, would yield 2,3,6-trimethoxybenzaldehyde. Accordingly, 2,6-dihydroxybenzaldehyde (A) was prepared by the hydrolysis of the known 8-formyl-7-hydroxy-4-methylcoumarin[7] or from 2,6-dihydroxy-3-methoxycarbonylbenzaldehyde[8] by boiling with excess of water. The first method gave very poor yields of (A) and was abandoned. The second afforded a 48% yield of (A). However, persulfate oxidation of 2-hydroxy-6-methoxybenzaldehyde under different conditions proved to be unsuccessful. 2,3,6-Trimethoxybenzaldehyde was finally prepared as described by Merchant *et al.*[5]

During the course of the synthetic work, the decarboxylation of 3-carboxy-2-hydroxy-6-methoxybenzaldehyde, 3-carboxy-2,5-dihydroxy-6-methoxybenzaldehyde, and their respective anils, was studied under different conditions. It has been observed by Weijlard *et al.*[9] that the anil of opianic acid could be decarboxylated by heating with copper bronze. However, in the above two cases the desired decarboxylated product could not be isolated. Methylation of 3-carboxy-2,5-hydroxy-6-methoxybenzaldehyde resulted in the formation of 3-methoxycarbonyl-2,5,6-trimethoxybenzaldehyde, obtained as an oil and characterized by the preparation of a 2,4-dinitrophenylhydrazone. Hydrolysis of the above oily product gave instead of the expected 3-carboxy-2,5,6-trimethoxybenzaldehyde, a substance of melting point 224–225°, having a different molecular composition. From the analytical data, no definite structure could be assigned to it.

A detailed account regarding the pharmacological properties of the amines will be published elsewhere.

EXPERIMENTAL[10]

β-Nitrostyrenes. A mixture of 5 g. of the aldehyde, 5 ml. of nitromethane, 2 g. of ammonium acetate, and 20 ml. of glacial acetic acid, was refluxed at 130° for 2 hr. The reaction mixture was cooled, and the solid which separated was collected and crystallized from methanol or acetic acid. If no solid separated, the resulting solution was poured into ice water, and the precipitated semisolid mass or oil was extracted with ether. The ether solution was washed with water, dried, and the solvent distilled, when either a solid or an oil was left behind. The solid was purified by crystallization, whereas the oil was directly subjected for reduction.

β-Phenethylamines. The reduction of the β-nitrostyrene with lithium aluminum hydride, to the corresponding β-phenethylamine, was carried out according to the general method followed by Erne and Ramirez.[3]

A solution of 3 g. of the β-nitrostyrene in dry ether was added dropwise to a well stirred suspension of 2 g. of lithium aluminum hydride, in 100 ml. of dry ether. A mixture of ether and benzene was employed for styrenes which were sparingly soluble in ether. The reaction mixture was gently refluxed for 2 hr., and then decomposed with 2*N* sulfuric acid. To the aqueous layer, solid lithium carbonate was

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(10) Melting points are uncorrected and were taken in open capillary tubes.

MELTING POINTS AND ANALYSES OF THE β-NITROSTYRENES AND THE β-PHENETHYLAMINE DERIVATIVES

		β-Nitrostyrene							β-Phenethylamine Picrate				
					Analysis						Analysis		
					Found		Calcd.				Found		Calcd.
No.	Compound	Ref.[a]	M. P., °C.	Formula	C, %	H, %	C, %	H, %	M.P., °C.	Formula	C, %	H, %	C, %	H, %
I	2,4-Diethoxy-	11	92–93	$C_{12}H_{15}NO_4$	61.0	6.6	60.8	6.3	184–185	$C_{18}H_{22}N_4O_9$	49.0	5.0	49.3	5.0
II	2-Ethoxy-4-methoxy-	12	95–96	$C_{11}H_{13}NO_4$	59.4	6.0	59.2	5.8	161–162	$C_{17}H_{20}N_4O_9$	48.5	4.7	48.1	4.7
III	2-Benzyloxy-2-methoxy-	13	Oil[b]	$C_{16}H_{15}NO_4$	...	...	...	...	143–145	$C_{22}H_{22}N_4O_9$	54.3	5.0	54.3	4.5
IV	2,4-Dimethoxy-6-methyl-	14	117–118	$C_{11}H_{13}NO_4$	59.1	5.6	59.2	5.8	219–221[dec]	$C_{17}H_{20}N_4O_9$	48.0	5.0	48.1	4.7[a]
V	2,4-Diethoxy-6-methyl-	...	115–117	$C_{13}H_{17}NO_4$	62.4	6.7	62.2	6.7	178–180	$C_{19}H_{24}N_4O_9$	50.1	5.4	50.4	5.3
VI	2-Ethoxy-4-methoxy-6-methyl-	15	135–136	$C_{12}H_{15}NO_4$	61.1	6.2	60.8	6.2	188–189	$C_{18}H_{22}N_4O_9$	49.3	5.1	49.3	5.0[b]
VII	2,6-Dimethyl-4-methoxy-	16	115–116	$C_{11}H_{13}NO_3$	63.8	6.2	63.8	6.3	215–216[dec]	$C_{17}H_{20}N_4O_8$	50.3	5.2	50.1	4.9[c]
VIII	2,6-Dimethyl-4-ethoxy-	17	81–82	$C_{12}H_{15}NO_3$	65.4	7.1	65.2	6.8	185–186	$C_{18}H_{22}N_4O_8$	51.2	5.2	51.2	5.2
IX	2,4-Dimethyl-6-methoxy-	18	144–145	$C_{11}H_{13}NO_3$	63.9	6.5	63.8	6.3	188–189	$C_{17}H_{20}N_4O_8$	50.3	5.1	50.1	5.0
X	2,4-Dimethyl-6-ethoxy-	...	113–114	$C_{12}H_{15}NO_3$	65.0	6.5	65.2	6.8	173–174	$C_{18}H_{22}N_4O_8$	51.7	5.2	51.2	5.2
XI	2,6-Dimethoxy-4-methyl-	19	Oil[b]	$C_{11}H_{13}NO_4$	...	...	...	...	178–180[dec]	$C_{17}H_{20}N_4O_9$	48.2	4.6	48.1	4.7
XII	5-Bromo-2,3-dimethoxy-	20	107–108	$C_{10}H_{10}BrNO_4$	41.9	3.3	41.7	3.5	190–192	$C_{16}H_{17}BrN_4O_9$	39.7	3.8	39.3	3.5
XIII	2,3,5-Trimethoxy-	5,6	102–103	$C_{11}H_{13}NO_5$	55.3	5.8	55.2	5.4	158–159	$C_{17}H_{20}N_4O_{10}$	46.7	4.6	46.4	4.5
XIV	2,3,6-Trimethoxy-	6	Oil[b]	$C_{11}H_{13}NO_5$	...	...	...	...	166–167	$C_{17}H_{20}N_4O_{10}$	46.8	4.3	46.4	4.5

[a] The index numbers refer to the methods of preparation.
[b] Subjected directly for reduction without further purification.
[c] Amine Hydrochlorides (a) M.p. 251–252°; Calcd. for $C_{11}H_{18}ClNO_2$: N, 6.3. Found N, 6.1.
(b) M.p. 225–226°; Calcd. for $C_{12}H_{20}ClNO_4$: N, 6.0, Found N, 6.7.
(c) M.p. 225–226°; Calcd. for $C_{11}H_{18}ClNO$: N, 6.9, Found N, 6.8.

(11) F. Tieman and L. Lewy, *Ber.*, **10**, 2215 (1877).
(12) Srinivas Rao, C. Srikantia,, and M. S. Iyengar, *J. Chem. Soc.*, **127**, 558–60 (1925).
(13) H. Richtzenhain, *Ber.*, **77B**, 1–6 (1944).
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(20) W. Davies, *J. Chem. Soc.*, **123**, 1586 (1923).

added until its *p*H was about 6. The hot solution was filtered through Kieselguhr and the clear filtrate and washings were added to an alcoholic solution of picric acid. On cooling, the amine picrate separated out, which was recrystallized from methanol. The yield of the picrate in almost all cases ranged from 60 to 70%.

Two grams of the above picrate was boiled with 14 ml. of concentrated hydrochloric acid. After cooling, the precipitated picric acid was filtered. The filtrate was extracted with nitrobenzene and then with ether. The aqueous layer was evaporated to dryness under vacuum. The dark hydrochloride thus obtained was recrystallized from a mixture of methanol and ethyl acetate.

2,6-Dihydroxybenzaldehyde. A mixture of 3 g. of 3-carboxy-2,6-dihydroxybenzaldehyde and 200 ml. of water was refluxed for about 4 hrs. The resulting solution was filtered and the clear filtrate repeatedly extracted with ether. The ether extract was washed with a saturated solution of sodium bicarbonate, and then with water. Evaporation of ether afforded the aldehyde, which was crystallized from water as 1.1 g. of pale yellow needles, m.p. 154°–155°.

Anal. Calcd. for $C_7H_6O_3$: C, 60.9; H, 4 3. Found: C, 60.8; H, 4.2.

Anil of 3-carboxy-2-hydroxy-6-methoxybenzaldehyde. The anil of 3-carboxy-2-hydroxy-6-methoxybenzaldehyde was prepared according to the general method described by Weijlard *et al.*[9] It was crystallized from alcohol in orange colored needles of m.p. 203–205° (dec.).

Anal. Calcd. for $C_{16}H_{13}NO_4$: N, 5.1. Found: N, 5.5.

Anil of 3-carboxy-2,5-dihydroxy-6-methoxybenzaldehyde. The anil was crystallized from alcohol in red needles, of m.p. 223–225° (dec.).

Anal. Calcd. for: $C_{15}H_{13}NO_5$: N, 4.9. Found: 5.0.

3-Methoxycarbonyl-2,5,6-trimethoxybenzaldehyde. A mixture of 1 g. of 3-carboxy-2,5-dihydroxy-6-methoxybenzaldehyde, 2 g. of anhydrous potassium carbonate, 2 ml. of dimethyl sulfate, and 55 ml. of dry acetone was gently refluxed for 12 hr. Filtration and removal of acetone left an oil which was washed with dilute sodium hydroxide and extracted with ether. Evaporation of the ether gave 3-methoxycarbonyl-2,5,6-trimethoxybenzaldehyde as an oil.

Its *2,4-dinitrophenylhydrazone* crystallized from alcohol in tiny needles, m.p. 169°.

Anal. Calcd. for $C_{18}H_{18}N_4O_9$: N, 12.5. Found: 12.0.

Attempted hydrolysis of 3-methoxycarbonyl-2,5,6-trimethoxybenzaldehyde. One gram of 3-methoxycarbonyl-2,5,6-trimethoxybenzaldehyde and 50 ml. of 5% sodium carbonate was heated on a water bath for ½ hr., when the oil slowly went into solution. On cooling, and acidification with hydrochloric acid, a pale yellow compound was obtained, which was crystallized from alcohol in needles, m.p. 225°.

It did not give a coloration with alcoholic ferric chloride solution, but dissolved in sodium bicarbonate; nor did it form a 2,4-dinitrophenylhydrazone or an "anil."

Anal. Found: C, 58.1; 58.4; H, 5.4; 5.8.

No definite structure could be assigned to it from the analytical data.

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Synthesis of 3-Indoleacetamides[1,2]

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The enhancement of activity for parthenocarpic fruit development in the tomato by changes in the ring structure and side chain of 3-indoleacetic acid[4,5] has prompted the preparation of several 3-indoleacetamides.

Various 3-indoleacetyl amino acids have been prepared by using the mixed anhydride procedure[6,7] and the carbodiimide method.[8–10] The classical method of amide formation, Schotten-Baumann reaction, was not used by these investigators since this procedure is contingent upon the preparation of 3-indoleacetyl chloride. This was generally assumed not possible until reported by Shaw and Woolley.[11] The Schotten-Baumann reaction has been used in this laboratory for the preparation of 3-indoleacetamides.

The properties of various 3-indoleacetamides are given in Table 1. All of the compounds exhibited ultraviolet absorption characteristic of the indole nucleus except the *p*-aminobenzoic acid derivative where the strong absorption of the *N*-substituted *p*-aminobenzoic acid moiety masked completely the typical indole ultraviolet absorption (280 to 300 mμ).

EXPERIMENTAL

3-Indoleacetyl chloride.[11] This compound was prepared in 60–70% yields by the reaction of 3-indoleacetic acid with phosphorus pentachloride in anhydrous ether solution at 0°. The product was recrystallized from a mixture of ether and petroleum ether to yield colorless to pink crystals, m.p. 68–70°, trinitrobenzene adduct[12] m.p. 88°.

3-Indoleacetyl derivatives. 3-Indoleacetyl derivatives were synthesized by a method similar to the one used by Wood and Fontaine[13] for the preparation of substituted phenoxyacetyl derivatives. The following description illustrates the general procedure for the synthesis of all of the amino acid derivatives of 3-indoleacetic acid.

Glycine (0.75 g., 0.01 mole) was dissolved in 30 ml. of *N* sodium hydroxide (0.03 mole) and the solution cooled in an ice bath to 0–5°. 3-Indoleacetyl chloride (1.93 g., 0.01 mole) was dissolved in 10 ml. of anhydrous ether, cooled to 0°, and added dropwise with efficient mechanical stirring to the alkaline glycine solution. After 0.5 hr. the ice bath was removed to permit the solution to reach room temperature, and stirring was continued for an additional hour. The alkaline mixture was then thoroughly extracted with ether, the aqueous fraction cooled to 0°, and acidified to *p*H 2 with

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(2) This research was supported by the Horace H. Rackham Research Endowment.

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TABLE 1

PROPERTIES OF 3-INDOLEACETAMIDES

3-Indoleacetamides	Formula	M.p.	$[\alpha]_D^{27}$	Yield %	Nitrogen % Calcd.	Nitrogen % Found	Neutralization Equivalent Calcd.	Neutralization Equivalent Found
N-(3-Indoleacetyl)-glycine	$C_{12}H_{12}N_2O_3$	86–87[a]		17	12.1	12.1	232	232
N-(3-Indoleacetyl)-DL-isoleucine	$C_{16}H_{20}N_2O_3$	102		34	9.7	9.9	288	290
N-(3-Indoleacetyl)-DL-methionine	$C_{15}H_{18}N_2O_3S$	169–171d		19	9.1	9.2	306	302
N-(3-Indoleacetyl)-L-tryptophan	$C_{21}H_{19}N_3O_3$	181–183	+14.56	9	11.6	11.7	361	358
N-(3-Indoleacetyl)-L-aspartic acid	$C_{14}H_{14}N_2O_5$	164.5d	−4.5	29	9.7	9.4	145	144
N-(3-Indoleacetyl)-L-glutamic acid	$C_{15}H_{16}N_2O_5$	162.5d	−10.57	20	9.3	9.3	151	152
N-(3-Indoleacetyl)-6-aminopurine	$C_{15}H_{12}N_6O$	242–244		30	28.8	28.5		
N-(3-Indoleacetyl)-*p*-aminobenzoic acid	$C_{17}H_{14}N_2O_3$	253–255d		45	9.5	9.6	294	296
N-(3-Indoleacetyl)-*m*-aminobenzoic acid	$C_{17}H_{14}N_2O_3$	246d		37	9.5	9.7	294	297

[a] *Cf.* reference 6.

dilute phosphoric acid. After standing for 1 hr. in the cold, the precipitate was collected by filtration. The product was further purified by recrystallizations from water coupled with carbon decolorizations. The yield of the recrystallized product was 380 mg., m.p. 86–87°.

Those 3-indoleacetamides, which possessed limited water solubility, were recrystallized from dilute ethanol or ethanol alone (adenine derivative). The yield of the recrystallized products was usually 25–30%.

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Structural Studies of the Isoximes of Weygand and Bauer

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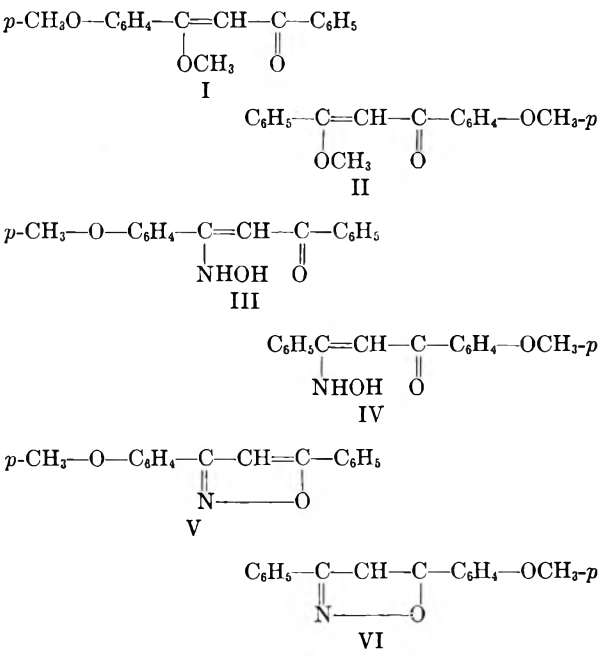
The infrared and ultraviolet spectra of the isoximes of Weygand and Bauer indicate that these substances are represented best as the more stable of the configurational isomers of the oximes. Chemical evidence points to facile rearrangement of the more stable isomers to the less stable forms which undergo ring closure with formation of isoxazoles.

Weygand and Bauer[2] reported that on treating the "A-ether" (I) and the "B-ether" (II) with hydroxylamine, they isolated compounds III and IV, respectively, which they called isoxime A and isoxime B. They showed that they obtained isoxazoles V and VI when they treated the isoximes with acids.



It is common knowledge that β-diketones yield isoxazoles when treated with hydroxylamine. Blatt[3] showed that methoxyamine hydrochloride, in contrast to the free base, adds to the ketonic carbonyl group. Barnes and Pinkney[4] showed that the free base, hydroxylamine, adds 1,4 to α,β-unsaturated ketones, and that in isoxazoline formation, nitrogen is found on the carbon atoms that was previously the carbonyl carbon. Blatt[3] showed that acetylenic ketones also add the free base, methoxyamine.

We believe that the structural formula III and IV should be designated as oximes with the following configurational formulas VII and VIII, and that these anti forms, on acidification, rearrange to the syn forms which then enolize and undergo

(1) In partial fulfillment of the requirements for the Master's degree.

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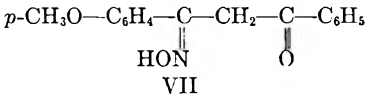
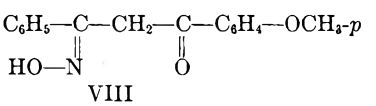
ring closure with the formation of isoxazoles V and VI.



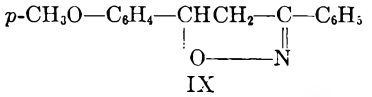
VII



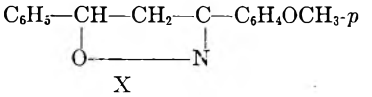
VIII

We have investigated the isoximes of Weygand and Bauer and have concluded that they are actually oximes. We believe that oximes VII and VIII are formed by 1,4-addition of hydroxylamine to ethers I and II with the elimination of methanol. These isoximes do not yield to ozonization.

p-Methoxybenzalacetophenone[5] and benzal-*p*-methoxyacetophenone[6] were converted into their respective isoxazolines IX and X by treatment with hydroxylamine in aqueous alcoholic solution in the presence of potassium hydroxide. These isoxazolines IX and X upon oxidation with chromic acid yielded the expected isoxazoles VI and V, respectively.

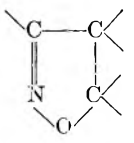


IX

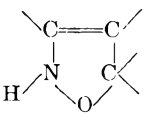


X

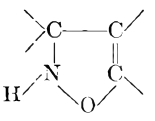
We examined the infrared and ultraviolet spectra[7] of the isoximes. Recently, G. W. Perold[8] *et al.* observed no infrared absorption band in the N—H stretching region around 3300 cm.$^{-1}$ and on this basis assigned structure XI to isoxazoles rather than XII or XIII.



XI



XII



XIII

We also examined infrared absorption spectra for several compounds in the range 5.88–6.00 μ and around 3300 cm.$^{-1}$ In the 5.88–6.00 μ region we observed no absorption band for the isoximes of Weygand and Bauer. This region has been assigned to α,β-unsaturated ketones.[9]

Below are listed several ketones and their infrared and ultraviolet bands.

Compound	3500–3200 cm.$^{-1}$	5.88–6.00 μ
Isoxime A, III	3330	...
Isoxime B, IV	3300	...
N-methyl ether of isoxime A, XIV	...	...
II(s)	3580	6.01
Mes—C(=O)—C(=NOH)—CH_2—C_6H_5(*s*)[10]	3300	5.92
, XV		
Mes—C(=O)—C(=N—O—CO)—CH_2—C_6H_5(*s*)[10]	3320 Not developed	...
Mes—C(=O)—CH_2—CH_2—C_6H_5(*l*)[10]	3400	5.85

s = Nujol mull. *l* = liquid

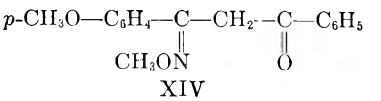
Ultraviolet Data

Compound	Absorption Band, Mμ	E_{max}
Isoxime A, III	270	1.92×10^4
Isoxime B, IV	260	1.50×10^4
XV	235	...

The infrared absorption in the region 5.88–6.00 μ (1700–1665 cm.$^{-1}$)[9] shows that compound II has a band at 6.01 μ, corresponding to α,β-unsaturated ketones. We obtained no absorption in this region for isoximes III and IV. This indicates that their structures could not be as represented.

We note that Perold[8] assigned an absorption band at 3300 cm.$^{-1}$ to N—H stretching. It is interesting to note that while the *N*-methyl ether of isoxime A, XIV, does not have an absorption band in this region, isoximes III and IV do.

Comparing the isoxime structures III and IV and the proposed configurational oxime formulas VII and VIII with the oxime structure XV, we find that isoximes III and IV and oxime XV all absorb in the range 3300–3340 cm.$^{-1}$ This band cannot be assigned to N—H stretching since the reference oxime XV does not have an N—H linkage. Instead, this band should be assigned to OH absorption. Hence the isoximes seem to be represented best as the configurational oximes VII and VIII. This is further confirmed by the fact that the *N*-methyl ether of isoxime A, XIV, showed no absorption in this region. And so the *N*-methyl ether of isoxime A is



XIV

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(6) H. Staudinger and N. Kon, *Ann.*, **384**, 123 (1911).

(7) Infrared and ultraviolet spectra were measured by Messrs. J. E. Stewart and J. H. Gould of the National Bureau of Standards, Dept. of Commerce, Washington, D. C.

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(10) R. P. Barnes, *J. Am. Chem. Soc.*, **57**, 937 (1935).

Ferguson and Barnes[11] reported that ultraviolet absorption in conjugated systems involving α,β-unsaturated carbonyl compounds ranges above 319 mμ, whereas these isoximes absorb at 260 and 270 mμ. This does not lend support to the isoxime structures.

EXPERIMENTAL

Preparation of isoxazolines IX *and* X. 3-phenyl-5-anisyl-isoxazoline (IX) and 3-anisyl-5-phenylisoxazoline (X) were prepared according to Blatt[12] and Barnes[13] by treating *p*-methoxybenzalacetophenone and benzal-*p*-methoxyacetophenone, respectively, with excess hydroxylamine in alcoholic potassium hydroxide.

	M.P., ° C.	Color	Analysis
IX	101–102°	White	Calcd. for $C_{16}H_{15}NO_2$: C, 75.88; H, 5.92. Found: C, 75.85; H, 6.00.
X	96°	White	Calcd. for $C_{16}H_{15}NO_2$: C. 75.88; H, 5.92. Found: C, 75.83; H, 6.02

Preparation of isoxazoles V *and* VI. Chromic acid oxidation[12,13] of isoxazolines IX and X yielded isoxazoles VI and V, respectively, identified by mixture melting points with samples obtained by acidification of isoximes IV and III.

Treatment of isoximes with ozone. Prolonged treatment of alcoholic solutions of isoximes III and IV gave no cleavage products. The isoximes were recovered unchanged.

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(11) L. N. Ferguson and R. P. Barnes, *J. Am. Chem. Soc.*, **70**, 3907 (1948).
(12) A. H. Blatt, *J. Am. Chem. Soc.*, **53**, 1140 (1931).
(13) R. P. Barnes, G. Pinkney, and G. McK. Phillips, *J. Am. Chem. Soc.*, **76**, 276 (1954).

Thiol Addition of Thiourea in Heterocyclic Ring Formation: Preparation of 5-Ethyl-6-phenyl-*meta*-thiazane-2,4-dione

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Thiourea has been made to undergo a thiol-type addition to a monobasic, α,β-unsaturated acid and to its ethyl ester. A simultaneous condensation between the carboxyl group of the acid and the amine group of thiourea has resulted in the formation of a derivative of the six-membered, sulfur containing heterocycles the *meta*-thiazanes.

Several reactions of thiourea that have been previously observed by other workers indicate that in some instances the thiol tautomer is the predominant reacting species. Thus, upon alkylating thiourea with hydrocarbon halides or with alkyl sulfates, *S*-alkyl- and *S*-arylthiouronium salts are formed.[1] Oxidation of thiourea in acid solution leads to the formation of dithiodiformamidine.[2] Andreasch[3] has reacted thiourea with maleic or fumaric acid to give I and with citraconic to give II (Fig. 1). These reactions were carried out by heating a fused mixture of the reactants either dry or with a small amount of water. The products obtained indicate that both a thiol addition of the thiourea to the unsaturated acid and a condensation, involving the elimination of water from the carboxyl group and from the amine group of the thiourea, occur. Attempts to repeat this reaction with such monobasic, unsaturated acids as oleic, crotonic, cinnamic, 2-phenyl-3-methylacrylic, and methacrylic were not successful. Either polymeric products were obtained or else amine addition by the thiourea occurred forming thiopyrimidines.[3,4] Thus with cinnamic acid, 4-phenyl-2-thio-6-keto-pyrimidine was obtained.[4] However, a thiol addition reaction between thiourea and acrylic acid has been accomplished by hydrogen chloride catalysis in alcohol to give *S*-(β-carboxyethyl)-isothiouronium hydrochloride[5] without accompanying cyclization.

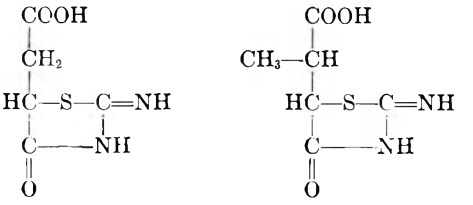

Figure 1

In the present work, a sulfuric acid solution of thiourea was treated with the α,β-unsaturated acid *trans*-α-ethylcinnamic acid, and with its ethyl ester, and in both cases the same *meta*-thiazane derivative was obtained. This product which no longer contains unsaturation can only arise from a reaction where the thiol tautomer of thiourea adds to the unsaturated system, since the sulfur is part of the heterocyclic ring. The possible sequences of reactions which would result in such a product are shown in Fig. 2. Both the addition and the condensation reaction occur under the same conditions. Upon running the above reaction for shorter times and using the same

(1) (a) G. G. Urquhart, J. W. Gates, and R. Connor, *Org. Syntheses*, **21**, 36 (1941); (b) A. I. Vogel, *J. Chem. Soc.*, 1822 (1948); (c) H. J. Backer and N. D. Dijkstra, *Rec. trav. chim.*, **51**, 290 (1932); (d) J. T. Hackmann and R. Berkenbosch, Rec. trav. chim., **68**, 752 (1949); (e) F. Arndt, *Ber.*, **54**, 2236 (1921); (f) H. J. Backer, *Rec. trav. chim.*, **54**, 216 (1935).
(2) J. Boeseken, *Rec. trav. chim.*, **55**, 1040 (1936).
(3) R. Andreasch, *Monatsh.* **16**, 789 (1895); **18**, 56 (1897).
(4) H. Erlenmeyer and F. Heitz, *Helv. Chim. Acta*, **25**, 832 (1942).
(5) (a) E. H. Behringer and P. Zillikens, German Patent-Anm. B. **16741** (1951); (b) O. Bayer, *Angew. Chem.*, **61**, 236 (1949); (c) J. Houben, *Methoden der Organischen Chemie*, vol. IX, G. Thiele, Leipzig, Germany, 1955, p. 902.

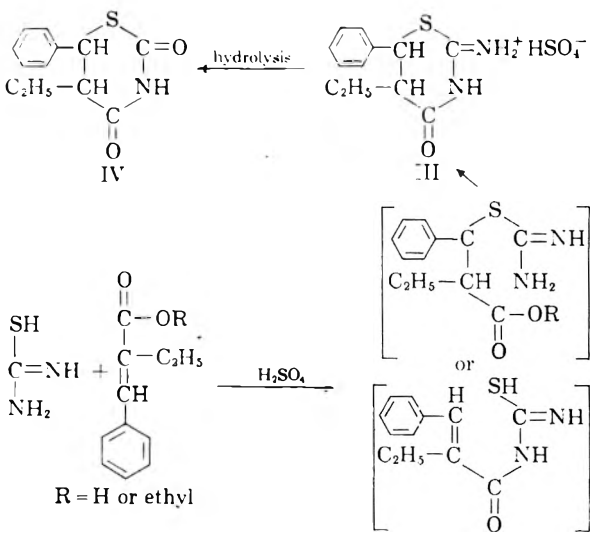

Figure 2

isolation procedures used throughout in this work, no other compounds than the *meta*-thiazane derivative have been isolated. Therefore, no information is available on the comparative rates of the condensation and addition reactions. III, an imine sulfate could not be isolated because of its solubility in concentrated and dilute sulfuric acid. Therefore, it was converted to the *meta*-thiazane-2,4-dione (IV), by acid hydrolysis which was then readily isolated in a 51.5 % yield.

5-Ethyl-6-phenyl-*meta*-thiazane-2,4-dione (IV) had been previously prepared from thiourea and 2-ethyl-3-bromo-3-phenylpropionic acid.[6] That reaction was repeated in the present work to obtain a 35% yield of the dione. In that reaction, the imine salt analogous to III was obtained and also converted to IV by acid hydrolysis. The methods of preparation of a number of other substituted *meta*-thiazane-2,4-diones are given in the above reference. Langlet,[7] in considerably older literature, describes the preparation of a number of 2-imino-4-oxo-*meta*-thiazanes by the reaction of thiourea and *N*-substituted thioureas with β-iodopropionic acid. This same worker also prepared a number of substituted *meta*-thiazane-2,4-diones by reaction of *N*-substituted thiocarbamates with β-iodopropionic acid.[7]

EXPERIMENTAL

trans-α-Ethylcinnamic acid was prepared by the Perkin reaction; however earlier methods of preparation were modified by using potassium carbonate as catalyst and by simplification of the isolation and purification procedures. A mixture of 272.0 g. (2.55 mole) of benzaldehyde, 508 g. (3.2 mole) of butyric anhydride, and 178.0 g. (1.3 mole) of anhydrous potassium carbonate was stirred and gradually heated to 140°. At this temperature an exothermic reaction occurred, causing considerable foam formation accompanied by a rapid temperature rise. The foaming was controlled by occasionally cooling the reaction flask in cold water. After reheating and cooling the reaction mixture three times, it was heated to 180°. After heating at this temperature for 20 hr., the mixture was poured with stirring into 1900 ml. of water containing 454.0 g. of sodium carbonate. After allowing this mixture to stand for 30 min., the dark oil that separated from the aqueous phase was discarded. The product was precipitated from the aqueous phase by the addition of 110.0 ml. of concentrated sulfuric acid with vigorous stirring, bringing the *p*H to 5.0. The mixture was stirred for 30 min. and the precipitate was removed by vacuum filtration. The filter cake was washed three times with water and then dried at 70° for 16 hr. to give 225.3 g. (50.2%) of *trans-α*-ethylcinnamic acid, m.p. 103–104° (lit.[8b] m.p. 104°).

Ethyl trans-α-ethylcinnamate was prepared by the Claisen reaction from benzaldehyde and ethyl butyrate.[8c]

Authentic 5-ethyl-6-phenyl-meta-thiazane-2,4-dione was prepared according to the method of Wheeler and Gash[6] from thiourea and 2-ethyl-3-bromo-3-phenylpropionic acid. Upon recrystallization from alcohol this material melted at 160–162° [lit.[6] m.p. (of unrecrystallized material) 153–155°] and was obtained in a 35% yield.

Reaction of thiourea with trans-α-ethylcinnamic acid. Two hundred and sixteen g. (2.8 mole) of thiourea was dissolved, with stirring and cooling, into one liter of 100% technical sulfuric acid, keeping the temperature below 55°. To the mixture, with mechanical stirring, was added 250.0 g. (1.4 mole) of *trans-α*-ethylcinnamic acid, then heating and stirring the mixture at 52–55° for 16 hr. The mixture was poured into 6.0 liters of water and the water solution refluxed for 16 hr. The solution was then cooled to 70° and 750 ml. of benzene was added. The mixture was then vigorously stirred for 5 min. and allowed to separate into two phases. The benzene layer was separated and filtered and its volume reduced to one-half on a steam bath. Upon cooling the residual benzene solution at room temperature, 170 g. (51.5% yield) of 5-ethyl-6-phenyl-*meta*-thiazane-2,4-dione, m.p. 155–158° (lit.[6] m.p. 153–155°) was obtained after vacuum filtering and drying the crystals for 4 hr. at 100°. The solid obtained above was dissolved into 800 ml. of boiling ethanol, the solution filtered and the volume reduced to one half. On cooling at room temperature for 16 hr., 155 g. of the dione, m.p. 162–163° was obtained.

Anal. Calcd. for $C_{12}H_{13}O_2NS$: C, 61.25; H, 5.57. Found: C, 61.33; H, 5.50.

Admixture of this product with an authentic sample of 5-ethyl-6-phenyl-*meta*-thiazane-2,4-dione caused no depression of its melting point.

Reaction of thiourea with ethyl trans-α-ethylcinnamate. Ten and seven tenths g. (0.14 mole) of thiourea was dissolved into 75 ml. of concentrated sulfuric acid, with stirring and cooling, keeping the temperature below 55°. To this solution, with stirring, was added 14.3 g. (0.07 mole) of ethyl *trans-α*-ethylcinnamate. The mixture was heated at 52° for 7 hr. and then poured into 300 ml. of water. The water mixture was refluxed for 16 hr. and then cooled for 16 hr. at 5°. An amorphous lump which settled out of solution was dissolved into 35 ml. of boiling alcohol. The resultant solution was filtered and cooled at 5° for 16 hr. From two crops, there was obtained 5.1 g. (31.0% yield) of 5-ethyl-6-phenyl-*meta*-thiazane-2,4-dione, m.p. 157–159° (lit.[6] m.p. 153–155°). Admixture of this material with an authentic sample of the dione and with the dione prepared from thiourea and trans-α-ethylcinnamic acid (above) caused no depression of its melting point.

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(6) K. W. Wheeler and V. W. Gash, U. S. Patent 2,585,-064, Example II (1952).

(7) N. A. Langlet, *Ber.* **24**, 3851 (1891); *Ofver. Svenska Vetenskaps-Akad. Forh.*, **166**, 306 (1892); 376 (1894); 37 (1895), *Beilstein*, XXVII, 246.

(8) (a) W. H. Perkin, *J. Chem. Soc.* **31**, 393 (1877); (b) R. Fittig and F. L. Slocum, *Ann.* **227**, 53 (1885); (c) L. Claisen, *Ber.* **23**, 978 (1890); (d) A. Michael, *Ber.* **34**, 928 (1901); (e) E. Alber and F. Fichter, *J. prakt. Chem.* (2), **74**, 337 (1906); (f) T. Posner, *J. prakt. Chem.* (2) **82**, 436 (1910).

Reactions with Mercaptans. V. Action of Aromatic Thiols on Furocoumarins, Furochromones, and 2-Aralkylidene-3(2*H*)-thianaphthenone-1,1-dioxides

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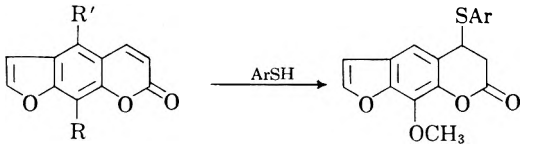
In conjunction with the study of the pharmacological action of sulfur-containing compounds,[1] we now have found that the addition products (IIa–b) are obtained upon treatment of xanthotoxin (Ia) with thiophenol and *p*-thiocresol, respectively, in the presence of piperidine. Structure II is assigned for the sulfides.[1] The unreac-



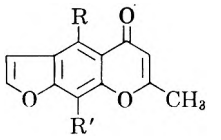
Ia, R = OCH_3, R′ = H
b, R = $OCH_2CH{=}C(CH_3)_2$, R′ = H
c, R = H, R′ = OCH_3
d, R = OH, R′ = $CH_2CH{=}C(CH_3)_2$

IIa, Ar = C_6H_5
b, Ar = $C_6H_4CH_3$-*p*

tivity of the unsaturated system in the furan ring in Ia may be deduced from the unreactivity of coumarilic acid and/or its methyl ester toward the action of thiophenol (*cf.* Experimental).

Treatment of bergapten (Ic) and imperation (Ib) with thiophenol under given experimental conditions results in the recovery of unchanged Ic and the formation of alloimperation (Id).[2]

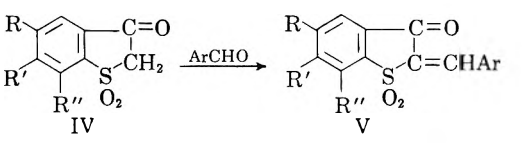
Khellin (IIIa) and visnagin (IIIb) undergo demethylation by the action of thiophenol and/or *p*-thiocresol under the described experimental conditions to give IIIc[3–5] and IIId, respectively.



IIIa, R = R′ = OCH_3
b, R′ = H, R = OCH_3
c, R = OH, R′ = OCH_3
d, R = OH, R′ = H

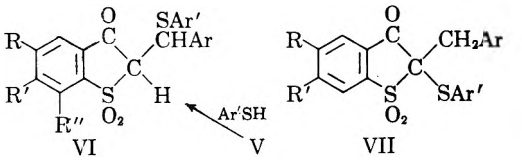
Parallel experiments with phenol results in recovery of the unchanged IIIa. We believe that demethylation is to be connected with the methoxyl group in position 5, since IIIc is insoluble in alkali and is stable toward ethereal diazomethane.[5,6] Methylation of IIIc with diazomethane in the presence of methyl alcohol regenerates[7] IIIa.

Aromatic thiols now have been found to add to the double bond at position 2, which is conjugated with the unsaturated group in the newly prepared 2-aralkylidene-3(2*H*)-thianaphthenone-1,1-dioxide [prepared from the condensation of 3(2*H*)-thianaphthenone-1,1-dioxide (IV) with benzaldehyde] (V *cf.* Table I) in the absence of catalyst to yield the colorless thiol adducts[8] (*cf.* Table II), believed to have structure VI and not VII. Compound VIb, for example, dissolves in cold sodium hydroxide solution to give a yellow solution and is regenerated upon neutralization. It is decomposed when heated above its melting point to give Vb. The ease of removal of the addend indicates that the substance is the result of simple addition and that no unexpected reaction has occurred. Attempts to oxidize VIb with hydrogen peroxide in glacial acetic acid on the water bath also led to the formation of Vb.[9]



IV V

a, R = R′ = R″ = H; Ar = C_6H_5
b, R = CH_3, R′ = R″ = H, Ar = C_6H_5
c, R = R″ = H, R′ = CH_3, Ar = C_6H_5
d, R = R′ = H, R″ = CH_3, Ar = C_6H_5
e, R = R′ = H, R″ = Cl, Ar = C_6H_5
f, R = R′ = R″ = H, Ar = $C_6H_4OCH_3$-*p*



VI V VII

EXPERIMENTAL

Thiol adducts: General procedure. A mixture of 0.5 g. of the substance under investigation, 0.5 g. of the aromatic thiol, and a few drops of freshly distilled piperidine was warmed on a steam bath for 10 hr. in the case of Ia. In the case of Vb–f, the reaction mixture was heated at the stated temperature (*cf.* Table II) for 3 hr. in the absence of a catalyst.

(1) A. Mustafa, M. Kamel, M. A. Allam, A. H. E. Harhash, and A. E. A. A. Hassan, *J. Am. Chem. Soc.*, **78**, 5011 (1956).

(2) E. Späth and H. Holzen, *Ber.*, **68B**, 1123 (1935).

(3) Mukerjee and T. R. Seshadri, *Proc. Indian. Acad. Sci.*, **35A**, 323 (1952).

(4) H. Abu-Shadi and T. O. Soine, *J. Am. Pharm. Assoc., Sci. Ed.*, **41**, 325 (1952).

(5) A. Schönberg and G. Aziz, *J. Am. Chem. Soc.*, **75**, 3265 (1953).

(6) The failure of phenolic hydroxyl group ortho or peri to a carbonyl group to react with diazomethane under normal conditions is a well-known example and this is of diagnostic value in establishing the structure of hydroxyflavones, -xanthones, etc. [*cf.* V. C. Farmer, N. F. Hays, and R. H. Thomson, *J. Chem. Soc.*, 3600 (1956)].

(7) A. Schönberg and A. Mustafa, *J. Chem. Soc.*, 746 (1946).

(8) A. Mustafa and S. M. A. D. Zayed, *J. Am. Chem. Soc.*, **79**, 3500 (1957).

(9) ω-*p*-Dinitrostyrene thiol adducts behave similarly when heated with hydrogen peroxide under the same conditions [*cf.* A. Mustafa, A. H. E. Harhash, and M. Kamel, *J. Am. Chem. Soc.*, **77**, 3860 (1955)].

TABLE I

2-ARALKYLIDENE-3(2*H*)-THIANAPHTHENONE-1,1-DIOXIDES (V)

Arylidene Deriv.[a]	Reaction Temp., °C.	M.P., °C.[b]	Yield, %	Solvent for Cryst.	Formula	Analysis					
						Carbon		Hydrogen		Sulfur	
						Calcd.	Found	Calcd.	Found	Calcd.	Found
Vb	150	209	92	A (Pale yellow)	$C_{16}H_{12}O_3S$	67.61	67.54	4.23	4.02	11.27	11.10
Vc	160	210	78	A (Pink)	$C_{16}H_{12}O_3S$	67.61	67.38	4.23	4.13	11.27	11.21
Vd	160	158	75	B (Pale yellow)	$C_{16}H_{12}O_3S$	67.61	67.51	4.23	4.00	11.27	11.19
Ve	170	216	85	A (Brownish)	$C_{15}H_9ClO_3S$[c]	59.11	58.93	2.95	3.00	10.51	10.29
Vf	150	165	71	B (Yellow)	$C_{16}H_{12}O_4S$	64.00	63.89	4.00	3.85	10.67	10.36

[a] For the method of preparation, *cf.* A. Mustafa, S.M.A.D. Zayed (ref. 8). [b] All melting points are uncorrected. A, Acetic acid; B, ethyl alcohol. [c] Calcd.: Cl, 11.67. Found: 11.34.

The cooled reaction mixture was washed with light petroleum (b.p. 40–60°) and the resulting solid was crystallized from the proper solvent.

IIa formed colorless crystals from ethyl alcohol, m.p. 132°, in *ca.* 80% yield.

Anal. Calcd. for $C_{18}H_{13}O_4S$: C, 66.46; H, 4.00; S, 9.84. Found: C, 66.12; H, 4.00; S, 10.02.

It is soluble in hot benzene, but difficultly soluble in light petroleum and gives yellowish green color with concentrated sulfuric acid.

IIb formed colorless crystals from ethyl alcohol, m.p. 136°, in *ca.* 72% yield.

Anal. Calcd. for $C_{19}H_{15}O_4S$: C, 67.25; H, 4.42; S, 9.43. Found: C, 67.00; H, 4.49; S, 9.11.

It is soluble in hot benzene and gives an orange-yellow color with concentrated sulfuric acid.

IIa and IIb are insoluble in cold aqueous sodium hydroxide solution (10%), their alcoholic solutions give no color with ferric chloride, and are stable under normal conditions.

The thiol adducts (VI), listed in Table II, are colorless, soluble in hot benzene, but are difficultly soluble in ether, ethyl alcohol and in glacial acetic acid.

Action of potassium hydroxide on IIa. The thiol adduct (1 g.) was refluxed with 100 ml. of alcoholic potassium hydroxide solution (4%) for 4 hr. The cooled reaction mixture was poured into ice cold water, acidified with hydrochloric acid, and extracted with ether. The ethereal solution gave, on shaking with lead acetate solution, yellow crystals (*ca.* 0.25 g.) of the lead salt of thiophenol (melting point and mixed melting point[10]).

The ethereal solution, after thorough washing with water and drying, gave on evaporation a colorless solid (*ca.* 0.5 g.) which was identified as Ia (melting point and mixed melting point).

Thermal decomposition of VI ($R = CH_3$, $R' = R'' = H$, $Ar = Ar' = C_6H_5$). The thiol adduct (0.2 g.) was heated in a dry test tube at 140° (bath temperature) for 20 min. The cooled reaction mixture was crystallized from ethyl alcohol and identified as Vb (melting point and mixed melting point).

Action of thiophenol on Ib. A mixture of equimolecular amounts of Ib and thiophenol and few drops of piperidene was heated in an oil bath at (155–160°) for 3 hr. The cooled reaction mixture was washed with light petroleum (b.p. 40–60°) and the resulting solid was crystallized from benzene as colorless crystals of Id, m.p. 233°, not depressed when mixed with an authentic sample of Id;[2] yield, *ca.* 85%.

Anal. Calcd. for $C_{16}H_{14}O_4$; C, 71.11; H, 5.18. Found: C, 71.23; H, 5.09.

It is soluble in hot benzene and in aqueous sodium hydroxide solution (10%). Id is recovered unchanged when heated with thiophenol at 160°.

Attempted action of thiophenol on bergapten, coumarilic acid, and its methyl ester. A mixture of 0.5 g. of each of the above mentioned compounds, one gram of thiophenol, and few drops of piperidine was heated at 100° for 10 hr. When the reaction mixtures were worked up, the starting materials were recovered essentially unchanged (melting point and mixed melting point determinations).

Repeating the experiments at 140° for the same time period resulted in the recovery of the unchanged materials.

Demethylation effected with aromatic thiols. (*a*) *Partial demethylation of* IIIa. A mixture of 1 g. of IIIa, 2 g. of thiophenol, and a few drops of freshly distilled piperidine was heated at 100°. After 10 min. heating, the color of the reaction mixture changed to yellow and then heating was continued for 3 hrs. The cooled reaction mixture was washed with petroleum ether (b.p. 60–80°) and the residual solid was crystallized from ethyl alcohol as yellow crystals of IIIc m.p. 204°, not depressed when admixed with an authentic sample of IIIc; yield *ca.* 0.8 g.

Anal. Calcd. for $C_{13}H_{10}O_5$: C, 63.41; H, 4.06. Found: C, 63.35; H, 4.11.

It is insoluble in aqueous sodium hydroxide solution (10%) and its alcoholic solution gives with aqueous ferric chloride a deep green color.

Treatment of IIIa with *p*-thiocresol as mentioned above led to the formation of 0.75 g. of IIIc.

(*b*) *Visnagin* (IIIb). The procedure was the same as in the case of IIIa and thiophenol. IIId was obtained, m.p. 155°. It is insoluble in sodium hydroxide solution.

Anal. Calcd. for $C_{12}H_8O_4$: C, 66.66; H, 3.70. Found: C, 66.58; H, 3.70.

Action of ethereal diazomethane on IIIc. To a suspension of 0.5 g. of IIIc in 30 ml. of dry ether and 2 ml. of methanol was added an ethereal solution of diazomethane (prepared from 4 g. of nitrosomethylurea). The cooled reaction mixture was kept aside in the ice chest for 24 hr., and then treated with another amount of freshly prepared ethereal diazomethane solution (from 4 g. of nitrosomethylurea). Then, it was left for 48 hr. at 0°. The solid, so obtained, was collected and the ethereal solution was allowed to evaporate slowly, whereas another crop of colorless crystals was obtained. The whole was crystallized from dilute methanol as color-

(10) B. H. Nicolet, *J. Am. Chem. Soc.*, **53**, 3066 (1931).

TABLE II

THIOL ADDUCTS (VI) FROM 2-ARALKYLIDENE-3(2*H*)-THIANAPHTHENONE-1,1-DIOXIDES (V)

Arylidene Deriv.	Thiol Adduct Ar′ =	Reaction Temp., °C.	M.p., °C.[a]	Yield, %	Solvent for Cryst.[c]	Color with H_2SO_4	Formula	Analysis % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Sulfur Found	Sulfur Calcd.
Vb	C_6H_5	100	116	85	A	Orange-red	$C_{22}H_{18}O_3S_2$	67.00	66.87	4.56	4.32	16.24	16.01
	$C_6H_4CH_3$-*p*	130	156	82	B	Red	$C_{23}H_{20}O_3S_2$	67.65	67.24	4.90	4.73	15.69	15.31
Vc	C_6H_5	120	155	79	B	Orange	$C_{22}H_{18}O_3S_2$	67.00	66.91	4.56	4.55	16.24	15.89
	$C_6H_4CH_3$-*p*	130	182	76	B	Red	$C_{23}H_{20}O_3S_2$	67.65	65.67	4.90	4.84	15.69	15.56
Vd	C_6H_5	100	137	92	B	Red	$C_{22}H_{18}O_3S_2$	67.00	66.69	4.56	4.41	16.24	15.90
	$C_6H_4CH_3$-*p*	100	135	91	A	Red	$C_{23}H_{20}O_3S_2$	67.65	67.59	4.90	4.77	15.69	15.60
Ve	C_6H_5	120	150	87	B	Yellow	$C_{21}H_{15}ClO_3S_2$[b]	60.79	60.81	3.61	3.42	15.44	15.19

[a] Melting points are uncorrected. [b] Calcd. for Cl: 8.56. Found: Cl, 8.32. [c] A, Benzene–petroleum ether (b.p. 50–70°). B, Benzene.

less crystals, m.p. 153° and identified as IIIa (melting point and mixed melting point).

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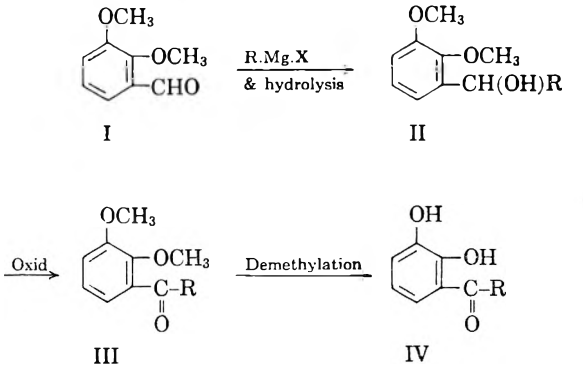
Studies on 3-Acylcatechols

W. I. AWAD, M. F. EL-NEWEIHY, AND S. F. SELIM

Received March 3, 1958

The methods available for the preparation of 3-acylcatechols, which are needed as starting materials in our work, are very limited. The most reliable method is that described by Krannichfeldt[1] for 2,3-dihydroxyacetophenone (IV, R= CH_3) according to the following scheme I–IV.



We have prepared 2,3-dihydroxypropiophenone (IV, R= C_2H_5) and 2,3-dihydroxybutyrophenone (IV, R= *n*-C_3H_7) according to the above scheme. These compounds are pale yellow in color, and give a green color with ferric chloride that changes to red by the addition of sodium carbonate solution, a characteristic color test for catechols.[2,3]

Miller, Hartung, Rock, and Crossley[4] referred to 2,3-dihydroxypropiophenone (IV, R= C_2H_5) as a by-product of the Fries rearrangement of the corresponding catechol diester. The melting point (102.5–103.5°) as reported by these authors[4] does not correspond to the melting point (53°) of the product which we have obtained. The position of the substituents in our products which are prepared by an orthodox method cannot be questioned. This leads us to doubt the correctness of the structure given to the by-product obtained by Miller *et al.*[4]

(1) H. V. Krannichfeldt, *Ber.*, **46**, 4017, 4018 (1913).

(2) Compare Paul Karrer, *Organic Chemistry*, Fourth English Edition, Elsevier Publ. Co., Inc., New York, N. Y., p. 435.

(3) A. Schönberg, W. I. Awad and G. A. Mousa, *J. Am. Chem. Soc.*, **77**, 3850 (1955).

(4) Ellis Miller, Walter H. Hartung, Henry J. Rock, and Frank S. Crossley, *J. Am. Chem. Soc.*, **60**, 7 (1938).

On repeating the experiment described for the Fries rearrangement of catechol dipropionate, we were able to isolate a lower boiling fraction (at approximately the same temperature described in reference 4) and which possessed the same melting point (104–105°) as described by these authors. This product proved to be catechol by melting point and mixture melting point determinations. It is to be noticed that no analytical figures are given for this compound.[4]

EXPERIMENTAL[5]

Preparation of 2,3-dihydroxypropiophenone (IV, R = C_2H_5). (*a*) *Action of ethylmagnesium iodide on 2,3-dimethoxybenzaldehyde.* A solution of the aldehyde (I) (5 g.) in anhydrous ether was added dropwise to the ethylmagnesium iodide (from 6.5 g. ethyl iodide and 0.9 g. magnesium) while cooling in ice. When the addition was complete the reaction mixture was refluxed for 1 hr. and left to stand, at room temperature, overnight. After decomposition with dilute acetic acid and ice, the ethereal layer was shaken with sodium bisulfite solution and then with water. It was then dried (Na_2SO_4), the ether driven off, and the remaining oil distilled to give II (R = C_2H_5) as a colorless liquid, b.p. 108–110°/2 mm., yield 3.9 g.

(*b*) *Preparation of 2,3-dimethoxypropiophenone.* The previously described carbinol (3.5 g.) was added to a mixture of potassium dichromate (7 g.), water (35 ml.), and concentrated sulfuric acid (3.2 g.). The reaction mixture was immediately steam-distilled, and the distillate was extracted with ether, dried (Na_2SO_4), and then the ether was driven off. III (R = C_2H_5) was obtained as a colorless oil b.p. 114°/2 mm. yield 2.48 g.

The *2,4-dinitrophenylhydrazone* derivative was crystallized from ethyl acetate in reddish brown crystals m.p. 219°.

Anal. Calcd. for $C_{17}H_{18}O_6N_4$: N, 14.97. Found: N, 15.20.

The *semicarbazone* was crystallized from methyl alcohol in colorless crystals m.p. 188°.

Anal. Calcd. for $C_{12}H_{17}N_3O_3$; C, 57.35; H, 6.8; N, 16.7. Found: C, 57.39; H, 6.8; N, 16.56.

(*c*) *Demethylation of 2,3-dimethoxypropiophenone* (III, R = C_2H_5). The previously described ketone (III, R = C_2H_5) (2.8 g.) was refluxed with hydriodic acid (sp. gr. 1.96) (11 g.) and an equal volume of glacial acetic acid for 6 hr. The reaction mixture was then poured onto ice and left overnight. The precipitated product was filtered off, dissolved in benzene, and the dark solution treated with charcoal. To the filtrate after concentration, a few drops of petroleum ether (40–60°) were added, whereby 2,3-dihydroxypropiophenone separated out. It was recrystallized from petroleum ether (40–60°) in pale yellow crystals, m.p. 53°, yield 41%. It gave a green color with alcoholic ferric chloride solution which changed to red on the addition of sodium carbonate solution.

Anal. Calcd. for $C_9H_{10}O_3$: C, 65.1; H, 6.1. Found: C, 65.7; H, 6.2.

The *2,4-dinitrophenylhydrazone* derivative was crystallized from ethyl acetate m.p. 229°.

Anal. Calcd. for $C_{15}H_{14}O_6N_4$: N, 16.2. Found: N, 15.7.

Preparation of 2,3-dihydroxybutyrophenone (IV, R = n-C_3H_7). (*i*). *Action of propylmagnesium iodide on 2,3-dimethoxybenzaldehyde.* A solution of the aldehyde (I) (5 g.) in anhydrous ether was added dropwise to propylmagnesium iodide (from 6.2 g. propyl iodide and 0.9 g. magnesium) while cooling in ice. The reaction mixture was treated as in (*a*) and the carbinol (II, R = n-C_3H_7) was obtained as a colorless liquid, yield 3.5 g.

Its *phenylurethane* derivative was crystallized from petroleum ether (60–80°) m.p. 130°.

Anal. Calcd. for $C_{19}H_{23}O_4N$: C, 69.3; H, 7.0; N, 4.25. Found: C, 69.4; H, 7.2; N, 4.4.

(*ii*). *Preparation of 2,3-dimethoxybutyrophenone* (III, R = n-C_3H_7). The above carbinol (II, R = n-C_3H_7) (3.5 g.) was oxidized as previously described in (*b*). It was obtained as a colorless liquid, b.p. 112–113°/0.6 mm., yield 2.5 g.

The *semicarbazone* was crystallized from ethyl alcohol in colorless crystals m.p. 153.5°.

Anal. Calcd. for $C_{13}H_{19}N_3O_3$: N, 15.84; Found: N, 15.99.

(*iii*). *Demethylation of 2,3-dimethoxybutyrophenone.* This ketone (2.1 g.) was similarly treated as in (c) to give 2,3-dihydroxybutyrophenone (IV, R = n-C_3H_7) in pale yellow crystals, "from petroleum ether (60–80°)" m.p. 61°, yield, 0.7 g. It gave a bluish green color with alcoholic ferric chloride solution which turned reddish brown on adding sodium carbonate solution.

Anal. Calcd. for $C_{10}H_{12}O_3$: C, 66.65; H, 6.7. Found: C, 66.5; H, 6.8.

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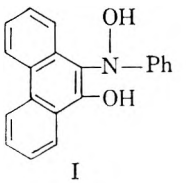
(5) Microanalyses were carried out by Alfred Bernhardt, Germany. Melting points are not corrected.

A Note on the Mode of Addition of Phenyllithium to Phenanthrenequinone Monoxime

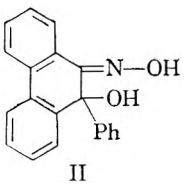
WILLIAM IBRAHIM AWAD AND ABDEL REHIM ABDEL RAOUF

Received April 14, 1958

Mustafa *et al.*[1] claimed that phenanthrenequinone monoxime reacts with phenyllithium by 1,4-addition to give 10-phenylhydroxylamino-9-hydroxyphenanthrene (I).



I



II

The main line of evidence upon which these authors assigned the above structure is that they obtained the same compound (I) by the action of phenylmagnesium bromide on the same oxime,[2] and they verified the identity of the two products by a mixture melting point experiment.

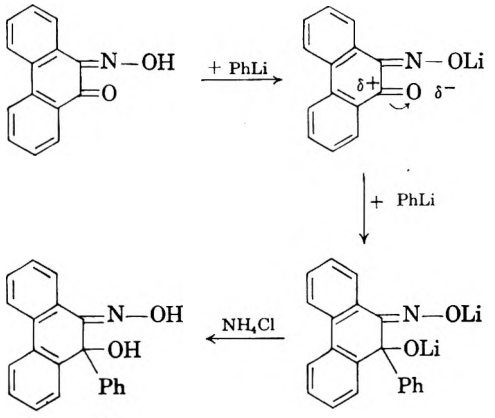
We have proved[3] that the mode of addition of phenylmagnesium bromide to phenanthrenequinone monoxime is 1,2-addition, thus produicng 9-phenyl-9,10-dihydro-10- oximino-9-hydroxyphenanthrene (II). We have now found that when phenyllithium is allowed to react with phenanthrenequinone monoxime, under the same conditions

(1) A. Mustafa, W. Asker, O. H. Hishmat, A. F. A. Shalaby, and M. Kamel, *J. Am. Chem. Soc.*, **76**, 5447 (1954).

(2) A. Mustafa and M. Kamel, *J. Am. Chem. Soc.*, **76**, 124 (1954).

(3) W. I. Awad and A. R. A. Raouf, *J. Org. Chem.*, **23**, 282 (1958).

described by Mustafa *et al.*[1] the same product 9-phenyl-9, 10-dihydro-10-oximino-9-hydroxyphenanthrene (II), is obtained according to the following scheme:



II

The identity of the phenyllithium product and the phenylmagnesium bromide product is again verified by melting point and mixture melting point experiment, as well as by ultraviolet spectrum, λ_{max} (mμ) 254, ϵ_{max} 23990, λ_{max} (mμ) 288, ϵ_{max} 8535, λ_{max} (mμ) 324, ϵ_{max} 1619.

In addition, it is noticed that the addition of organolithium compounds to the α,β-unsaturated ketones is a 1,2-addition even in cases where the organomagnesium compounds add by 1,4-addition.[4-7]

EXPERIMENTAL

Reaction of phenanthrenequinone monoxime with phenyllithium. A solution of phenanthrenequinone monoxime (1 g.) in dry benzene (40 ml.) was treated with phenyllithium (from 16 g. bromobenzene and 1.5 g. lithium). The reaction mixture was kept overnight at room temperature in a nitrogen atmosphere and under reduced pressure. The substance dissolved completely and the color of the solution changed from orange to reddish brown. The reaction mixture was poured slowly into 100 ml. of saturated aqueous ammonium chloride solution, and shaken thoroughly. The ether-benzene layer was separated, dried over anhydrous sodium sulfate, filtered, and evaporated. The solid residue upon crystallization from benzene gave 9-phenyl-9,10-dihydro-10-oximino-9-hydroxyphenanthrene, II, as colorless needles, m.p. 162° undepressed on admixture with a sample of the product from the interaction between phenanthrenequinone monoxime and phenylmagnesium bromide, yield 50%. It gave a blue color with concentrated sulfuric acid and the color then turned to purple.

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(4) H. Gilman and R. H. Kirby, *J. Am. Chem. Soc.*, **55**, 1265 (1933).

(5) A. Lüttringhaus, Jr., *Ber.*, **67**, 1602 (1934). C. F. Koelsch and R. H. Rosenwald, *J. Am. Chem. Soc.*, 59, 2166 (1937).

(6) H. Gilman and F. W. Breuer, *J. Am. Chem. Soc.*, **55**, 1262 (1933).

(7) *Newer Methods of Preparative Organic Chemistry*, Interscience Publishers, Inc., 215 Fourth Ave., New York 3, 1948, pp. 588, 589.

Preparation and Properties of Some Fluorohaloethyl Alkyl Ethers[1]

J. D. PARK, H. L. CUMMINGS, AND J. R. LACHER

Received May 2, 1958

In this study the following olefins were studied under base-catalyzed conditions: CF_2=$CHBr$, CF_2=CFI, CF_2=$CFBr$, CF_2=CH_2 and CF_2=CHI. This and other previously reported works[2] bring to completion the work on the ethers of the type R—O—CF_2—CXYH where X and /or Y is H, F, Cl, Br or I. It was found that CF_2=CH_2 did not react with methanol even under autogenous pressure, while CF_2=CHI (in the form of CF_2Cl—CH_2I) reacted quite readily with methanol but the ether, CH_3—O—CF_2CH_2I could not be isolated. Instead, only $CF_2ICOOCH_3$ was found. In contrast to this, C_2H_5—O—CF_2CH_2I[3] was isolated when CF_2=CHI was treated with ethanol. In the hydrolysis of CH_3—O—CF_2—CHFI we failed to obtain $CH_3OCOCHFI$. Each time the hydrolysis was attempted, the only product isolated was the free acid CHFICOOH. Here again, Seffl[4] reported no difficulty in hydrolyzing C_2H_5—O—CF_2CHFI to $C_2H_5OCOCHFI$ and isolating the ester.

In the present work, no difficulty was experienced in preparing C_2H_5—O—CF_2CH_2Br even after this ether had been in contact with water for moderate periods of time during its isolation and purification. In contrast to this stability, C_2H_5O—CF_2CH_2Cl as shown by others[2(d),5] undergoes hydrolysis to $C_2H_5OCOCH_2Cl$ quite readily when allowed to remain in contact with water even for short periods of time. We are unable to reconcile the differences in hydrolytic stability of the two ethers, $C_2H_5OCF_2CH_2Cl$ and $C_2H_5OCF_2CH_2Br$.

EXPERIMENTAL

The hydrolysis of the ethers, RO—CF_2CXYH, to the corresponding ester, CHXYCOOR, was carried out according to the method of Young and Tarrant.[6]

(1) This paper represents part of a thesis submitted by H. L. Cummings to the Graduate School, University of Colorado, in partial fulfillment of the requirements for the Ph.D. degree.

(2) (a) J. D. Park, K. R. Lea, D. K. Vail, and J. R. Lacher, *J. Am. Chem. Soc.*, **70**, 1550 (1948); (b) J. D. Park, C. M. Snow, and J. R. Lacher, *J. Am. Chem. Soc.*, **73**, 2342 (1951); (c) J. D. Park, W. R. Lycan, and J. R. Lacher, *J. Am. Chem. Soc.*, **73**, 711 (1951); (d) W. E. Hanford and G. W. Rigby, U. S. Patent 2,409,274 (1946); *Chem. Abstr.* **41**, 982 (1947); (e) W. H. Breen, unpublished work, University of Colorado.

(3) J. D. Park, J. Abramo, M. Hein, D. N. Gray, and J. R. Lacher, *J. Org. Chem.*, **23**, 1661 (1958).

(4) R. J. Seffl, unpublished work, University of Colorado.

(5) P. Tarrant and H. C. Brown, *J. Am. Chem. Soc.*, **73**, 1781 (1951).

(6) J. A. Young and P. Tarrant, *J. Am. Chem. Soc.*, **71**, 2432 (1949).

Preparation of C_2H_5—O—CF_2CH_2F. Reaction between CF_2=CHF and ethanol was carried out according to the procedure given in Ref. 2(d). B.p. 33° (253 mm.); n_D^{25} 1.3145, d_4^{25} 1.118.

Anal. Calcd. for $C_4H_7F_3O$: C, 37.51; F, 44.50. Found: C, 37.72; F, 44.3.

Hydrolysis of C_2H_5—O—CF_2CH_2F yielded $CFH_2COOC_2H_5$. B.p. 109° (629 mm.); n_D^{25} 1.3745, d_4^{25} 1.085. (Lit.[7] B.p. 117° at 760 mm.).

Preparation of C_2H_5—O—CF_2CH_2Br. Reaction between CF_2=CHBr and ethanol was carried out according to the method given in ref. 2(a). B.p. 55–56° (104 mm.); n_D^{25} 1.3980, d_4^{25} 1.512.

Anal. Calcd. for $C_4H_7F_2BrO$: C, 25.40; Br, 42.3. Found: C, 25.26; Br, 42.12.

Hydrolysis of C_2H_5—O—CF_2CH_2Br yielded $CH_2BrCOOC_2H_5$. B.p. 82° (55 mm.); n_D^{25} 1.4484, d_4^{25} 1.501. Lit.[8] d_{20}^{20} 1.5059; n_D^{13} 1.45420.

Preparation of CH_3—O—CF_2CHFI. Reaction between CF_2Cl—CHFI and methanol was carried out according to the method given in ref. 2(b). B.p. 59° (107 mm.); n_D^{25} 1.4188, d_4^{25} 2.022.

Anal. Calcd. for $C_3H_4F_3IO$: C, 15.02; F, 23.75. Found: C, 15.12; F, 23.46.

Hydrolysis of CH_3O—CF_2CHFI yielded CHFICOOH but no $CHFICOOCH_3$ m.p. 79.5°. The melting point of this acid has been variously reported as 74°[9] and 78.5–79°.[10]

Anal. Calcd. for $C_2H_2FIO_2$: C, 11.76; F, 9.31; I, 62.25. Found: C, 11.91; F, 9.51; I, 62.32.

Preparation of C_2H_5—O—CF_2—CHFBr. Reaction between CF_2=CFBr and ethanol was carried out according to the method given in ref. 2(a). B.p. 62–62.5° (167 mm.); n_D^{25} 1.3710, d_4^{25} 1.571.

Anal. Calcd. for $C_4H_6BrF_3O$: C, 23.19; F, 27.53. Found: C, 23.30; F, 27.26.

Hydrolysis of C_2H_5—O—CF_2CHFBr yielded $CHFBrCOOC_2H_5$. B.p. 98.5° (138 mm.), n_D^{25} 1.4248, d_4^{25} 1.565.

Anal. Calcd. for $C_4H_6BrFO_2$: C, 25.94; F, 10.27. Found: C, 26.24; F, 10.38.

Hydrolysis of $CHFBrCO_2C_2H_5$ with dilute HCl yielded the acid CHFBrCOOH, m.p. 51.5–52.5°, reported[9] 49°.

Anal. Calcd. for $C_2H_2BrFO_2$: C, 15.31; F, 12.11. Found: C, 15.45; F, 11.80.

Reaction between CF_2Cl—CH_2I and MeOH. Twenty-five grams (0.11 mole) of CF_2Cl—CH_2I and 25 ml. of methanol were placed in a 250 cc., three-neck flask equipped with a stirrer, dropping funnel, and reflux condenser. The reaction mixture was cooled to zero degrees, by means of an external bath, and a ten percent solution of potassium hydroxide dissolved in methanol was added dropwise with stirring. After a ten percent excess of the methanolic base had been added (total, 6.72 g. of potassium hydroxide dissolved in 70 ml. of methanol), the temperature of the reaction mixture was raised to reflux for 30 min., cooled to room temperature, poured into cold water, and the heavy ether layer separated. The crude, washed product was dried over anhydrous calcium sulfate and weighed 15.3 g. (62.2%). During the drying process the crude ether eliminated hydrogen fluoride and upon distillation at reduced pressure 5.96 g. (43.2%) of the ester, $CH_2ICO_2CH_2$, b.p. 90° (54 mm.), was isolated. n_D^{25} 1.5202, d_4^{25} 2.011. No CH_3—OCF_2CH_2I was isolated.

Anal. Calcd. for $C_3H_5IO_2$: C, 18.02; H, 2.52; I, 63.50. Found: C, 18.24; H, 2.38; I, 63.71.

Attempted preparation of CH_3—O—CF_2CH_3. A 50 percent solution of sodium methoxide in anhydrous methanol was introduced into the Parr hydrogenation bomb, and the bomb was sealed and tested for leaks. When leak-free, the bomb was cooled to −80° C, evacuated with a water aspirator, and 64 g. (1.0 mole) of CF_2=CH_2 were forced into the bomb under pressure. The bomb was removed from the cooling bath, placed in the rocker, and allowed to warm slowly to room temperature with constant agitation for about 24 hours. No fluorinated ether was isolated.

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(7) J. C. Bacon, C. W. Bradley, E. I. Hoegberg, Paul Tarrant, and J. T. Cassady, *J. Am. Chem. Soc.*, **70**, 2653 (1948).

(8) W. H. Perkin, *J. Chem. Soc.*, **65**, 427 (1894).

(9) F. Swarts, *Mem. Couronnes Acad. Roy. Belg.*, **61**, 94 (1901); *Chem. Abstr.* II, 12 (1901).

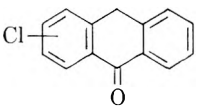
(10) J. D. Park, R. J. Seffl, and J. R. Lacher, *J. Am. Chem. Soc.*, **78**, 59 (1956).

An Unequivocal Synthesis of 3-Chloro-9-Anthrone[1]

F. A. VINGIELLO, P. E. NEWALLIS, AND M. SCHLECHTER

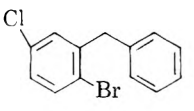
Received May 8, 1958

On reduction of 2-chloroanthraquinone with tin and glacial acetic acid, Barnett and Mathews[2] isolated a pure compound, m.p. 156°, which they designated as 2 (or 3) - chloro-9-anthrone (I). Several years later, Barnett and Wiltshire[3] un-

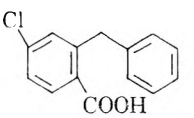


I

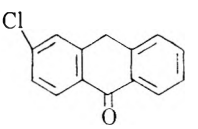
equivocally prepared 2-chloro-9-anthrone, m.p. 155°. Since a melting point of a mixture of these two showed a depression, it was concluded that I was 3-chloro-9-anthrone. In addition to this, a mixture of the acetate of I, m.p. 146°, and 2-chloro-9-anthryl acetate, m.p. 143°, showed a depression in the melting point.



II



III



IV

Since some of bromide II was available,[4] an unequivocal synthesis of IV was undertaken. The Grignard reagent of II was prepared, carbonated, and the adduct decomposed to give acid III. Cyclization of this acid with concentrated sulfuric acid gave 3-chloro-9-anthrone (IV) m.p. 155–156°.[2] Acetylation of IV with pyridine and acetic anhydride yielded 3-chloro-9-anthryl acetate, m.p. 146–146.5°.[3]

(1) This note has been abstracted from the Doctorate thesis of P. E. Newallis presented to the Virginia Polytechnic Institute in 1957.

(2) E. De Barry Barnett and M. A. Mathews, *J. Chem. Soc.*, **123**, 2549 (1923).

(3) E. De Barry Barnett and J. L. Wiltshire, *J. Chem. Soc.*, 1822 (1928).

(4) F. A. Vingiello, G. Buese, and P. E. Newallis, *J. Org. Chem.*, **23**, 1139 (1958).

The results obtained are tenable with those of Barnett and his coworkers.

EXPERIMENTAL

5-Chlorodiphenylmethane-2-carboxylic acid (III). A Grignard reagent was prepared under nitrogen from 8.0 g. (0.028 mole) of 2-bromo-5-chlorodiphenylmethane, 0.68 g. (0.028 mole) of magnesium, *ca.* 100 ml. of anhydrous ether and a crystal of iodine. After all of the magnesium had reacted, the reaction mixture was poured into a slurry of crushed Dry Ice and anhydrous ether. The ethereal solution was treated with dilute sodium hydroxide (trace of charcoal), cooled and filtered. The filtrate was acidified and the white precipitate was filtered. After drying in a desiccator overnight the solid had a melting range of 148–149°, 3.2 g. (46%). Recrystallization from ethanol gave an analytically pure sample, colorless rods, m.p. 149–151°.

Anal. Calcd. for $C_{14}H_{11}ClO_2$: C, 68.16; H, 4.50. Neut. Eq. 247. Found: C, 68.00; H, 4.47. Neut. Eq. 250.

3-Chloro-9-anthrone (IV). A mixture of 0.8 g. (0.00032 mole) of 5-chlorodiphenylmethane-2-carboxylic acid and 3 ml. of concentrated sulfuric acid was shaken vigorously and allowed to stand at room temperature for one hour. The mixture was poured into an ice-water mixture and a light yellow precipitate formed. This was filtered, washed with water, and recrystallized from ethanol yielding crystals which melted at 153–154°, 0.62 g. (83%). Further recrystallization from ethanol raised the melting point to 155–156° (Lit.,[2] m.p. 156°).

3-Chloro-9-anthryl acetate. A mixture of 0.4 g. (0.00018 mole) of 3-chloro-9-anthrone, 15 ml. of pyridine and 3 ml. of acetic anhydride was heated on a steam bath for 2 hr. under a nitrogen atmosphere. This was poured into an ice water mixture which gave a yellow powder which was filtered and recrystallized from ethanol. Fine yellow needles, 0.29 g. (42%) were obtained; m.p. 146–146.5° (Lit.,[3] m.p. 146°). The ethanolic solution displayed a strong blue fluorescence.

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An Ozonide of Cholestenone

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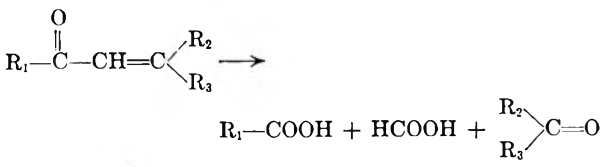
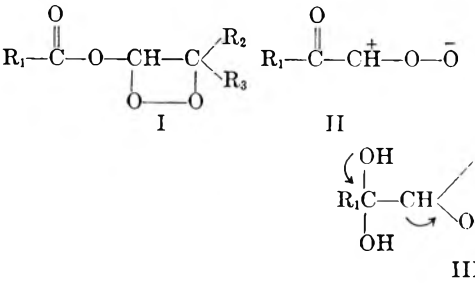
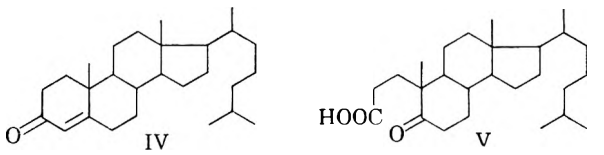
The ozonization of α,β-unsaturated carbonyl compounds occurs with what has been called an "abnormal" course, that is, both the olefinic bond and the adjacent single bond connecting the carbonyl group are cleaved.[1–4] It has been postulated that such a rearrangement occurs (1) through the formation of an abnormal ozonide (I),[1,2] (2) by rearrangement of the intermediate zwitter ion (II),[4] and (3) by abnormal cleavage of a normal ozonide (III) due to the electron release gained by O—H bond heterolysis.[5] In general, in the abnormal





reaction, the product of the reaction of the unsaturated carbonyl compound with ozone is not isolated due to its instability.[1]

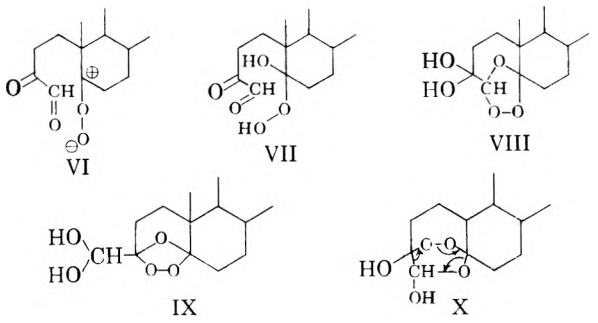
In the course of another investigation, the α,β-unsaturated ketone, cholestenone (IV), was ozonized at −15° in a mixture of aqueous acetic acid and ethyl acetate in order to prepare the *seco-nor-keto* acid (V). By concentration of the reaction mixture a 55% yield of crystalline white solid was



obtained and this material upon melting decomposed to yield the desired acid V. The composition of the initial product was that expected for the addition of one mole of ozone and one mole of water to the starting enone IV. The compound was peroxidic but not hydroperoxidic as shown by a positive test with potassium iodide and a negative test with lead tetraacetate.[6] The molecular weight was that for a monomer and the infrared spectrum possessed bands for hydroxyl groups but lacked band associated with carbonyl absorption. The material when stored in the dry was stable for many weeks but upon standing in air at room temperature gradually decomposed to give rise to the expected *seco-nor* acid V. Warming the material in benzene transformed it into the acid V and formic acid, demonstrating that it is an intermediate in the "abnormal" ozonization.

Based upon the foregoing data, there are at least three structures for a monomeric ozonide derivable from the intermediate hydroxylhydroperoxide VII which would arise by the well-established hydration[4,7] of the zwitterion VI. These structures are

(1) W. G. Young, A. C. McKinnis, I. D. Webb, and J. D. Roberts, *J. Am. Chem. Soc.*, 68, 293 (1946).
(2) J. E. Leffler, *Chem. Revs.*, 45, 385 (1949).
(3) J. Knights and E. S. Waight, *J. Chem. Soc.*, 2830 (1955).
(4) R. Criegee, *Record. Chem. Progr.*, 18, 111 (1957).
(5) D. H. R. Barton and E. Seone, *J. Chem. Soc.*, 4150 (1956).
(6) R. Criegee, *Fortschr. Chem. Forsch.* 1, 536 (1950).
(7) H. Lettre and A. Jahn, *Ann.*, 608, 43 (1957).



VIII, IX, and X, the first two representing hydrates of normal ozonides and the last a hemiketal-acetal. On the basis of the work of Criegee,[8] IX would seem to be the preferred structure since in the presence of a protic solvent cyclic monomeric ozonides appear to form only when a bicyclo-3:2:1-system results. The formation of a stable hydrate of a carbonyl group, however, should only occur if the ozonide linkage is strongly electronegative and from the acid strength of hydrogen peroxide such seems unlikely.

At the present time, structure X would appear to represent the most probable formulation for the product.[9] The decomposition of X to products most likely follows the intramolecular pathway indicated.

EXPERIMENTAL[10]

Ozonization of cholestenone. A solution of 7.78 g. (20.2 mmoles) of cholestenone, 135 ml. of C.P. ethyl acetate, 135 ml. of glacial acetic acid, and 8 ml. of water was cooled in an ice salt bath and then 2.5 mole-equivalents (at 0.5 mmole/min.) of ozone was passed through the solution. After standing at room temperature for 1 hr., the solution began to deposit white crystals and by removal of three fourths of the solvent under reduced pressure (20-mm. pressure at room temperature), a total of 5.0 g. (55%), m.p. 112–115° (dec.), of white crystalline solid was obtained. The crude material was dried for 24 hr. at room temperature under 20-mm. pressure. The dried material first melts at 117° with evolution of gas and then solidifies and remelts at 152–153°, the melting point of authentic seco-keto-acid V.[11] The infrared spectrum possessed bands at 2.94 μ (OH) and at 9.2, 9.5, 9.6 μ (ether—O).

Anal. Calcd. for $C_{27}H_{46}O_5$: C, 71.96; H, 10.29; peroxide, 7.10; mol. wt. 450.6. Found: C, 71.26; H, 10.50; peroxide, 6.86; mol. wt.[12] 439–481.

When the ozonide was heated with benzene and the solvent distilled and collected in an ice-cooled receiver, the residue after recrystallization from hexane amounted to 86% of the expected *seco-nor*-acid, m.p. 150–152°. To the benzene distillate (200 ml.) were added 2 ml. of glacial acetic acid and 4.8 g. of mercuric acetate and the mixture was refluxed for 3 hr. The evolved CO_2 was swept with nitrogen into a gas collection flask containing sodium hydroxide (CO_2-free). Precipitation of CO_2 as $BaCO_3$ with $BaCl_2$ yielded 70% of theory, based upon the oxidation of one mole of formic acid.

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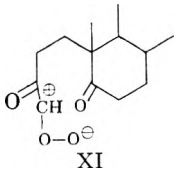
(8) R. Criegee, A. Kerchow, and H. Zinke, *Ber.*, **88**, 1878 (1955).

(9) The alternate zwitterion XI, which would appear to be a less favored intermediate, upon hydration and cyclization would give rise to a similar series of structures. Such structures cannot be differentiated from the above on the basis of the present work.



(10) All melting points corrected. Analyses by the Microanalytical Laboratory, University of California.

(11) R. Tschesche, *Ann.*, **498**, 185 (1932); R. B. Turner, *J. Am. Chem. Soc.*, **72**, 579 (1950).

(12) The mol. wt. determination was kindly performed for us by Professor P. S. Bailey, University of Texas, by the cryoscopic method using dioxane as solvent.

Preparation of Trialkylboranes or Primary Alcohols from Pyridine-Borane and Terminal Olefins

M. Frederick Hawthorne

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Two new synthetic methods for the preparation of trialkylboranes from olefins have recently been described. The first of these consists of treating the olefin with the sodium borohydride–aluminum chloride reagent of Brown and Rao.[1] The second new method is based on the direct addition of diborane to the olefin in diglyme solution at room temperature.[2] The diborane may be introduced as a gas or produced *in situ* by the reaction of sodium borohydride with boron trifluoride. The present paper describes a third method which is probably chemically similar to, but experimentally quite different from the second method above[3] and probably involves the electrophilic attack of thermally produced diborane upon the terminal olefin.

During the course of an examination of the chemistry of amine boranes it was observed that pyridine-borane would react with olefins in diglyme solvent and at temperatures near 100° to produce trialkylboranes. The reaction was conveniently carried out overnight in pressure bottles on the steam bath and with stoichiometric quantities of reactants.

(1) H. C. Brown and B. C. Subba Rao, *J. Am. Chem. Soc.*, **78**, 5694 (1956).

(2) H. C. Brown and B. C. Subba Rao, *J. Org. Chem.*, **22**, 1136 (1957).

(3) It was pointed out by a referee that Dr. R. Koster reported to the Inorganic Division of the XVIth International Congress of Pure and Applied Chemistry, Paris, France, that he had successfully added triethylamine borane to terminal olefins. This is not apparent in the abstracts (page 161) of the meeting.

TABLE I

HYDROBORINATION OF OLEFINS WITH PYRIDINE-BORANE

Olefin	Trialkylborane Yield, %	Analysis % C Calcd.	% C Found	% H Calcd.	% H Found	B.P., °C.	Alkanol Identity	Yield, %	B.P., °C.
1-Octene	82	82.24	81.85	14.67	14.55	166 (1.5 mm.)	1-Octanol	90	190–200
1-Hexene	70	81.18	80.90	14.76	14.66	127 (1.5 mm.)	1-Hexanol	66	155–160
2-Methylbutene-1							2-Methylbutanol-1	71	125–128
2-Methylpentene-1							2-Methylpentanol-1	50	145–150
2,2,4-Trimethylpentene-1	67	82.24	81.95	14.67	14.60	135 (1 mm.)	2,2,4-Trimethylpentanol-1[a]	58	168–170
Styrene							β-Phenylethanol	57	90–92 (6 mm.)
α-Methylstyrene	66	88.03	87.82	9.03	8.80	170 (10 mm.)	2-Phenylpropanol-1	64	125–126 (7 mm.)
Cyclohexene							Cyclohexanol	47	
Cyclopentene	60	82.57	82.20	12.47	12.19	140 (6 mm.)	Cyclopentanol	55	

[a] Characterized as 3,5-dinitrobenzoate, m.p. 73–74° (D. J. Hadley, R. H. Hall, and D. I. H. Jacobs, *J. Chem. Soc.*, 1416 (1954), report m.p. 73–74° for this derivative).

$$C_5H_5NBH_3 + 3\ CH_2{=}CHR \xrightarrow[100°]{\text{diglyme}} C_5H_5NB(CH_2CH_2R)_3$$

$$C_5H_5NB(CH_2CH_2R)_3 \rightleftharpoons C_5H_5N + B(CH_2CH_2R)_3$$

Acidification of reaction mixtures under a nitrogen atmosphere afforded, after extraction and washing, ethereal solutions of the corresponding trialkylborane. The borane was then isolated directly by fractionation or converted by hydrogen peroxide oxidation to the corresponding alcohol. The experimental simplicity of the method was enhanced by the use of pyridine borane, an air stable and essentially nonvolatile material which is easily prepared[4] in quantity if necessary but which is now commercially available.[5]

Table I lists the results of several representative reactions which were carried out with 0.20 mole of olefin and 0.07 mole of pyridine-borane. Several reaction mixtures were worked up to yield the trialkylboranes. In all cases a reaction mixture was directly converted to the primary alcohol by oxidation of the crude trialkylborane with hydrogen peroxide. The purified alcohols were identified by comparison of their infrared spectra with the spectra of authentic samples and by boiling point. In each case the trialkylborane produced was that which arises by addition of the borane fragment to the terminal carbon atom.[6]

The mechanism of this process probably involves the electrophilic addition of thermally produced diborane to the terminal olefin.

(4) M. D. Taylor, L. R. Grant, and C. A. Sands, *J. Am. Chem. Soc.*, **77**, 1506 (1955).

(5) Callery Chemical Co., Pittsburgh, Pa.

(6) H. C. Brown and B. C. Subba Rao, *J. Org. Chem.*, **22**, 1137 (1957) show that such adducts are the more stable and are readily formed.

EXPERIMENTAL

Pyridine-borane was prepared by the method of Taylor, Grant, and Sands[3] and melted at 10–11° after purification by fractional freezing. Material prepared in this manner was successfully stored for a year without signs of deterioration.

The olefins employed were obtained from commercial sources and fractionated before use with a 40-plate spinning band distillation column.

Pressure vessel. At the outset the reaction of pyridine borane with 1-octene was successfully carried out using a simple one-necked flask with a reflux condenser and a nitrogen atmosphere. However, this procedure was quite unsatisfactory when applied to the olefins of low molecular weight and low boiling point due to volatilization of the olefin. Therefore, a sealed system was employed in the form of glass pressure bottle of 200-ml. capacity and equipped with a spring held cap. In larger scale preparations an autoclave could no doubt be used to advantage.

General procedure. To 25 ml. of diglyme which had been dried by distillation from lithium aluminum hydride at reduced pressure under nitrogen was added 6.5 g. (0.07 mole) of pure pyridine-borane and 0.20 mole of the desired olefin. The solution was placed in the pressure bottle and the bottle swept with dry nitrogen and quickly stoppered. The pressure bottle was then placed in a steam bath for a period of 14 hr., cooled to room temperature, and the contents transferred to a separatory funnel equipped with a nitrogen inlet tube. Ice (50 g.) and 200 ml. of water were added followed by 150 ml. of ethyl ether. The mixture was then acidified with 100 ml. of 5*N* hydrochloric acid. Small quantities of hydrogen were evolved during acidification. The ether layer was washed three times with water in a nitrogen atmosphere and dried with magnesium sulphate while in the separatory funnel. The dried ether solution of trialkylborane was then transferred under nitrogen to a spinning band distillation column, the ether distilled, and the residue distilled in vacuum to yield pure trialkylborane.

Oxidation of trialkylboranes with hydrogen peroxide. Alternatively, the wet ethereal solution of trialkylborane was mixed with 50 ml. of 10% aqueous sodium hydroxide solu-

tion and vigorously stirred at the ether reflux temperature as 100 ml. of 20% hydrogen peroxide was added dropwise. After the oxidation step the ether layer was separated, washed with water, and then with a 5% ferrous ammonium sulfate solution until no further coloration of the aqueous layer occurred. The ether layer was then dried over magnesium sulfate and distilled through the spinning band column to yield the pure alcohol.

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The Basicities of Substituted Pyridine-1-oxides. A Reaction Series Requiring Use of σ^+ and σ^- [1]

H. H. JAFFÉ

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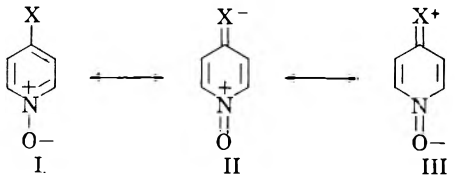
Some years ago we determined and examined the basicities of a series of substituted pyridine-1-oxides.[2] We recognized at that time that resonance between structures I, II, and III was important.[2a] II was expected to make a particularly important



I II III

contribution when X was electron attracting by a tautomeric effect (*e.g.* —NO_2, —COOR), and in the treatment of the data by the Hammett equation[3] we consequently used σ^--values[4] for these substituents. Similarly, we recognized that structure III would make a particularly large contribution to the resonance hybrid when X was capable of electron release by a tautomeric effect (*e.g.* —OR, —NR_2), and we assumed that the failure of the experimental points for 4-hydroxypyridine-1-oxide, 4-aminopyridine-1-oxide, and isoquinoline-1-oxide to fall on the line defined by the plot of the pK_a's[5] of the other compounds *vs.* σ-values was due to this reason. At that time, however, no special substituent constants were available for tautomerically electron releasing substituents in conjugation with electron withdrawing side chains or

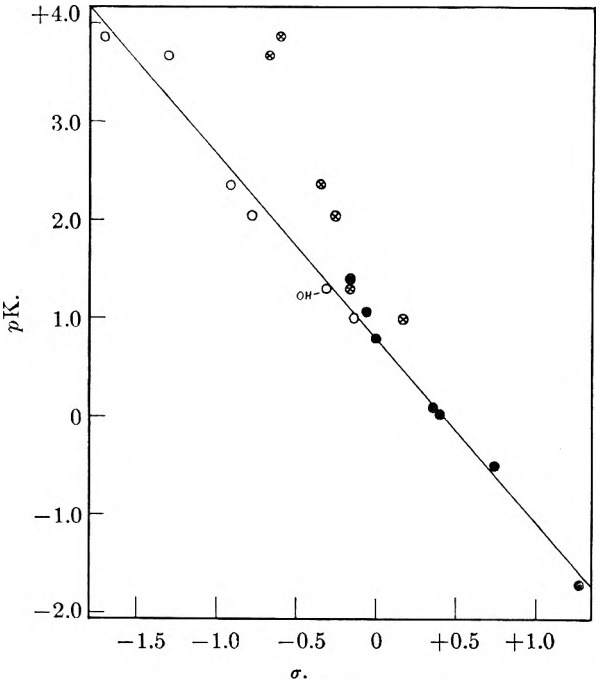


Fig. 1. Plot of the pK_a's of 1-hydroxypyridinium ions against σ. Open circles, σ^+ values; crossed circles, normal σ-values; full circles, normal σ-values or σ^--values for groups for which σ^+ is not applicable

reaction centers, and hence we were unable to adequately deal with the pK's of the three compounds mentioned in terms of the Hammett equation. The recent introduction of such constants (σ^+) by Brown and Okamoto[6] and by Deno and Evans[7] and the discussion of the tautomeric equilibria in 4-hydroxy- and 4-aminopyridine-1-oxides by Gardner and Katritzky[8] have prompted us to re-examine our data.

Fig. 1 shows a plot of our pK_a-values against σ; σ^--values are used for electron withdrawing, σ^+-values for electron releasing substituents. Since the data of Gardner and Katritzky were in reasonable agreement with ours where comparison was possible, their data are included for those compounds which we had not examined. Fig. 1 also shows (as crossed circles) the points for electron releasing substituents using the normal σ-values. The tremendous improvement in the fit resulting from the use of σ^+-values is immediately apparent. The 13 data, which cover a range of more than 5 log units are correlated with $\rho = 1.893 \pm 0.071$, r = 0.992, s = 0.201 $(-\log k°)_{calc.} = 0.812$ in excellent agreement with $pK° = 0.79$. Although the ρ-value is slightly lower than that previously reported, it still bears a striking resemblance to the value applicable to the pK's of phenols. The data of Gardner

(1) This work was supported by the office of Ordnance Research. U. S. Army.

(2) (a) H. H. Jaffé, *J. Am. Chem. Soc.*, **76**, 3527 (1954); (b) H. H. Jaffé and G. O. Doak, *J. Am. Chem. Soc.* **77**, 4441 (1955).

(3) (a) L. P. Hammett, *Physical Organic Chemistry*, McGraw-Hill Book Company, Inc., New York, 1940, Chapter VII; (b) H. H. Jaffé, *Chem. Revs.*, **53**, 191 (1953).

(4) By agreement between Prof. H. C. Brown, R. W. Taft, Jr., N. C. Deno, and the author, the constants designated as σ^* in ref. 3 b are now referred to as σ^-.

(5) As in earlier papers (ref. 2) all basicities are expressed as pK_a's of the conjugate acids.

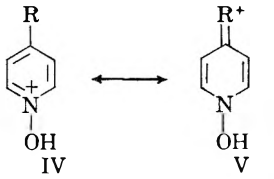
(6) Y. Okamoto and H. C. Brown, *J. Am. Chem. Soc.*, **79**, 1913 (1957); the σ^+ values used are the latest revised values of Prof. Brown.

(7) N. C. Deno and W. L. Evans, *J. Am. Chem. Soc.*, **79**, 5804 (1957).

(8) J. N. Gardner and A. R. Katritzky, *J. Chem. Soc.*, 4375 (1957).

and Katritzky[8] also permit the calculation of σ^+-values for two new groups: $-NHCH_3$, $\sigma^+ = -1.59$; $-OCH_2C_6H_5$, $\sigma^+ = -0.616$.

The basicities of the substituted pyridine-1-oxides are the first reaction series on record which, in the Hammett treatment, require the use of *both* σ^+- and σ^--values. A slightly more detailed discussion seems indicated. Although it was originally suggested that σ^--values were applicable to *all* reactions of anilines and phenols, evidence now appears to accumulate[9] that the requirement is an appreciable *difference* in conjugation of substituent and reaction site between initial and final (in the case of equilibria) or transition state (in the case of rates). Such a difference in conjugation between initial and final states obviously exists for electron releasing X, since it is impossible to write a plausible quinoid structure analogous to II for the conjugate acids. In the case of electron withdrawing X, however, it is suggested that the resonance IV↔V is sufficiently more important than I ↔ III to require use of σ^+-values.



IV V

In our previous paper[2b] we conclude that the tautomeric equilibria between 4-hydroxypyridine-1-oxide and 1-hydroxy-4-pyridone, and between 4-aminopyridine-1-oxide and 1-hydroxy-4-pyridone immine were overwhelmingly in favor of the pyridine rather than the pyridone structure. This conclusion was based on the estimation of the intrinsic basicities of the two pyridine structures by the Hammett equation, using standard σ-values, which lead to pK's for the conjugate acids appreciably *smaller* than the observed values, while in a tautomeric equilibrium of the type under investigation (single acid, tautomeric bases) the observed pK must be *at least as low* as the *lower* of tautomers. We doubted that the intrinsic pK's could have been underestimated by *more* than the discrepancy found.

Gardner and Katritzky[8] have examined the same tautomeric equilibria, and have confirmed our conclusion concerning 4-aminopyridine-1-oxide. They have used the pK's of 4-methoxypyridine-1-oxide ($pK = 2.04$) and of 1-methoxy-4-pyridone ($pK = 2.57$) and of the corresponding benzyl derivatives ($pK = 1.99$ and 2.58, respectively) to estimate the intrinsic basicities of the corresponding hydroxy compounds. These authors found themelves in the same dilemma as we had, since the 4-alkoxy compounds were weaker bases (their conjugate acids stronger acids) by 0.4–0.5 units than the hydroxy compound while the 1-alkoxy-4-pyridones were slightly stronger bases. From these data the authors conclude (rather unconvincingly) that 4-hydroxypyridine-1-oxide must exist as an equilibrium mixture of roughly comparable quantities of the pyridine and pyridone forms. Examination of Fig. 1 shows that the point for 4-hydroxypyridine-1-oxide lies well on the best straight line. Calculations indicate that omission of this datum does not improve the correlation with σ. The inherent accuracy of the Hammett equation is insufficient to accurately evaluate the tautomeric equilibrium constant, or to categorically state that the pyridone form makes no substantial contribution to the tautomeric equilibrium. However, the data lend no support to Gardner and Katritzky's thesis of an *important* contribution from the pyridone structure, but are best interpreted as indicating an equilibrium predominantly in favor of the pyridine form, in agreement with our theoretical calculations.[10]

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(9) R. W. Taft, Jr., private communication.

(10) H. H. Jaffé, *J. Am. Chem. Soc.*, **77**, 4448 (1955).

Metalation of 1-Methylbenzimidazole with *n*-Butyllithium

PEGGY W. ALLEY AND DAVID A. SHIRLEY

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The reaction of 1-methyl-2-*t*-butylbenzimidazole with organolithium reagents has been reported[1] to involve addition across the azomethine linkage. Benzothiazole undergoes either metalation in the 2-position or addition across the azomethine linkage, depending upon the reaction temperature.[2,3] Benzoxazole apparently gives no metalation product with *n*-butyllithium.[3]

Treatment of 1-methylbenzimidazole with *n*-butyllithium at −60°, followed by carbonation, gave 1-methyl-2-benzimidazolecarboxylic acid in 45% yield. The high water solubility of the acid product, prepared previously from the reaction of glyoxylic acid and *N*-methyl-*o*-phenylenediamine,[4] prevented the quantitative isolation of the acid by precipitation with mineral acid from the aqueous layer of the carbonation mixture. A portion of the product was isolated in this manner, but the remainder was obtained as its water insoluble copper (II) complex. This complex is similar to the one

(1) R. C. Elderfield and V. B. Meyer, *J. Am. Chem. Soc.*, **76**, 1891 (1954).

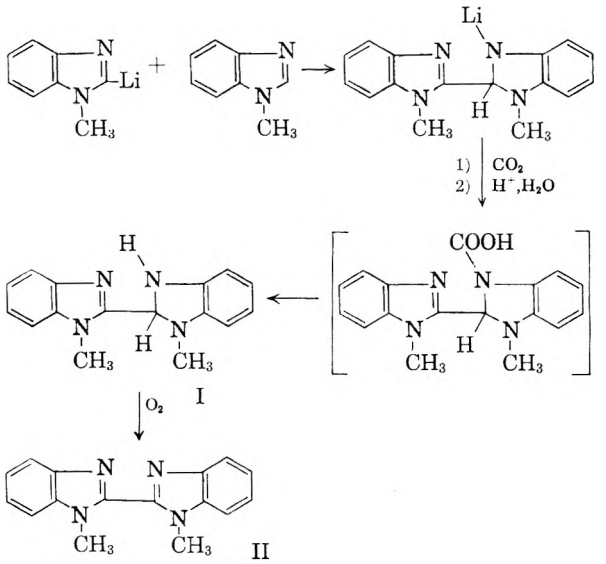
(2) H. Gilman and J. A. Beel, *J. Am. Chem. Soc.*, **71**, 2328 (1949).

(3) J. A. Beel, Doctoral Dissertation, Iowa State College, 1949; *Iowa State Coll. J. of Sci.*, **25**, 161 (1951).

(4) E. H. Usherwood and M A. Whitely, *J. Chem. Soc.*, **123**, 1069 (1923).

formed by 1-methyl-2-imidazolecarboxylic acid.[5] 1-Methyl-2-benzimidazolecarboxylic acid melts with decomposition and evolution of carbon dioxide forming 1-methylbenzimidazole.

When 1-methylbenzimidazole was metalated at room temperature with an excess of *n*-butyllithium, only a trace of acid product was isolated following carbonation. Instead, a mixture of 1,1′-dimethyl-2,3-dihydro-2,2′-bibenzimidazole, I, (m.p. 139–140°) and 1,1′-dimethyl-2,2′-bibenzimidazole, II (m.p. 213–214°), was obtained in total yield of 53.5%. The lower melting material could be converted to the higher by air oxidation. These products apparently arose by initial metalation of 1-methylbenzimidazole followed by addition of 1-methyl-2-lithiobenzimidazole to another molecule of 1-methylbenzimidazole. On acidification, the carbamic acid type decarboxylated to the products as shown in the figure.



EXPERIMENTAL[6]

The following procedure for the preparation of 1-methylbenzimidazole was better in our hands than the reported methods of methylation of benzimidazole.[7,8]

1-Methylbenzimidazole. Benzimidazole (17.5 g., 0.15 mole) moistened with 20 ml. of dry ether was cautiously added to a stirred solution of 3.8 g. of sodium and 0.15 g. of ferric nitrate in 200 ml. of liquid ammonia. The resulting solution was stirred for 15 min. and methyl iodide (24 g.) was added dropwise. The ammonia was allowed to evaporate and 50 ml. of water was added to the residue. The aqueous solution was extracted continuously overnight with ether. The ether was evaporated and the residue dried by distilling benzene from it. The product was fractionally distilled twice *in vacuo*, and 1-methylbenzimidazole was obtained as a colorless solid, b.p. 99–102°/0.5 mm., m.p. 60–61°. The yield of product was 8.0 g. or 40.5%. 1-Methylbenzimidazole is reported to melt at 66°.[8]

Low temperature metalation of 1-methylbenzimidazole. To a solution of 1-methylbenzimidazole (4.3 g., 0.0325 mole) in 130 ml. of dry ether was added at −60° a solution of 0.036 mole of *n*-butyllithium in 40 ml. of ether. The resulting solution was stirred with continued cooling for 3 hr., and the resulting colorless solution was carbonated. The carbonation mixture was hydrolyzed with 50 ml. of water. The ether layer was separated and washed with additional water. The combined aqueous layers were cooled in an ice salt bath and carefully acidified with concentrated hydrochloric acid. The white solid which formed was collected by filtration and dried. The product weighed 1.3 g. A sample of the acid product, after recrystallization from a small amount of water, melted at 93° (dec.). Usherwood and Whitely[4] report the melting point of 1-methyl-2-benzimidazolecarboxylic acid as 98–99° (dec.).

Anal. Calcd. for $C_9H_8N_2O_2$: C, 61.36; H, 4.58; N, 15.90; Neut. eq. 176. Found: C, 60.94, 61.01; H, 4.64, 4.62; N, 16.30, 16.30; Neut. eq. 182.

The filtrate from the 1.3 g. of crude acid product was treated with a concentrated solution of copper sulfate. A light blue water-insoluble powder separated which, after careful washing and drying, weighed 1.70 g.

Anal. Calcd. for $C_{18}H_{14}CuN_4O_4$: C, 52.32; H, 3.41; N, 13.54. Found: C, 52.30; H, 3.27; N, 13.50.

The yield of 1-methyl-2-benzimidazolecarboxylic acid from the acid precipitation and the copper (II) complex was 45%.

Room temperature metalation of 1-methylbenzimidazole. 1-Methylbenzimidazole (10.9 g., 0.0825 mole) in 50 ml. of dry ether was placed in a flask, and a solution of *n*-butyllithium [prepared from 18.5 g. (0.2 mole) of *n*-butyl chloride and 3.0 g. (0.43 g.-atom) of lithium[9]] was added in a dropwise fashion to the stirred solution. The resulting solution was stirred at room temperature for 2.5 hr. At the end of this period the solution was red and a copious amount of greenish yellow solid was present. This mixture was carbonated with solid carbon dioxide and then hydrolyzed with 50 ml. of water. The yellow ether layer was separated and extracted with three 30-ml. portions of water. The basic aqueous extracts were combined with the aqueous layer and the solution was neutralized. At the neutral point a copious amount of precipitate was present, and acidification was stopped when the solution was only faintly acid. The solid was collected by filtration and dried over phosphorous pentoxide *in vacuo*. The product weighed 5.63 g. and melted from 140° to 210°. By fractional crystallization of a portion of this material from absolute ethanol, two products were obtained. The first fraction was the lower melting material, which after recrystallization from acetone melted at 139–140°. Elemental analysis and molecular weight determination indicated an empirical formula of C_4H_4N and a molecular formula of $C_{16}H_{16}N_4$.

Anal. Calcd. for $C_{16}H_{16}N_4$: C, 72.70; H, 6.10; mol. wt. 264. Found: C, 72.80, 72.64; H, 6.13, 5.93; mol. wt. 240 by Rast camphor method.

Elemental analysis of the second fraction, m.p. 213–214°, indicated an empirical formula of $C_8H_7N_2$.

Anal. Calcd. for $C_{16}H_{14}N_4$: C, 73.26; H, 5.38; N, 21.36. Found: C, 73.26; H, 5.16; N, 21.32.

The molar ratio of the lower melting material to the higher melting material was approximately 3:1. Passing oxygen through an acetone solution of the lower melting compound converted it into the higher melting material. The ether layer from the metalation reaction was evaporated and the residue sublimed to produce an additional 0.18 g. of the higher melting product. The lower melting product was assigned structure I, 1,1′-dimethyl-2,3-dihydro-2,2′-bibenzi-

(5) D. A. Shirley and P. W. Alley, *J. Am. Chem. Soc.*, **79**, 4922 (1957).

(6) Microanalyses by Galbraith Microanalytical Laboratories, Knoxville, Tenn., and Weiler and Strauss, Oxford, England. All melting points are uncorrected.

(7) E. Bamberger and J. Lorenzen, *Ann.* **273**, 269 (1893).

(8) M. A. Phillips, *J. Chem. Soc.*, **1931**, 1143.

(9) H. Gilman, E. A. Zoellner, and W. M. Selby, *J. Am. Chem. Soc.*, **54**, 1957 (1932).

midazole, and the higher melting material (II) was designated 1,1′-dimethyl-2,2′-bibenzimidazole. Formation of the bibenzimidazole derivatives occurred in 53.5% yield.

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Acetylation of Imides with Ketene

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Previous studies, in our laboratories, have involved an extension of the acetylation of alcohols, mercaptans, carboxylic acids, glycols, polyhydroxy compounds, amides, hydrocarbons, nitroparaffins, and carbohydrates, with ketene. All of the above classes of compounds are similar in that they contain activated or readily replaceable hydrogen. Ketene is characterized by its ability to form combinations with such organic substances. Although somewhat toxic and difficult to prepare, it ranks first in reactivity among the common acetylating reagents. The predominating advantage of ketene, as compared to acetic acid, acetyl halides, and acetic anhydride, is the fact that it theoretically produces no objectionable by-products.

Since amides have been found to be readily acetylated with ketene to form monoacetyl derivatives,[1] it seemed highly probable, by analogy, that imides could be similarly acetylated to the corresponding *N*-acetyl derivatives. In addition, several similar reactions have been observed during recent years. Rice and coworkers,[2] for instance, prepared *N*-phenyldiacetylimide by passing ketene into acetanilide at 140°. They suggested that *N*-acetylbenzamide was formed similarly from benzamide at 180°, but that it decomposed into benzonitrile as the reaction progressed. Later, Padgham and Polya[3] isolated *N*-acetylbenzamide and diacetylimide by passing ketene into molten benzamide and acetamide, respectively. The use of sulfuric acid in the production of *N*-phenyldiacetylimide from ketene and molten acetanilide was reported by Smirnova[4] and others, who also reported the preparation of *N*-formyldiacetylimide, and described it as a liquid. Our findings, however, indicate that this triacylated ammonia is a crystalline product.[1] For these reasons it seemed desirable to conduct an extended study of the reaction of ketene with any and all available imides.

The first difficulty encountered in this study was the selection of a suitable inert solvent. Among those employed were carbon tetrachloride, benzene, ether, ligroin, dioxane, and chloroform. Hot benzene seemed to be the most efficient solvent for the imides, but it also induced excessive polymerization. Dioxane appeared to be a better solvent but could not be readily removed without causing the acetylated imide to decompose. This was probably due to the formation of peroxides while the dioxane was exposed to air. Also, acetylation was extremely slow when this solvent was employed. A suspension of the imide in carbon tetrachloride yielded maximum acetylation with little or no polymerization.

It was found that the imides could not be acetylated when treated with ketene alone. A catalyst was therefore necessary. Concentrated sulfuric acid has been found, by other investigators, to be a very satisfactory catalyst in similar reactions. When concentrated sulfuric acid was used with the imides, however, no acetylation took place. There was no change in the melting point from that of the parent compound, either before or after the attempted acetylation. Fused sodium acetate produced positive results. The compounds which were unaffected by the ketene in previous attempts, acetylated readily with no noticeable by-products when sodium acetate was used. This catalyst was found to be satisfactory with every imide treated.

This work could be valuable from the standpoint of the organic analytical student, because derivatives of imides are as yet little known. The literature is very sketchy concerning imide derivatives, and they are difficult to prepare. The acetyl derivatives of imides have previously been prepared by reaction with acetic anhydride followed by long hours of refluxing to affect a reaction. The yields are low. Attempts to acetylate imides using acetic acid or acetyl halides have been unsuccessful. Ketene will react readily with the imides producing satisfactory yields in a matter of minutes. The gas can be produced satisfactorily on a laboratory scale. Seven imides, namely naphthalimides, 4-nitrophthalimide, pyromellitic diimide, tetrahydrophthalimide, phthalimide, saccharin, and succinimide; and one anilide, namely acetanilide, have been successfully acetylated with ketene for the first time. Of these, the first four were acetylated for the first time by any means. The other four compounds involved in the study have been previously acetylated by using acetic anhydride. The results are summarized in Table I.

EXPERIMENTAL

The ketene for this study was prepared by the use of a Hurd type "lamp."[5] It was prepared by the pyrolysis of purified acetone. The acetone was vaporized by boiling, and the vapors were passed over an electrically heated wire. It

(1) R. E. Dunbar and Gerald C. White, *J. Org. Chem.*, **23**, 915 (1958).

(2) F. O. Rice, J. Greenberg, C. E. Waters, and R. E. Vollrath, *J. Am. Chem. Soc.*, **56**, 1760 (1934).

(3) D. N. Padgham and J. B. Polya, *Australian J. Sci.*, **13**, 113 (1951).

(4) N. V. Smirnova, A. P. Skoldinov, and K. A. Kocheshkov, *Doklady Akad. Nauk S.S.S.R.*, **84**, 737 (1952).

(5) W. E. Hanford and J. C. Sauer, *Org. Reactions*, III, 108 (1946).

TABLE I

KETENE ACETYLATION PRODUCTS OF IMIDES

Imide Employed	Solvent	Catalyst	Appearance of Acetylated Product	M.P., °C.	Yield, %	Nitrogen, % Theor.	Nitrogen, % Exptl.
Acetanilide[a]	CCl_4	H_2SO_4	White crystals	38[b]	76	7.91	7.65
Naphthalimide	$C_2H_5OC_2H_5$	AcONa	Pink crystals	275–277(dec.)	57	5.86	5.98
4-Nitrophthalimide	CCl_4	AcONa	Yellow crystals	105–107	22	11.96	11.67
Phthalimide	CCl_4	AcONa	Butter-scotch crystals	128–130[c]	18	7.41	7.30
Pyromelliticdiimide	C_6H_6	AcONa	Tan crystals	138–140(dec.)	50	9.34	9.31
Saccharin	C_6H_6	AcONa	White crystals	196–200(dec.)[d]	70	6.23	6.25
Succinimide	hot CCl_4	AcONa	Yellow crystals	38[e]	51	9.93	9.82
Tetrahydrophthalimide	CCl_4	AcONa	White crystals	123–124	27	7.26	7.23

[a] Not an imide but an *N*-phenyl amide. [b] J. J. Sudborough, *J. Chem. Soc.*, 533 (1901), reports a m.p. of 37°. [c] T. W. Evans and W. M. Dehn, *J. Am. Chem. Soc.*, **51**, 3651 (1929), reports a m.p. of 135–136°. [d] A mixed melting point also. [e] C. Djerassi and C. T. Lenk, *J. Am. Chem. Soc.*, **75**, 3493 (1953), reports a m.p. of 40–41°.

was then mixed with the compound to be acetylated in an absorption apparatus[6] that had been previously designed in our laboratories. The compound being acetylated was dissolved in a suitable solvent placed in the absorption apparatus.

The imides for this study were all suspended in carbon tetrachloride, benzene, or ethyl ether at room temperature, with the exception of succinimide, which was suspended in hot carbon tetrachloride. A common catalyst found to be effective with all the imides acetylated was sodium acetate. The imide was weighed out in a 0.03-mole quantity. This, together with 0.03 grams of catalyst, was added to an 80-ml. portion of the solvent in the absorption flask. Ketene was passed through the reaction mixture until an equivalent molar amount had been added. A slight excess was added to ensure complete reaction. After the addition was complete, the mixture was separated from any residue which failed to dissolve. This residue was found in each case to be traces of unreacted parent compound and was, therefore, discarded. The mixture was then cooled and the acetylated imide crystallized out in surprisingly pure form.

All acetylated imides were verified and identified by mixed melting points with samples of the same compounds prepared by other approved means, or by micro-Kjeldahl and micro-Dumas nitrogen determinations.

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(6) A. N. Bolstad and R. E. Dunbar, *Ind. Eng. Chem., Anal. Ed.*, 18, 337 (1946).

The Structure of Amidoximes[1]

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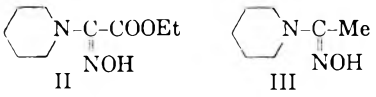
Amidoximes result primarily from the action of hydroxylamine on cyanides or the amination of hydroxamic acid chlorides with amines or ammonia. Neither the method of synthesis nor the reactions, however, permit a distinction between the isomeric structures Ia and Ib.

Ia Ib

For this purpose the infrared absorption spectra of a few selected amidoximes have been compared with those of authentic oximino compounds of similar structure and with amidoximes derived from secondary amines (II and III) which can only possess structures corresponding to Ib.



II III

A recent investigation of a series of amidoximes has described infrared absorption bands for these compounds which were assigned to NH stretching, OH stretching, NH deformation, C=N stretching, and N—O stretching.[2]

Similar bands have been observed in the present investigation (Table I). The broad bands in the region of 3.04–3.22 μ are probably due to associated NH and OH. They are much weaker in dilute solutions while the monomer bands at 2.80–2.93 μ are increased in intensity.

Strong bands at 5.95–6.24 μ are assigned to C=N stretching. Theoretical considerations permit the

(1) This work was performed under the auspices of the U. S. Atomic Energy Commission.

(2) J. Barrans, R. Mathis-Noël, and F. Mathis, *Compt. rend.*, 245, 419 (1957).

TABLE I

INFRARED ABSORPTION SPECTRA OF AMIDOXIMES AND OTHER OXIMINO COMPOUNDS

Compounds	OH	OH	C=O	C=N	C—O—C	
		Amidoximes				
HN=CHNHOH	2.89	3.20[a]	..	5.95[b]	..	[c]
HONH—C(=NH)COOEt	2.88	3.16[a]	5.80	6.01[d]	8.19	[e]
III	2.84	3.12	..	6.17	..	[e]
II	2.81	3.09	5.77	6.21	8.16	[e]
		Oximino Acids				
$CH_3C(=NOH)COOH$	..	3.04	5.78	6.15	..	[c]
$C_2H_5C(=NOH)COOH$	..	3.04	5.78	6.14	..	[c]
$N\equiv CC(=NOH)COOH$	2.92	3.22	5.74	6.15	..	[c]
		Oximino Esters				
HON=CHCOOEt	2.84	3.04	5.79	6.14	8.00	[e]
$CH_3C(=NOH)COOEt$	2.85[sh]	3.12	5.82	6.16	8.75	[e]
$C_2H_5C(=NOH)COOEt$	2.82	3.10	5.81	6.16	8.70	[e]
HON=CClCOOEt	2.86[sh]	3.06	5.75	6.24	7.81	[e]
$N\equiv CC(=NOH)COOEt$	2.86	3.12	5.75	6.24	7.74	[e]
$CH_3COC(=NOH)COOEt$	2.83	3.16	5.73	6.14	8.15	[e]

[a] Probably combined OH and NH absorption. [b] In KBr (0.5%) the C=N band occurred at 5.96 μ. [c] 2% solution in acetonitrile. [d] In KBr (0.5%) the C=N band was found at 5.99 μ. [e] 5% solution in chloroform. *sh* = shoulder.

TABLE II

INFRARED ABSORPTION SPECTRA OF ETHYL AMINO-OXIMINOACETATE

Compounds	Solvent[a]	OH	OH[b]	C=O	C=N	NH	C—O—C
Hydrochloride	MeCN	[c]	3.18	5.65	5.85	6.21	8.08
Ester	MeCN	2.96	[c]	5.78	6.02	6.36	8.16
Ester	KBr[d]	2.89	3.18	5.80	5.99	6.37	8.11
Ester	$CHCl_3$	2.88	3.16	5.80	6.01	6.41	8.19
Ester	MeOH	[c]	[c]	5.78	6.04	6.40	8.30
Ester	$(CH_2)_5NH$	2.93	3.09	5.80	6.04	6.35	8.33
Sodium salt	KBr[d]	[c]	[c]	5.86	6.20	6.40	8.26

[a] Determined in concentrations of 5 and 10%. [b] Probably combined OH and NH absorption. [c] These bands could not be observed. [d] Potassium bromide pressing, 0.5 mm. thick, concentration 0.5%.

conclusion that the C=N frequency for C=NH compounds will be found at values about 40 $cm.^{-1}$ higher than that for similarly constituted C=NOH compounds.[3] The results show that oximino compounds including the amidoximes II and III have C=N stretching bands at 6.14–6.24 μ. Formamidoxime, ethyl amino-oximinoacetate (I, R=H and COOEt), and a series of other amidoximes (I, R = alkyl and aryl),[2] however, absorb at 5.95–6.02 μ, *i.e.* approximately at the predicted wave length for C=NH compounds both in neutral solution and in the solid state.

The formation of the sodium salt of ethyl amino-oximinoacetate by reaction with sodium alkoxides is accompanied by a shift of the C=N stretching band from 6.01 to 6.20 μ (Table II), corresponding to an isomerization from the imino structure Ia to the oximino structure Ib, presumably due to the greater acidity of the latter. In neutral or acid solvents, in piperidine, and in the solid state the C=N band for this ester is found at values below 6.05 μ and the compound is best represented by the imino structure Ia. The assignments of the C=N frequencies are in agreement with the literature values.[4]

Unsubstituted amidoximes I (a or b) have NH deformation bands of medium intensity at 6.2–6.4 μ (see also ref. 2) which must be absent in amidoximes corresponding to structures II and III. Absorption bands at 10.50–10.87 μ, assigned to N—O stretching,[2,5] occur in all amidoximes which have been examined.

It may be concluded that the infrared evidence favors the imino structure Ia rather than the oximino structure for the unsubstituted amidoximes except in strongly basic solutions.

Subject to the usual limitations of deducing structure from reactions, this conclusion is further indicated by the action of formaldehyde on amidoximes. Ethyl amino-oximinoacetate (I, R = COOEt) fails to react to any appreciable extent with formaldehyde in aqueous solution. Formamidoxime (I, R = H), on the other hand, gives a good yield of a

(3) Calculations from force constants by E. Dan Loughran, Los Alamos Scientific Laboratory.

(4) S. Califano and W. Lüttke, *Z. physik. Chem., N.F.*, **5**, 240 (1955); **6**, 83 (1956); J. Fabian, M. Legrand, and P. Poirier, *Bull. soc. chim. France*, **10**, 1499 (1956); G. Duyckaerts, *Bull. soc. roy. sci. Liege*, **21**, 196 (1952).

(5) A. Palm and H. Werbin, *Can. J. Chem.*, **32**, 858 (1954).

crystalline alcohol, which is stable at 0° but is gradually dehydrated at 25°. The dehydration can be accelerated in boiling benzene and the formed water removed as benzene azeotrope. The dehydration product is a polymer rather than a trimethylenetriamine derivative which is the expected product if formaldehyde reacts with the amide nitrogen of structure Ib.

Compounds II and III have been prepared by amination of the respective hydroxamic acid chlorides with piperidine.

EXPERIMENTAL[6]

Formamidoxime, ethyl amino-oximinoacetate, α-oximino esters, and α-oximino acids were prepared according to literature methods. It was found, however, that ethyl amino-oximinoacetate could be prepared much more easily by amination of ethyl chloro-oximinoacetate.

Ethyl amino-oximinoacetate. Ethyl chloro-oximinoacetate (1.0 g., 0.0066 mole), dissolved in 50 ml. of dry ether, was treated with dry ammonia gas at 0°. The precipitated ammonium chloride was filtered with suction and the filtrate was evaporated under reduced pressure. The crystalline residue, m.p. 97–98°, weighed 0.51 g. (58%) and did not depress the melting point of authentic material.

The *sodium salt* was obtained as a yellow solid in 97% yield by evaporating an ethanol solution of the ester (0.002 mole) and sodium ethoxide (0.002 mole) in a high vacuum at room temperature.

Anal. Calcd. for $C_4H_7N_2NaO_3$: Na, 14.92. Found: Na, 15.08.

Ethyl piperidino-oximinoacetate (II). Ethyl chloro-oximinoacetate (2.0 g., 0.014 mole) in 100 ml. of dry ether was treated with shaking at 0° with a solution of piperidine (2.4 g., 0.028 mole) in 50 ml. of ether. The precipitated hydrochloride was filtered after 0.5 hr. at 0° and 1.5 hr. at 25° and the filtrate was evaporated under reduced pressure. The pale yellow oil (2.7 g., 96%) was distilled from a molecular still and boiled at 120° (0.05 mm.), n_D^{25} 1.5042, yield 1.26 g.

Anal. Calcd. for $C_9H_{16}N_2O_3$: C, 53.99; H, 8.05; N, 14.00. Found: C, 54.60; H, 8.13; N, 13.79.

Hydroxymethylformamidoxime. Formamidoxime (3.0 g., 0.05 mole) was dissolved in 5 ml. of water and 5 ml. of 95% ethanol. To this solution was added with stirring formalin (5 ml., 0.06 mole) and the warm mixture was cooled to 0°. The solid mass was diluted with an equal volume of 95% ethanol, filtered, washed with ethanol and ether, and dried, yielding 2.8 g. (62%), m.p. 102–103° (dec.), λ(C=N) 5.95 μ, λ(NH def.) 6.31 μ. OH, NH, and CH stretching bands were not resolved in KBr.

Anal. Calcd. for $C_2H_6N_2O_2$: C, 26.67; H, 6.71; N, 31.11. Found: C, 26.26, 26.24; H, 6.74, 6.67; N, 31.07.

The solid alcohol was stable at 0° but liquefied on standing at room temperature over a period of several weeks. The infrared spectrum of the product was identical with that of the polymer below.

Poly(methyleneformamidoxime). Hydroxymethylformamidoxime (0.53 g., 0.0059 mole) was suspended in 25 ml. of benzene and refluxed over a water trap for 24 hr. A red insoluble resin separated from solution and a drop of water collected in the trap. The resin weighed 0.42 g. (98%) and had broad bands in the infrared at 3.15 μ (CH), 6.01 μ (C=N), and 13.0 μ. It was insoluble in acetone (suggesting cross-linking), benzene, and chloroform.

Anal. Calcd. for $C_2H_4N_2O$: C, 33.32; H, 5.59; N, 38.89. Found: C, 32.87, 33.56; H, 6.84, 6.72; N, 38.83, 39.39.

(6) Microanalyses by M. J. Naranjo. All temperatures are uncorrected.

Infrared absorption spectra were determined with a Perkin-Elmer Model 21 spectrophotometer with sodium chloride prisms in matched cells of 0.1-mm. path length for solutions and in KBr pellets of 0.5-mm. thickness for solids.

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Mechanism of Reduction of Alkylmercuric Salts with Sodium Stannite

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Three methods generally employed to reduce alkylmercuric salts to dialkylmercury compounds are the following:

$$2\ RHgX \longrightarrow R_2Hg$$

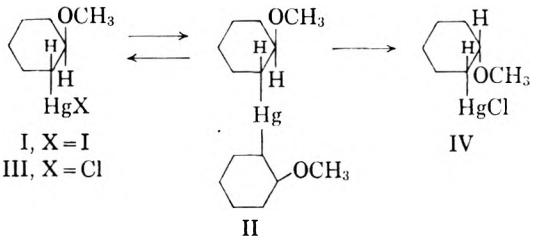
1. N_2H_4
2. $Na_2S_2O_3$
3. Na_2SnO_2

The first has been shown to result in racemization about the carbon-mercury bond, suggesting formation of free radical intermediates.[1,2] The second method, applied to 3-bromomercuricamphor,[2] gives rise to retention of configuration, suggesting an S_E2 mechanism.[3] Using the third method, Sand[4] isolated an intermediate mercurous compound R-HgHgR which decomposed to R_2Hg on heating. For this transformation of the mercurous intermediate to R_2Hg and mercury one can visualize either some type of rearrangement process involving retention of configuration or a free radical mechanism permitting racemization, such as the following:

$$RHgHgR \longrightarrow RHg\cdot + Hg + R\cdot$$

$$RHg\cdot + R\cdot \longrightarrow RHgR$$

In this connection the reduction of *trans*-2-methoxycyclohexylmercuric iodide (I) is of interest.



trans-2-Methoxycyclohexylmercuric iodide (I) was reduced to a dialkylmercury II, which was not examined directly, but was converted with mercuric

(1) G. F. Wright, *Can. J. Chem.*, **30**, 268 (1952).

(2) O. A. Reutov and Tsin-Chzhu Lu, *Doklady. Akad. Nauk. S.S.S.R.*, **110**, 575 (1956); *Chem. Abstr.*, **51**, 8042 (1957).

(3) S. Winstein, T. G. Traylor, and C. S. Garner, *J. Am. Chem. Soc.*, **77**, 3741 (1955).

(4) J. Sand, *Ber.*, **34**, 2913 (1901).

chloride to methoxycyclohexylmercuric chloride. Since electrophilic substitution by mercuric chloride on 2-methoxycyclohexylmercury compounds in ether is known to proceed with retention of configuration,[3] the configuration of the final 2-methoxycyclohexylmercuric chloride may be used as a guide to the configuration of the dialkylmercury II.

The 2-methoxycyclohexylmercuric chloride produced from the dialkylmercury II proved to be a mixture of the *trans*- and *cis*-isomers III and IV, quite analogous to the mixture obtained by Wright from the use of hydrazine.[1] The *trans*-isomer III crystallized directly from the reaction mixture in relatively pure form. The *cis*-isomer IV was obtained in pure form by treatment of the residual methoxycyclohexylmercuric chloride with hot acetic acid, taking advantage of the much greater rate of elimination displayed by the *trans*-compound compared to the *cis*-isomer.[3]

Retention of configuration is not complete during conversion of 2-methoxycyclohexylmercuric iodide (I) to dialkylmercury II with sodium stannite, the most likely explanation being that intermediate methoxycyclohexyl free radicals are involved. The *cis*-2-methoxycyclohexylmercuric chloride (IV) represented *ca.* 15% of the product from mercuric chloride cleavage of the dialkylmercury II, less than the figure of 25% which would result if the methoxycyclohexyl radical showed equal preference for *trans*- or *cis*-configurations in the bond-making step of the reaction leading to dialkylmercury II. While some preference for the *trans*-configuration seems indicated, more quantitative interpretation is precluded by the low yield of dialkylmercury II obtained from reduction of *trans*-2-methoxycyclohexylmercuric iodide (I).

EXPERIMENTAL

A 45 g. (0.1 mole) quantity of I was treated with excess sodium stannite by a standard procedure.[5] The resulting crude liquid II, testing negatively for halogen, was obtained in 13% yield. From treatment of this material with an equivalent quantity of mercuric chloride in 40 ml. of ether was obtained an 89% yield of mixed 2-methoxycyclohexylmercuric chlorides III and IV, m.p. 92–106°, m.p. 88–106° after one recrystallization from methanol.

The treatment of the di-(methoxycyclohexyl)mercury(II) with mercuric chloride was repeated using 4.6 g. of II and 2.94 g. of mercuric chloride in *ca.* 75 ml. of technical grade ether. After 3 min. at room temperature, 2.40 g. of a rather pure white solid crystallized out, m.p. 111–112°, mixed m.p. with authentic III 111–112°, mixed m.p. with authentic IV 87–92°. When the ethereal filtrate was evaporated to dryness, 4.94 g. of a solid containing only traces of mercuric chloride was obtained. A 0.78-g. sample of this residue was heated in 3 ml. of glacial acetic acid to 100° for 5 min. Then the resulting solution was poured into 50 ml. of 6*N* sodium hydroxide, mercuric oxide precipitating and the *cis*-mercurial IV being converted to the soluble hydroxide. After removal of the mercuric oxide by centrifugation, the alkaline supernatant was poured into a solution of 2 g. of sodium chloride in 20 ml. of water and acidified with glacial acetic acid. The white solid which precipitated weighed 0.125 g. (11%) and melted at 108.5–111°, mixed m.p. 112–113° with authentic IV, mixed m.p. 88–95° with III. The material gave a negative test[3] for III.

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(5) S. Winstein and T. G. Traylor, *J. Am. Chem. Soc.*, **77**, 3751 (1955); See preparation of di-*s*-butylmercury.

Concerning the Synthesis of Methyl (11-Deoxycorticosteron-21-yl 2,3,4-Tri-*O*-acetyl-β-D-glucosid)uronate

W. Werner Zorbach

Received May 26, 1958

In response to a need for a water-soluble derivative of 11-deoxycorticosterone (I), the preparation of a 21-glucosiduronic acid was undertaken. The preparation of the 21-glucoside of I has been previously reported,[1] as well as the 21-glucosides of both cortisone and 17α-hydroxy-11-deoxycorticosterone[2]; however, the solubility in water of these derivatives is limited.

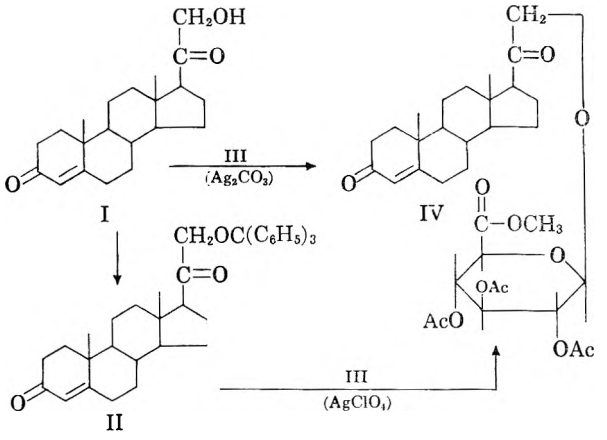
Particularly significant is the coupling of methyl 2,3,4-tri-*O*-acetyl-1-bromo-1-deoxy-α-D-glucuronate (III) with 21-acetoxy-3α,17α-dihydroxypregnane-11,20-dione.[3] The protecting groups were not removed, however, and the glucosiduronate thus secured was compared directly with the methylated and fully acetylated derivative of the glucosiduronic acid recovered from the urine after administration of 3α,17α,21-trihydroxypregnane-11,20-dione. This work strongly supports the general belief that conjugation of glucuronic acid with metabolic reduction products of corticoids, as well as of certain steroid hormones, takes place at C(3). Reported also is the synthesis of the 3,21-bis(methyl 2,3,4-tri-*O*-acetyl-β-D-glucosiduronate) of 3β,17α,-21-trihydroxy*allo*pregnan-20-one.[4] Both of these, however, are conjugates of inactive corticoids. The preparation of a 21-glucosiduronic acid of 11-deoxycorticosterone (I) would be of especial interest for I is an active corticoid; further, the attachment of the glucuronic acid would be at a point other than C(3). Such a derivative might, therefore, display interesting biological properties.

(1) (a) W. S. Johnson, *J. Am. Chem. Soc.*, **63**, (1941); (b) K. Miescher, W. H. Fischer, and C. Meystre, *Helv. Chim. Acta*, **25**, 40 (1942).

(2) C. Meystre and K. Miescher, *Helv. Chim. Acta*, **34**, 2286 (1951).

(3) J. J. Schneider, M. L. Luobart, P. Levitan, and S. Lieberman, *J. Am. Chem. Soc.*, **77**, 4184 (1955).

(4) H. H. Wotiz, J. H. Leftin, E. Smakula, and N. N. Lichtin, Abstracts, Div. Biol. Chem., American Chemical Society 131 National Meeting, April 1957, p. 58C.



Treatment of 11-deoxycorticosterone with methyl 2,3,4-tri-*O*-acetyl-1-bromo-1-deoxy-α-D-glucuronate (III) under conditions essentially the same as described by Meystre and Miescher[2] in their modification of the Königs-Knorr synthesis gave 52% of methyl (11-deoxycorticosteron-21-yl 2,3,4-tri-*O*-acetyl-β-D-glucosid)uronate (IV). Attempts, however, to secure a crystalline 21-glucosiduronic acid of I were unsuccessful. Removal of the blocking groups from the sugar moiety of IV by various hydrolytic measures always resulted in a hygroscopic glass-like material, which could not be brought to a state of sufficient purity for a satisfactory analysis. Attempts to determine the neutral equivalent of the amorphous material resulted in values which deviated 10–15% from the calculated value. The substance gave an acid reaction, was extremely soluble in water, and reacted with diazomethane to give a methylated derivative which was likewise amorphous.

An alternate route to IV was investigated in which application of an ingenious oligosaccharide synthesis, recently described by Bredereck and coworkers,[5] was made. Thus, by converting I to 21-trityloxyprogesterone (II) and allowing the latter to react with molar equivalents of III and of silver perchlorate at 0°, IV was obtained and subsequently identified by ultraviolet and infrared spectral comparisons. Although this reaction was virtually instantaneous, yields were of a very low order. In spite of this, the latter method may have some value, particularly in cases where heat-sensitive acylglycosyl halides are involved. Extension of this work relative to the preparation of the 21-glucosiduronic acid derivatives of other active corticoids is in progress in this laboratory.

EXPERIMENTAL

All melting points were determined using a Kofler hot-stage.

Methyl (11-deoxycorticosteron-21-yl 2,3,4-tri-O-acetyl-β-D-glucosid) uronate (IV) *via the Königs-Knorr Syntheses.* To a magnetically stirred solution of 500 mg. (1.5 mmole) of 11-deoxycorticosterone (I) in 80 ml. of anhydrous carbon tetrachloride was added 1450 mg. of dry silver carbonate. By heating the flask and contents in an oil bath, approximately one-half of the solvent was caused to distill over at a moderate rate. The flask was then fitted with a graduated dropping funnel which contained a solution of 1500 mg. of methyl 2,3,4-tri-*O*-acetyl-1-bromo-1-deoxy-α-D-glucuronate (III) in 40 ml. of anhydrous carbon tetrachloride. This was added drop-wise to the stirring mixture in the flask over a period of 1 hr., during which time the solvent from the reaction flask was permitted to distill over at the same rate. Finally, the temperature of the bath was adjusted so that an additional 20 ml. of the solvent distilled over during a period of 40 min.

To the material remaining in the flask was added 20 ml. of acetone and a small amount of Darco. The solution was filtered by suction and evaporated *in vacuo* at 40°, yielding a syrupy residue which was triturated with ether-ethanol (1-1). The crude crystalline material thus obtained was recrystallized three times from absolute ethanol giving 511 mg. (52%) of material melting at 201–207.5°. Repeated crystallization from absolute ethanol gave pure IV, m.p. 205–207.5°, $[\alpha]_D^{20°}$ +68° (c 2.0, $CHCl_3$), λ_{max}^{alc} 240 mμ (4.2).

Orientation at the glycosidic linkage in IV was determined by the method of molecular rotational additivities according to Klyne.[6] Calcd. for [M] [11-deoxycorticosterone (I) + [M] [methyl (methyl 2,3,4-tri-*O*-acetyl-α-D-glucosid) uronate][7a]: +587° + 605° = +1192°. Calcd. for [M] (I) + [M] [methyl (methyl 2,3,4-tri-*O*-acetyl-β-D-glucosid) uronate][7b] +587° − 101° = +486°. Found for [M] (IV): + 439°. The glycosidic linkage in IV has, therefore, the β configuration.

Anal. Calcd. for $C_{34}H_{46}O_{12}$: C, 63.18; H, 7.13. Found: C, 62.89; H, 7.26.

21-Trityloxyprogesterone (II). To a solution of 990 mg. (3.0 mmole) of 11-deoxycorticosterone (I) in 3.0 ml. of anhydrous pyridine was added 921 mg. of trityl chloride. The solution was warmed on a steam bath (under exclusion of moisture) for 3 hr., then extracted successively with *N* sulfuric acid, dilute sodium bicarbonate, and water. The dried extract was evaporated *in vacuo* at 40°, the oily residue triturated with absolute ethanol, and the resulting crystalline material recrystallized once from the same solvent, yielding 1161 mg. (67%) of material melting at 168–172°. Repeated recrystallization from dry 2-propanol gave analytically pure 21-trityloxyprogesterone (II), m.p. 170–173°, $[\alpha]_D^{20°}$ +90.2°.

Anal. Calcd. for $C_{40}H_{44}O_3$: C, 83.87; H, 7.74. Found: C, 83.57; H, 7.89.

The conversion of 21-trityloxyprogesterone (II) to IV. To a solution of 191 mg. (0.33 mmole) of II and 69 mg. (0.33 mmole) of silver perchlorate in 4 ml. of pure, anhydrous nitromethane previously cooled to 0°, was added a solution of 132 mg. (0.33 mmole) of the bromide III in the same solvent. The mixture was filtered immediately to remove insoluble by-products, the filtrate dissolved in methylene chloride, and extracted rapidly with aqueous sodium bicarbonate. After drying over sodium sulfate, the extract was evaporated *in vacuo* at 40° and the oily residue dissolved in a small amount of absolute ethanol. By refrigerating for 24 hr., 11 mg. (5%) of IV was secured which, when recrystallized twice from absolute ethanol, melted at 205.5–208°, λ_{max}^{alc} 240 mμ (4.2). When admixed with a specimen obtained in the foregoing preparation, no depression in the melting point was observed. The ultraviolet and infrared spectra of IV prepared by the two routes were identical in all respects.

(5) H. Bredereck, A. Wagner, and G. Faber, *Angew. Chem.*, **69**, 438 (1957).

(6) W. Klyne, Proc. Biochem. Soc., 288 Meet., *Biochem. J.*, **47**, xli (1950).

(7) E. Hardegger and D. Spitz, *Helv. Chim. Acta*, (a) **32**, 2165 (1949); (b) **33**, 337 (1950).

Acknowledgments. The author is indebted to Mr. Harold K. Miller and Mrs. Anne H. Wright for preparing the infrared and ultraviolet spectra, respectively. For the combustion analyses, he wishes to thank Miss Paula M. Parisius of this Institute's Microanalytical Laboratory, under the direction of Dr. W. C. Alford. He is especially grateful to Dr. Erich Mosettig for his interest and encouragement during the course of this investigation.

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Desulfurization of Thiiranes with Triethyl Phosphite

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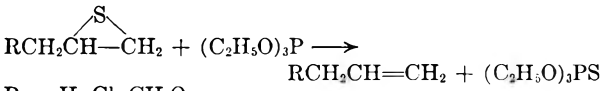
Recently Scott has reported[2] that the reaction of ethylene oxides with triethyl phosphite, results in the reduction of the epoxide to the corresponding olefin and oxidation of the phosphite to phosphate. For example, when equivalent amounts of triethyl phosphite and either ethylene or propylene oxide were heated in a stainless steel bomb at 150–175° for several hours, high yields of the corresponding olefin and triethyl phosphate were obtained.

In the course of recent investigations in these laboratories concerned with the synthesis and ring opening reactions of unsymmetrically substituted thiacycloalkanes, it was observed that heating an equimolar mixture of triethyl phosphite and a thiirane at its reflux temperature for a short period of time resulted in the formation of triethyl thionophosphate with the simultaneous conversion of the thiirane to its corresponding unsaturated compound.

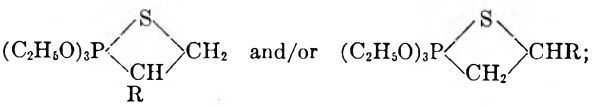


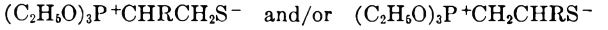
Preliminary results indicate that a wide variety of thiiranes are susceptible to this desulfurization process. In each instance, the reaction yields, within experimental limits, quantitative amounts of triethyl thionophosphate and the unsaturate under much milder conditions than those employed with the oxygen analogs.

(1) Abstracted in part from the doctoral thesis of R. L. Jacobs.

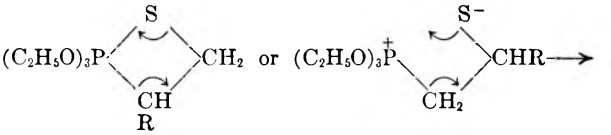
(2) C. B. Scott, *J. Org. Chem.*, **22**, 1118 (1957).

With regard to the reaction of thiiranes with triethyl phosphite, a mechanistic interpretation similar to that offered by Scott[2] may be applicable. Thus, a nucleophilic attack by phosphite on either ring carbon atom could produce intermediates such as the following

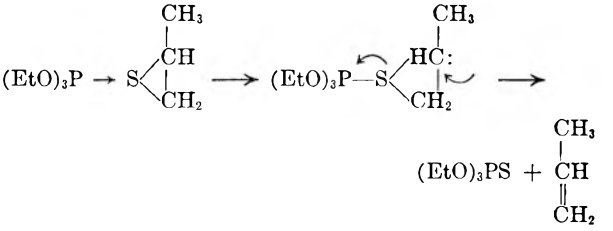




A subsequent rearrangement of such intermediates could then account for the observed products



However, while the above mechanism would satisfactorily account for the observed products, the recent work of Bordwell[3] and collaborators on 1,2 elimination reactions of thiacyclopropanes with organolithium compounds, which give rise to olefins, would suggest an alternative mechanism in which direct attack by phosphite on sulfur occurs. This mechanism can be formulated as,



The first step in the reaction is facilitated by coordination of sulfur with phosphite and breaking of the carbon-sulfur bond. This yields a pair of electrons which could initiate a 1,2-elimination reaction resulting in the simultaneous formation of olefin and thionophosphite. It was found that the ethylene sulfides react readily under the mild conditions described in the experimental section while the corresponding ethylene oxides gave little or no reaction under the same experimental conditions.

The present work extends the list[4] of types of organosulfur compounds that are desulfurized by triethyl phosphite.

EXPERIMENTAL

Materials. Propylene oxide and epichlorohydrin were obtained from commercial sources and were used as received.

(3) F. G. Bordwell, H. M. Anderson, and B. M. Pitt, *J. Am. Chem. Soc.*, **76**, 1082 (1954).

(4) (a) H. I. Jacobsen, R. G. Harvey, and E. V. Jensen, *J. Am. Chem. Soc.*, **77**, 6064 (1955); (b) F. W. Hoffman, R. J. Ess, T. C. Simmons, and R. S. Hanzel, *J. Am. Chem. Soc.*, **78**, 6414 (1956); (c) C. Walling and R. Rabinowitz, *J. Am. Chem. Soc.*, **79**, 5326 (1957).

Methyl glycidyl ether was obtained by the method of Pollard.[5] The thiiranes were prepared from the corresponding epoxides following the procedure of Bordwell and Anderson.[6] Triethyl phosphite was obtained from the Virginia-Carolina Chemical Corporation and purified prior to use by distillation from metallic sodium.

Reaction of 2-chloromethylthiirane with triethyl phosphite. A mixture of 21.6 g. (0.20 mole) of 2-chloromethylthiirane and 33.2 g. (0.20 mole) of triethyl phosphite was distilled at atmospheric pressure employing a 30 cm. Fenske type column, removing distillate at such a rate that the distillate temperature remained in the range 45–46°. At the end of a 5 hr. period the temperature of the residual material remaining in the distillation flask had reached 180°. At this point 14.8 g. (0.195 mole) of allyl chloride had been obtained as distillate. Redistillation of the chloride gave 14.6 g. (0.190 mole), a 95% yield of allyl chloride, b.p. 44.8–45°/741.4 mm., n_D^{25} 1.4116. Literature values,[7] b.p. 44.7–44.8/760 mm., n_D^{25} 1.4116. Distillation of the liquid residue in the distillation flask under reduced pressure afforded 39.6 g. (0.20 mole) of triethyl thionophosphate distilling at 82–83°/5 mm., n_D^{25} 1.4460, n_D^{20} 1.4481. The reported[4,6] physical constants of thionophosphate are: b.p. 45°/0.5 mm., 105–106°/20 mm., n_D^{20} 1.4480, n_D^{25} 1.4461. Thus, a quantitative yield of triethyl thionophosphate was obtained. When the original distillation residue was heated above 180° or kept at about that temperature for long periods of time, the liquid became dark colored and subsequent distillation failed to give quantitative yields of triethyl thionophosphate. A possible explanation of this is found in the work of Emmett and Jones[8] who observed that thionophosphates readily undergo thermal isomerization to phosphorothiolates.

Reaction of 2-methylthiirane with triethyl phosphite. A mixture of 14.8 g. (0.20 mole) of 2-methylthiirane and 33.2 g. (0.20 mole) of triethyl phosphite was distilled employing the experimental procedure described above except that bromine-carbon tetrachloride traps were installed to collect any propylene liberated. At the end of 3 hr. of distillation the temperature of the residue had reached 180° at which point heating was discontinued. Vacuum distillation of the liquid residue gave 39.2 g. (0.199 mole) a 99% yield of triethyl thionophosphate. Treatment of the material in the bromine-carbon tetrachloride traps, following standard procedures, afforded a 97% yield of 1,2-dibromopropane, b.p. 137°/734.6 mm, n_D^{20} 1.5193. Literature[9] values for this dibromide are: b.p. 139°–142°, n_D^{20} 1.5194.

Reaction of 2-methoxymethyl thiirane[10] *with triethyl phosphite.* Distillation of a mixture containing 20.8 g. (0.20 mole) of 2-methoxythiirane and 33.2 g. (0.20 mole) of triethyl phosphite by experimental techniques already described gave a 94% yield of methyl allyl ether, b.p. 42°/746.5 mm, n_D^{20} 1.3786. The reported[11] physical constants for allyl ether are: b.p. 42.5–43°/757 mm, n_D^{25} 1.3778–1.3803. The other product in this reaction, triethyl thionophosphate, was obtained in a 96% yield.

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(5) H. Flores-Gallard and C. B. Pollard, *J. Org. Chem.*, **12**, 831 (1947).
(6) F. G. Bordwell and H. M. Anderson, *J. Am. Chem. Soc.*, **75**, 4959 (1953).
(7) C. A. Vernon, *J. Chem. Soc.*, 4462 (1954).
(8) W. G. Emmett and H. O. Jones, *J. Chem. Soc.*, 99, 713 (1911).
(9) M. S. Kharasch, J. C. McNab, and M. C. McNab, *J. Am. Chem. Soc.*, **57**, 2463 (1935).
(10) The preparation and properties of unsymmetrically substituted thiiranes will be reported in a forthcoming publication.
(11) S. C. Irvine, J. A. Macdonald, and C. W. Soutar, *J. Chem. Soc.*, **107**, 337 (1915).

Nitration Studies. X. Reaction of Dinitrogen Tetroxide with Hydrazides and Isocyanates[1]

G. BRYANT BACHMAN AND W. MICHALOWICZ[2]

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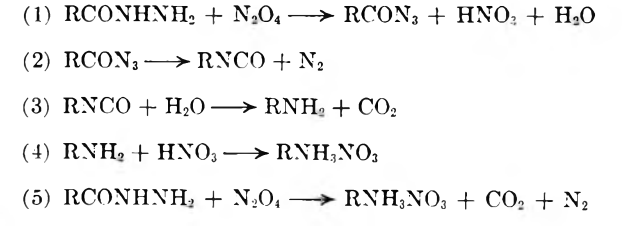
In its reactions with organic compounds, dinitrogen tetroxide sometimes behaves like a pseudo halogen and sometimes like a mixed anhydride of nitrous and nitric acids. Thus it reacts with aliphatic hydrocarbons to produce nitro alkanes in much the same way that chlorine produces chloro alkanes. However it reacts with aromatic amines to produce diazonium salts in much the same way that nitrous acid does. In continuing our efforts to clarify its chemical behavior we have investigated the reaction of dinitrogen tetroxide with acid hydrazides.

Carpino[3] has recently shown that acid hydrazide hydrochlorides react with chlorine to give acid chlorides. However, much earlier Curtius[4] showed that acid hydrazides react with nitrous acid to form acid azides, then isocyanates, and finally the solvolysis or solvation products of isocyanates. We have found that ethanoyl hydrazide reacts with dinitrogen tetroxide in a 1:1 mole ratio to give methyl amine nitrate, nitrogen, carbon dioxide, and acetic acid. The methyl amine nitrate was obtained in a 56% yield; the nitrogen and carbon dioxide evolved corresponded to 100% and 40% respectively of the expected amounts. The amount of acetic acid isolated was small, about 10% of theory, and probably arose from partial hydrolysis of the hydrazide or the azide. The methyl amine nitrate was identified by comparison with an authentic synthetic sample and by conversion to sodium nitrate and to the phenyl isothiocyanate derivative of methyl amine.

Butanoyl hydrazide reacts with dinitrogen tetroxide in an approximately 1:1 mole ratio to give propyl amine nitrate in 54% yield together with nitrogen, carbon dioxide, and some butyric acid.

The above reactions are assumed to proceed according to the following equations.



(1) $RCONHNH_2 + N_2O_4 \longrightarrow RCON_3 + HNO_2 + H_2O$

(2) $RCON_3 \longrightarrow RNCO + N_2$

(3) $RNCO + H_2O \longrightarrow RNH_2 + CO_2$

(4) $RNH_2 + HNO_3 \longrightarrow RNH_3NO_3$

(5) $RCONHNH_2 + N_2O_4 \longrightarrow RNH_3NO_3 + CO_2 + N_2$

(1) From the M. S. thesis of W. Michalowicz, Purdue University, January 1958.
(2) Present address: Koppers Company, Inc., Pittsburgh, Pa.
(3) L. A. Carpino, *Chem. and Ind. (London)*, 123 (1956).
(4) T. Curtius, *J. prakt. Chem.* **50**, 285 (1894).

On mixing the reagents at ice bath temperatures, a vigorous reaction occurs. The resulting solution gives a positive test for azides. A steady evolution of gas develops and grows more vigorous as the temperature of the mixture is allowed to approach and exceed room temperature. This decomposition may be completed by warming the mixture on a water bath. The product remaining in the reaction flask is a solution of the amine nitrate in chloroform contaminated with a small amount of the corresponding carboxylic acid.

Since isocyanates are assumed to be intermediates in the above reaction, it was decided to investigate their behavior with dinitrogen tetroxide also. Phenyl isocyanate gives immediately a brown precipitate with liquid dinitrogen tetroxide. Upon complete evaporation of the excess liquid dinitrogen tetroxide the brown solid explodes violently. However phenyl isocyanate reacts smoothly with dinitrogen tetroxide in chloroform solution in a 1:1 mole ratio to yield benzene diazonium nitrate in 56% yield. The carbon dioxide evolved cor-

(6) $C_6H_5NCO + N_2O_4 \longrightarrow C_6H_5N_2NO_3 + CO_2$

responds to 76% of the expected amount. The benzene diazonium nitrate decomposes slowly if left in the chloroform solution to form a tar from which *o*-nitrophenol may be isolated.

(7) $C_6H_5N_2NO_3 \longrightarrow N_2 + o\text{-}HOC_6H_4NO_2$

Ethyl isocyanate reacts with dinitrogen tetroxide in chloroform solution in a 1:1 mole ratio to give ethyl nitrate, carbon dioxide, nitrogen and traces of ethylene and nitric acid. Since ethyl isocyanate

(8) $C_2H_5NCO + N_2O_4 \longrightarrow [C_2H_5N_2NO_3] + CO_2$

(9) $[C_2H_5N_2NO_3] \longrightarrow C_2H_5ONO_2 + N_2$

(10) $C_2H_5ONO_2 \longrightarrow C_2H_4 + HNO_3$

reacts with dinitrogen tetroxide under anhydrous conditions to give ethyl nitrate instead of ethyl amine nitrate, it must be presumed that the formation of amine nitrates by reaction of acid hydrazides with dinitrogen tetroxide requires the presence of the water generated in the first step of the reaction (Equation 1) to form the amine nitrate.

EXPERIMENTAL

Reaction of ethanoyl hydrazide with dinitrogen tetroxide. Ethanoyl hydrazide,[5] m.p. 66.5–67.0°, 3.70 g. (0.05 mole), dissolved in 30 ml. of chloroform was placed in a 100 ml. 3-necked flask equipped with a dropping funnel, a gas inlet tube, and a gas exit tube leading to a gas buret. The system was flushed with dry nitrogen gas, cooled in an ice bath, and then 4.6 g. (0.05 mole) of dinitrogen tetroxide in 20 ml. of chloroform was added dropwise to moderate the vigorous reaction. A small sample of the reaction mixture was removed and found to give a strong positive test[6] for an azide. The ice bath was removed and the azide decomposed by warming gradually. The gases evolved were analyzed and found to contain 0.02 mole (40% theory) of carbon dioxide and 0.05 mole (100%) of additional nitrogen. The liquid product was distilled at 30° under diminished pressure (eventually 1 mm.). An aliquot of the distillate was titrated with base using phenolphthalein as an indicator. The results corresponded to 0.005 mole of monobasic acid, shown to be acetic acid by conversion to its phenylhydrazine derivative, m.p. 127–128° (lit. m.p. 128°).

The residue from the distillation solidified in part on cooling. Some of the solid was purified by recrystallization from ethanol and drying over phosphorus pentoxide under vacuum. It was identified as methylamine nitrate by its m.p. (108.0–108.5° in a sealed capillary tube), its mixture m.p. with an authentic sample, and its conversion to *N*-methyl-*N'*-phenylthiourea, m.p. 113°, by treatment with base and then with phenyl isothiocyanate. The nitrate radical was identified by conversion to sodium nitrate, m.p. 298–299°, on mixing with aqueous sodium hydroxide and evaporating to dryness. An aliquot of the distillation residue was submitted to a Van Slyke analysis[7] for a primary amine and yielded nitrogen gas corresponding to 0.028 mole (56% yield) of methylamine.

Reaction of butanoyl hydrazide with dinitrogen tetroxide. In an experiment similar to the above butanoyl hydrazide,[8] m.p. 46–47°, 24.5 g. (0.24 mole), in chloroform, 80 ml., was treated with dinitrogen tetroxide, 24.6 g. (0.275 mole), in chloroform, 30 ml., added over a period of 1.25 hr. At this time the solution gave a strong positive test for azide with ferric chloride solution. After warming carefully to decompose the azide, the product was distilled to remove the solvent and to obtain a small amount of butyric acid, 3.0 ml. The residue was extracted with ether, converted to propylamine with aqueous alkali, and to *N*-propyl-*N'*-phenylthiourea, m.p. 62° (yield 54% based on butanoyl hydrazide), with phenyl isothiocyanate. The aqueous alkali layer gave sodium nitrate, m.p. 298–299°, on evaporation and recrystallization.

Reaction of phenyl isocyanate with dinitrogen tetroxide. Phenyl isocyanate, 5.95 g. (0.05 mole), in chloroform, 120 ml., was treated with 4.6 g. (0.05 mole) of dinitrogen tetroxide in chloroform, 30 ml., at 0–5°. The unstable brownish crystals of benzenediazonium nitrate which formed were quickly filtered and dried on filter paper; yield, 4.7 g. (56% theory); m.p. 85° (detonation). They coupled with β-naphthol in basic solution to form the orange dye, 1-phenylazo-2-naphthol, m.p. 129–130°, and with β-naphthylamine to form 1-phenylazo-2-naphthylamine, m.p. 100°.

In another experiment using the same amounts of reactants the diazonium nitrate was not isolated and the reaction mixture was allowed to stand over night at room temperature. The gases evolved were collected in a gas buret and analyzed. They contained 0.038 mole (76%) of carbon dioxide. Evaporation of the solvent left a tar from which *o*-nitrophenol, 1.25 g. (18%), was isolated by extraction with base, acidification, and recrystallization from ligroin. It was identified by its m.p. of 45° and by conversion to 2-nitro-4-bromophenol, m.p. 116°.

Reaction of ethyl isocyanate with dinitrogen tetroxide. Ethyl isocyanate,[9] 25.27 g. (0.356 mole), was treated with 32.80 g. (0.356 mole) of dry dinitrogen tetroxide in 330 ml. of chloroform at 0–5°. The mixture was allowed to warm to room temperature and the evolved gases were collected in a gas buret. Analysis showed that they contained 0.290 mole (81.5%) of carbon dioxide, 0.314 mole (88.0%) of evolved nitrogen, and 0.018 mole (5.1%, based on one mole per mole of isocyanate) of ethylene. Distillation of the liquid product

(5) T. Curtius and T. S. Hofmann, *J. prakt. Chem.* [2] **53**, 524 (1896).

(6) Feigl, *Spot Tests*, Elsevier Publishing Company, New York, 1954, Fourth Edition, Vol. 1, p. 268.

(7) D. D. Van Slyke, *J. Biol. Chem.*, **16**, 121 (1913).

(8) R. Stolle, *J. prakt. Chem.*, (2), **69**, 486 (1904).

(9) K. H. Slotta and L. Lorenz, *Ber.* **58B**, 1323 (1925).

gave 13.0 g. of ethyl nitrate (40% theory), b.p. 85.0–85.4°, n_D^{23} 1.3834. Its infrared spectrum was identical with that for an authentic sample of ethyl nitrate.

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Reactions of Nucleophilic Reagents with Cyanuric Fluoride and Cyanuric Chloride

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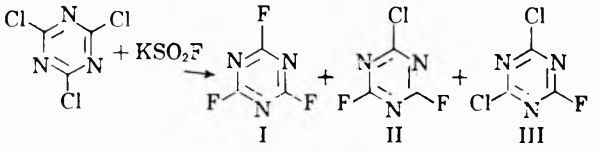
Recently, the preparation of cyanuric fluoride (I) was reported.[1] This novel compound was synthesized by reaction of cyanuric chloride with antimony trifluoride dichloride. It has been found in this laboratory that the action of potassium fluorosulfinate on cyanuric chloride yields a mixture of products as shown:



The physical properties observed are in essential agreement with those reported. Due to the novelty of the fluorine containing *s*-triazines, their infrared spectra are included, (Fig. 1).

Cyanuric chloride has long been known to react readily with nucleophilic reagents.[2] Cyanuric fluoride was reported to be hydrolytically unstable,[1] but its reactivity toward other reagents has not been established. Therefore, it was of interest to compare cyanuric fluoride and cyanuric chloride directly with respect to the replaceability of their halogens by certain bases. The results are summarized in Table I.

It can be seen that in contrast to the fluoride, the chloride yielded, in each case, a mixture of reaction products. The compositions of these mixtures were determined qualitatively by their amount of residual chloride coupled with previous evidence that nucleophiles (1–3) and (5) involve stepwise replacement of chlorine.[2] The reaction (4) of cyanuric chloride with water, differs in that the intermediate chlorohydroxy *s*-triazines are more easily hydrolyzed than cyanuric chloride.[3]

From the data given in Table I, it is concluded that with the general types of reagents illustrated by the examples used that cyanuric fluoride is qualitatively more reactive or as reactive as cyanuric chloride.

EXPERIMENTAL

Materials. Ether was of anhydrous analytical grade (Mallinckrodt). Tetrahydrofuran was purified by washing repeatedly with 40% sodium hydroxide solution, dried over calcium chloride, and then distilled from sodium. Gaseous ammonia (Matheson) was passed over sodium hydroxide pellets and used directly. Diethylamine was purified by distilling from sodium hydroxide pellets b.p. 55–56°, (lit., b.p. 55.5°).[4] Aniline was distilled from zinc dust. Methanol (Mallinckrodt Reagent Grade) was purified by the method of Vogel.[5] Cyanuric chloride (Matheson) was purified by preparing a saturated solution in dry chloroform, filtering off the insoluble solid and evaporating the filtrate to yield the pure material, m.p. 145–146°.

TABLE I

REPLACEMENT OF THE HALOGENS OF CYANURIC FLUORIDE AND CYANURIC CHLORIDE BY NUCLEOPHILES UNDER IDENTICAL CONDITIONS

	Nucleophile	No. of Equivs.	Product from Cyanuric Fluoride	Yield %	Product from Cyanuric Chloride	Yield %
1	Ammonia[a]	...	2,4-Diamino-6-fluoro-*s*-triazine	90	2,4-Diamino-6-chloro-*s*-triazine and 2-amino-4,6-dichloro-*s*-triazine	...
2	Diethylamine	7.0	2,4-Bis(diethylamino)-6-fluoro-*s*-triazine	74	2,4-Bis(diethylamino)-6-chloro-*s*-triazine	100[b]
3	Aniline	6.0	Triphenylmelamine	100[b]	2,4-Bis(phenylamino)-6-chloro *s*-triazine	100[b]
4	Water	5.5	Cyanuric acid	94	Mixture of cyanuric acid and cyanuric chloride	...
5	Methanol[c]	3.0	2,4,6-Tris(methoxy)-*s*-triazine	77	2,4,6-Tris(methoxy)-*s*-triazine and 2-chloro-4,6-bis(methoxy)-*s*-triazine	...

[a] An indeterminate excess was used. [b] Crude product. [c] Potassium carbonate added as HCl acceptor.

Apparatus. For the reactions of cyanuric fluoride and cyanuric chloride with the nucleophilic reagents, a Mini-Lab (Ace Glass Inc.) reaction assembly was used. To insure dryness, immediately before use, the apparatus was fitted with a drierite tube, flamed, and allowed to cool. All

(1) A. F. Maxwell, J. S. Fry, and L. A. Bigelow, *J. Am. Chem. Soc.*, 80, 548 (1958).

(2) (a) J. T. Thruston, J. R. Dudley, I. Hechenbleikner, F. Schaefer, D. Holm-Hansen, *J. Am. Chem. Soc.*, **73**, 2981 (1951). (b) D. W. Kaiser, J. T. Thurston, J. R. Dudley, F. Schaefer, I. Hechenbleikner, and D. Holm-Hansen, *J. Am. Chem. Soc.*, **73**, 2984 (1951). (c) J. R. Dudley, J. T. Thurston, F. Schaefer, D. Holm-Hansen, C. Hull, and P. Adams, *J. Am. Chem. Soc.*, **73**, 2986 (1951) and other references contained therein.

(3) J. L. Comp, private communication.

(4) Heilbron, *Dictionary of Organic Compounds*, Oxford University Press, New York, N. Y., 1953, Vol. II, p. 180.

(5) A. Vogel, *Practical Organic Chemistry*, Longmans Green and Company, London, 1948, p. 168.

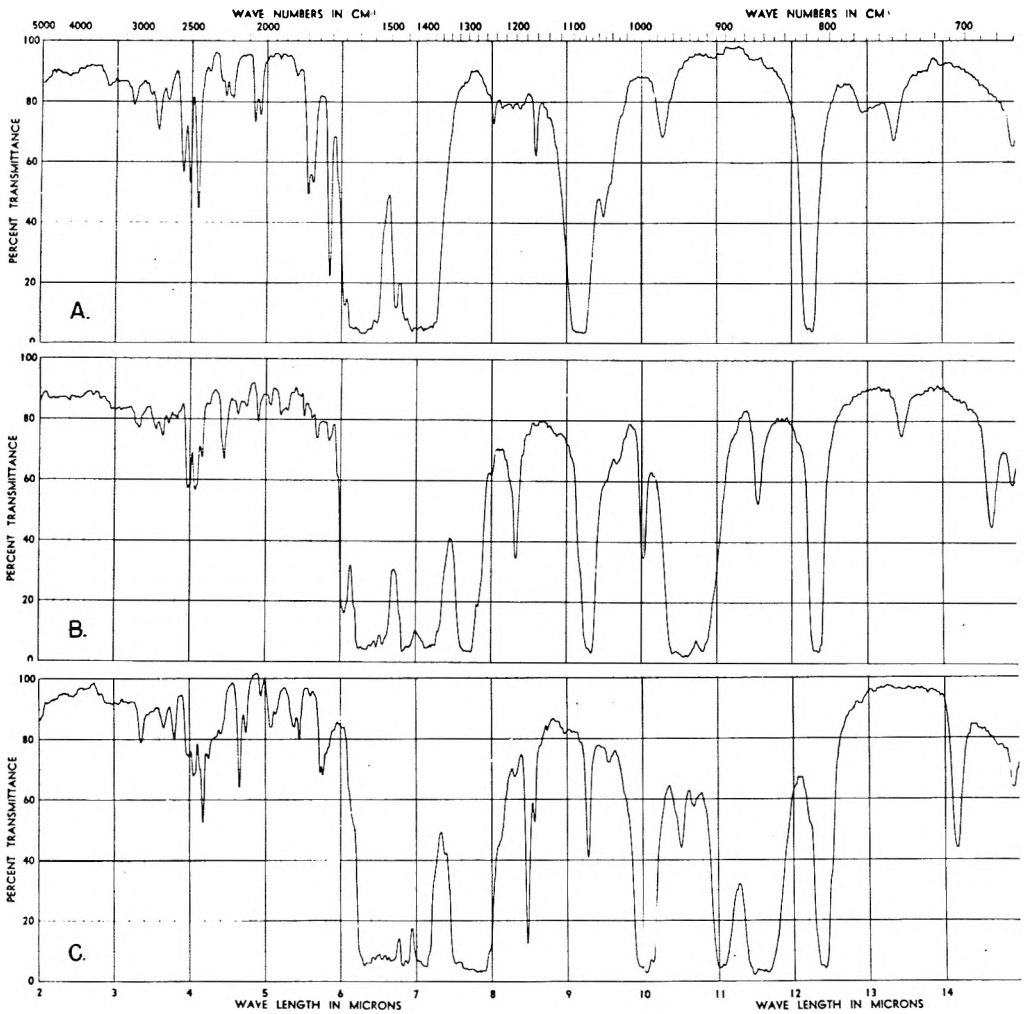


Fig. 1. Infrared absorption spectra (neat): Curve A, cyanuric fluoride; Curve B, 2-chloro-4,6-difluoro-*s*-triazine; Curve C, 2,4-dichloro-6-fluoro-*s*-triazine

operations were carried out in a well-ventilated hood because of the extreme odor and lacrymatory properties of the fluoro-*s*-triazines.

Cyanuric fluoride, 2-chloro-4,6-difluoro-s-triazine and 2,4-dichloro-6-fluoro-s-triazine. A finely-ground mixture of cyanuric chloride (368 g., 2 moles) and potassium fluorosulfinate (944 g.)[6,7] was placed in a flask equipped with a mechanical Hershberg stirrer and a distilling head connected to an ice-cooled receiver. The apparatus was protected from moisture by a drying tube. The stirred mixture was heated slowly with an oil bath to 120°. At this temperature, a colorless liquid began distilling from the reaction mixture. The temperature was maintained at 120° until the rate of distillation slowed noticeably; then the temperature was raised to 150° until distillation ceased. The clear distillate was redistilled through a 12″ helices-packed column. The following fractions were collected:

Cyanuric fluoride (85 g., 0.62 mole, 31% yield), b.p. 69–71°. This fraction was redistilled to yield the colorless, sharp smelling lacrymatory liquid (76.2 g., 0.56 mole, 28% yield), b.p. 69.5–70.8°,[8] (lit. b.p. 74°).[1]

Anal. Calcd. for $C_3F_3N_3$: C, 26.68; F, 42.21; N, 31.11. Found: C, 26.85; F, 42.41; N, 31.22.[9]

(6) Seel, *Anorg. Chem.*, **282**, 293 (1955).
(7) Seel, *Angew. Chem.*, **68**, 461 (1956).
(8) All boiling points are uncorrected.
(9) Analyses were performed by the Schwarzkopf Microanalytical Laboratory, Woodside 77, N. Y.

2-Chloro-4,6-difluoro-*s*-triazine (34 g., 0.22 mole, 11% yield), b.p. 107.8–109.5°, (lit. b.p. 113.5°).[1]

Anal. Calcd. for $C_3ClF_2N_3$: C, 23.79; Cl, 23.40; F, 25.08; N, 27.73. Found: C, 23.84; Cl, 23.16; F, 25.33; N, 27.49.

2,4-Dichloro-6-fluoro-*s*-triazine (6.2 g., 0.06 mole, 3% yield), b.p. 59–60°/20 mm., (lit. b.p. 155°).[1]

Anal. Calcd. for $C_3Cl_2FN_3$: C, 21.45; Cl, 42.22; F, 11.31; N, 25.01. Found: C, 21.62; Cl, 42.21; F, 11.12; N, 25.19.

Reactions of cyanuric fluoride and cyanuric chloride with nucleophilic reagents. Ammonia and cyanuric fluoride. Ammonia was passed into a solution of cyanuric fluoride (2.72 g., 20 mmoles) in ether (50 ml.) at 0° for 1 hr. The ether was evaporated *in vacuo* at room temperature and the residue washed with ice water, filtered, and the solid washed with acetone and then with ether. The white solid was dried at 50° *in vacuo* (20 mm.) to yield 2,4-diamino-6-fluoro-*s*-triazine (2.35 g., 18 mmoles, 90% yield).

Anal. Calcd. for $C_3H_4FN_5$: C, 27.90; H, 3.12; F, 14.72; N, 54.25. Found: C, 27.98; H, 3.20; F, 14.90; N, 54.25.

Ammonia and cyanuric chloride. The procedure was that used for cyanuric fluoride except that (3.68 g., 20 mmoles) of cyanuric chloride was used. The product was washed with water until the aqueous filtrate was free of chloride ion. The product was pressed dry on a suction filter with a rubber dam for 3 hr. and then dried at room temperature at 0.5 mm. to constant weight. There was obtained a white solid, crude 2,4-dichloro-6-amino-*s*-triazine (2.45 g., 15 mmoles, 75% yield).[2a]

Anal. Calcd. for $C_3H_4ClN_5$: C, 24.76; H, 2.77; Cl, 24.37;

N, 48.14. *Anal.* Calcd. for $C_3H_2Cl_2N_4$: C, 21.73; H, 1.22; Cl, 42.79; N, 33.96. Found: C, 24.08; H, 2.62; Cl, 36.58; N, 36.48.

Diethylamine and cyanuric fluoride. A solution of cyanuric fluoride (1.36 g., 10 mmoles) in tetrahydrofuran (5 ml.) was added to a stirred solution of diethylamine (5.1 g., 70 mmoles) in tetrahydrofuran (25 ml.) at 20° during 15 min. The reaction mixture was stirred for an additional 80 min. The tetrahydrofuran then was evaporated *in vacuo* (surrounding bath at 60°) to yield an oily residue. This was stirred for 15 min. with 50 ml. of water, extracted with ether, and the organic layer was dried ($MgSO_4$), filtered, and evaporated *in vacuo* to yield a colorless solid. There was obtained 2,4-bis(diethylamino)-6-fluoro-*s*-triazine (1.77 g., 7.4 mmoles, 74% yield), m.p. 37–44°. A small amount of the material was sublimed (60°/0.5 mm.) to yield crystals, soften 37°, m.p. 44–45.5°.[10]

Anal. Calcd. for $C_{11}H_{20}FN_5$: C, 54.75; H, 8.35; F, 7.87; N, 29.03. Found: C, 54.79; H, 8.58; F, 8.08; N, 29.24.

Diethylamine and cyanuric chloride. The procedure was like that used for cyanuric fluoride except that (1.84 g., 10 mmoles) of cyanuric chloride was used. The oily solid was dissolved in chloroform and the chloroform extracted with water until the aqueous phase remained neutral. The organic layer was dried (Na_2SO_4), filtered, and evaporated *in vacuo* to yield an oil which was taken to constant weight (25°/0.5 mm.). There was obtained crude 2,4-bis-(diethylamino)-6-chloro-*s*-triazine, (2.57 g., 10 mmoles, 100%).[2a]

Anal. Calcd. for $C_{11}H_{20}ClN_5$: C, 51.24; H, 7.82; Cl, 13.75; N, 27.17. Found: C, 50.67; H, 8.05; Cl, 12.72; N, 26.19.

Aniline and cyanuric fluoride. Cyanuric fluoride (1.36 g., 10 mmoles) in tetrahydrofuran (10 ml.) was added over 5 min. to a stirred solution of aniline (5.58 g., 60 mmoles) in tetrahydrofuran (25 ml.) at room temperature. The reaction mixture was stirred for 2 hr. The tetrahydrofuran was evaporated *in vacuo* to yield a white solid which was triturated thoroughly with 5% HCl. The solid was filtered, washed with water until the filtrate remained neutral, and then dried *in vacuo* (80°/20 mm.) to constant weight. There was obtained crude triphenylmelamine (3.53 g., 10 mmole, 100%), soften 215°, m.p. 222–227°, (lit. m.p. 229–231°).[2b] A small sample was sublimed (140°/0.5 mm.) to yield a white crystalline sublimate I, m.p. 222–227°,[11] and a small amount of non-sublimated amorphous tan solid II, m.p. 300°.

Anal. Calcd. for I, $C_{21}H_{18}N_6$: C, 71.17; H, 5.12; N, 23.71. Found: C, 69.74; H, 5.47; N, 19.98; F. 0.00.

Aniline and cyanuric chloride. The procedure and work-up followed those used for cyanuric fluoride except that (1.84 g., 10 mmoles) of cyanuric chloride was used. The white solid was dried at (25°/0.5 mm.) to constant weight. There was obtained crude 2,4-bis(phenylamino)-6-chloro-*s*-triazine (3.05 g., 10 mmoles, 100%), m.p. 187–191°, (lit. m.p. 199–201°).[2a]

Anal. Calcd. for $C_{15}H_{12}ClN_5$: C, 60.49; H, 4.06; Cl, 11.91, N, 23.52. Found: C, 61.99; H, 4.49; Cl, 9.16; N, 22.89.

Water and cyanuric fluoride. A solution of cyanuric fluoride (2.72 g., 20 mmoles) in tetrahydrofuran (10 ml.) was added to a stirred solution of water (2.0 g., 110 mmoles) in tetrahydrofuran (25 ml.) at 0° over 10 min. The tetrahydrofuran was evaporated at room temperature *in vacuo* to yield a white solid which was dried *in vacuo* (25°/0.5 mm.) to constant weight. There was obtained cyanuric acid (2.45 g., 18.8 mmoles, 94%).

Anal. Calcd. for $C_3H_3N_3O_3$: C, 27.91; H, 2.34; N, 32.55. Found: C, 27.74; H, 2.56; N, 32.47; F, 0.00.

Water and cyanuric chloride. The procedure and work-up were those used for cyanuric fluoride except that (3.69 g., 20 mmoles) of cyanuric chloride was used. There was obtained a white solid, a mixture of cyanuric chloride and cyanuric acid[12] (3.33 g.).

Anal. Calcd. for $C_3Cl_3N_3$: C, 19.54; Cl, 57.70; N, 22.79. Found: C, 20.76; H, 3.07; Cl, 48.07; N, 23.25.

Methanol and cyanuric fluoride. A solution of cyanuric fluoride (2.78 g., 20 mmoles) in tetrahydrofuran (10 ml.) was added to a stirred mixture of anhydrous potassium carbonate (8.2 g., 60 mmoles) and methanol (25 ml.) at 10° over 5 min. The reaction mixture was stirred for 2 hr. at room temperature, filtered, and the residue I was washed with chloroform. The chloroform was combined with the filtrate; the resulting mixture was evaporated *in vacuo* at room temperature to yield a white solid II. The solid II was triturated with cold water (50 ml.), pressed dry on a filter, and dried to constant weight *in vacuo* (95°/20 mm.). There was obtained 2,4,6-tris(methoxy)-*s*-triazine (2.65 g., 15.5 moles, 77%), m.p. 133–135.5°, (lit. m.p. 134–136°).[2c]

Anal. Calcd. for $C_6H_9N_3O_3$: C, 42.10; H, 5.29; N, 24.55. Found: C, 42.04; H, 5.44; N, 24.42.

Methanol and cyanuric chloride. The procedure and work-up were those used for cyanuric fluoride except (2.68 g., 20 mmoles) of cyanuric chloride was used. The white solid was dried to constant weight on a suction filter with a rubber dam. There was obtained crude 2,4,6-tris(methoxy)-*s*-triazine (2.03 g., 12 mmoles, 60%), m.p. 94–120° (lit. m.p. 134–136°).[2c]

Anal. Calcd. for $C_5H_6ClN_3O_2$: C, 34.20; H, 3.45; Cl, 20.20, N, 23.93. Found: C, 39.43; H, 4.84; Cl, 5.43; N, 21.45.

Acknowledgment. The authors gratefully acknowledge the assistance of the infrared spectroscopy group of Dr. William Cave and also wish to thank W. Morgan Padgett for several valuable suggestions concerning this work.

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(10) All melting points were taken with a Fisher-Johns melting point apparatus and are uncorrected.

(11) Repeated recrystallization from hot 1-butanol did not improve the purity of the product.

(12) The infrared spectrum of the solid (KBr disk) contained all the bands of cyanuric chloride in addition to those of cyanuric acid.

Synthesis of 2-Chlorophenothiazine *via* a Smiles Rearrangement[1]

ROBERT J. GALBREATH[2] AND ROBERT K. INGHAM

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2-Chlorophenothiazine (I) is the parent compound of chloropromazine [2-chloro-10-(3-dimethylaminopropyl)phenothiazine] (II) and of related biologically active substances. The principal method of preparation of 2-chlorophenothiazine involves the reaction of 3-chlorodiphenylamine with sulfur.[3] Both the 2-chloro and 4-chloro isomers are obtained from this reaction; the 2-chloro derivative

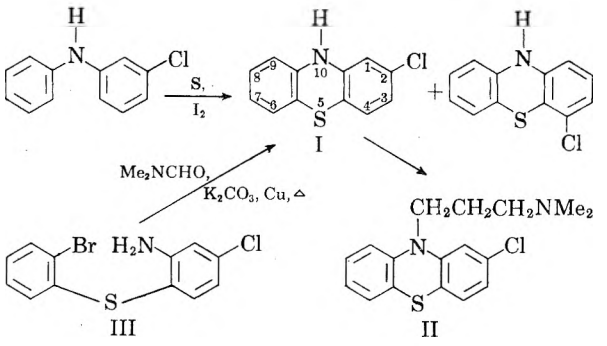
(1) Abstracted from an undergraduate research project of Robert J. Galbreath, Ohio University, 1957.

(2) Present address: School of Medicine and Dentistry, The University of Rochester.

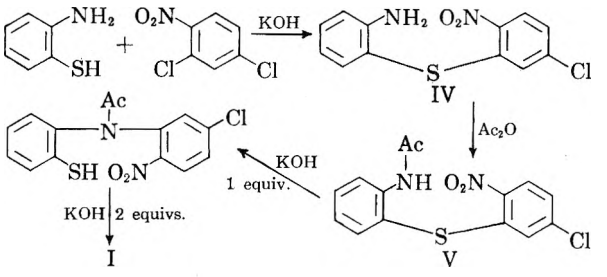
(3) P. Charpentier, P. Gailliot, R. Jacob, J. Gaudechon, and P. Buisson, *Compt. rend.*, **235**, 59 (1952); P. Charpentier, U. S. Patent **2,645,640** [*Chem. Abstr.*, **49**, 3268 (1955)]; British Patent **716,205** [*Chem. Abstr.*, **50**, 1929 (1956)].

is the dominant isomer, although no yields appear in the reports.

Recently, a synthesis of 2-chlorophenothiazine from 2-bromophenyl 2-amino-4-chlorophenyl sulfide (III) has been reported.[4]



Our synthesis of 2-chlorophenothiazine involves the following reactions:



A number of halophenothiazines have been prepared *via* the Smiles rearrangement and it is rather surprising that the synthesis of the important 2-chloro compound by this method has not been reported. Related compounds which have been prepared in this manner include the 3-chloro-,[5,6] 3-bromo-,[7] 3-iodo-,[7] and 3-fluorophenothiazine.[8]

Roe and Little[8] have attempted the preparation of 2-fluorophenothiazine from 2-formamidophenyl 5-fluoro-2-nitrophenyl sulfide. The desired sulfide was obtained but a subsequent rearrangement was not successful; an unidentified substance containing no fluorine was the only product isolated.

Similarly, an attempt to prepare 2-bromophenothiazine from 2-acetamido-4-bromophenyl 2-nitrophenyl sulfide failed; the sulfide could not be made to undergo a Smiles rearrangement.[9] An attempt to deaminate 2-bromo-7-aminophenothiazine was also unsuccessful.[9]

Recently, Farrington and Warburton[10] attempted the preparation of 2,8-dichlorophenothiazine by rearrangement and ring closure of 2-acetamido-4-chlorophenyl 5-chloro-2-nitrophenyl sulfide; rearrangement occurred but heating with sodium hydroxide, sodium ethoxide, or sodium isopropoxide in various solvents failed to give the phenothiazine compound. These authors concluded that a chlorine atom *ortho* or *para* to the nitro group interferes with ring closure.

Similarly, Fujii[11] reported that 2-chloro-10-methylphenothiazine could not be obtained by subjecting 2-methylamino-4-chlorophenyl 2-nitrophenyl sulfide to Smiles rearrangement conditions.

The above-mentioned work plus other literature reports[12] left no doubt that the nucleophilic attack on 2,4-dichloronitrobenzene would take place preferentially at the 2-position. Indeed, the 2-aminophenyl 5-chloro-2-nitrophenyl sulfide (IV) was obtained in 78% yield. Acetylation occurred readily and, in spite of the discouraging reports mentioned above, rearrangement and subsequent ring closure were accomplished to give the desired 2-chlorophenothiazine.

EXPERIMENTAL[13]

2,4-Dichloronitrobenzene. There are numerous references in the literature to the preparation of 2,4-dichloronitrobenzene; almost all reports conclude that the method of choice is the nitration of *m*-dichlorobenzene. Since all of the procedures for this reaction are somewhat short on detail,[14] the following procedure is included.

To 75.0 g. (0.51 mole) of *m*-dichlorobenzene at 0° was added dropwise, with stirring, 140 ml. of fuming nitric acid (sp. gr. 1.50). The mixture was stirred at 0° for 1 hr.; it was then slowly warmed to 65° and maintained at this temperature for 20 min. After pouring the mixture into ice water, the resulting light yellow solid was removed by filtration and washed with water. This material was recrystallized from ethanol; the filtrate was twice heated, diluted and cooled to give additional product. The light yellow needles were washed with cold petroleum ether (b.p. 30–60°) and dried to give a total yield of 80.5 g. (82%) of 2,4-dichloronitrobenzene melting at 31.5–32°.

(4) P. J. C. Buisson, P. Gailliot, and J. Gaudechon, U. S. Patent 2,769,002 [*Chem. Abstr.*, **51**, 6709 (1957)].

(5) W. J. Evans and S. Smiles, *J. Chem. Soc.*, 1263 (1935).

(6) H. L. Yale, *J. Am. Chem. Soc.*, **77**, 2270 (1955).

(7) J. Cymerman-Craig, W. P. Rogers, and G. P. Warwick, *Australian J. Chem.*, **8**, 252 (1955) [*Chem. Abstr.*, **50**, 3449 (1956)].

(8) A. Roe and W. F. Little, *J. Org. Chem.*, **20**, 1577 (1955).

(9) R. Baltzly, M. Harfenist, and F. J. Webb, *J. Am. Chem. Soc.*, **68**, 2673 (1946).

(10) K. J. Farrington and W. K. Warburton, *Australian J. Chem.*, **9**, 480 (1956) [*Chem. Abstr.*, **51**, 4379 (1947)].

(11) K. Fujii, *J. Pharm. Soc., Japan*, **77**, 3 (1957) [*Chem. Abstr.*, **51**, 8756 (1957)].

(12) For a review of the reaction of nucleophilic reagents with 2,4-dihalonitrobenzenes, see J. F. Bunnett and R. J. Morath, *J. Am. Chem. Soc.*, **77**, 5051 (1955); see also, M. W. J. De Mooy, *Rec. trav. chim.*, **35**, 5 (1915) and J. F. Bunnett, *Quart. Revs.*, **11**, 1 (1958).

(13) All melting points are uncorrected. Analyses were performed by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

(14) A. F. Holleman, *Rec. trav. chim.*, **23**, 369 (1904); E. Roberts and E. E. Turner, *J. Chem. Soc.*, **127**, 2004 (1925); L. M. F. van de Lande, *Rec. trav. chim.*, **51**, 98 (1932); and C. C. Price and C. A. Sears, *J. Am. Chem. Soc.*, **75**, 3276 (1953).

2-Aminophenyl 5-chloro-2-nitrophenyl sulfide (IV). To a solution of 38.4 g. (0.20 mole) of 2,4-dichloronitrobenzene and 25.2 g. (0.20 mole) of 2-aminobenzenethiol in 670 ml. of isopropyl alcohol was added dropwise, with stirring, a solution of 13.2 g. of 85% potassium hydroxide in 30 ml. of 95% ethanol. The mixture was then refluxed for 3 hr. After refluxing, a bright orange precipitate was present in the mixture.

The mixture was then evaporated, under vacuum, to dryness; the residual solid was washed well with water and air-dried. The crude product melted from 124–132°. Recrystallization from absolute ethanol gave 43.8 g. (78%) of orange crystals, melting at 132–133.5°. This material was employed in the subsequent experiment without further purification. An analytical sample of the 2-aminophenyl 5-chloro-2-nitrophenyl sulfide melting at 135–136° was obtained by an additional recrystallization from absolute ethanol.

Anal. Calcd. for $C_{12}H_9ClN_2O_2S$: Cl, 12.63; N, 9.98; S, 11.42. Found: Cl, 12.57; N, 9.93; S, 11.52.

2-Acetamidophenyl 5-chloro-2-nitrophenyl sulfide (V). A mixture of 16.3 g. (0.058 mole) of the above sulfide, 110 ml. of acetic anhydride, 7 ml. of pyridine, and 2 g. of charcoal was heated for 2 hr. on a steam bath and filtered hot. The pale yellow filtrate was concentrated to dryness, leaving 17.4 g. (93%) of a bright yellow solid. The material melted from 143–150° and was found suitable for the next experiment without further purification.

Recrystallization of a portion of the crude 2-acetamidophenyl 5-chloro-2-nitrophenyl sulfide, first from benzene and then from absolute ethanol, gave an analytical sample as pale yellow needles, m.p. 154.4–155°.

Anal. Calcd. for $C_{14}H_{11}ClN_2O_3S$: Cl, 10.99; N, 8.68; S, 9.93. Found: Cl, 10.80; N, 8.77; S, 9.91.

2-Chlorophenothiazine (I). To 888 ml. of acetone was added a solution of 6.8 g. of 85% potassium hydroxide in 51 ml. of 95% ethanol. After this mixture had been stirred and diffused with nitrogen for 15 min., 16.1 g. (0.05 mole) of the crude acetamido derivative was added and the solution was refluxed for 3 hr. Approximately 600 ml. of the acetone was removed by distillation under a nitrogen atmosphere; 500 ml. of petroleum ether (b.p. 90–120°), and 700 ml. of water were then added to the residual liquid. A small amount of insoluble material present was removed by filtration. After separation of the two layers, the aqueous layer was washed with an additional 200 ml. of petroleum ether and the organic layer was washed with 200 ml. of water. The combined petroleum ether solutions were dried over magnesium sulfate and reduced in volume to 60 ml. by distillation. Cooling, filtering, and washing the resulting precipitate with cold petroleum ether (b.p. 20–40°) gave 5.5 g. of a brown solid which melted from 180–193°, with prior shrinkage. This material was recrystallized (Norit) from xylene to give 4.3 g. (37%) of pale yellow crystals melting at 194.5–196.5°. An additional recrystallization from xylene gave 3.6 g. of almost colorless crystals, m.p. 196–197°. A mixture melting point with an authentic sample[15] of 2-chlorophenothiazine showed no depression; also, the infrared spectra[16] of the two specimens were identical.

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(15) The authors wish to express their appreciation to Dr. Eugene L. Wittle, Research Laboratories, Parke, Davis & Co., Detroit, Mich., who generously supplied a sample of 2-chlorophenothiazine.

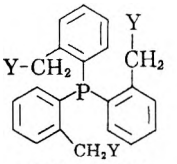
(16) The authors acknowledge with gratitude the financial aid provided by the National Science Foundation for the purchase of the Perkin-Elmer Model 21 infrared spectrophotometer used in this study (NSF-G3912).

Tris(*o*-methoxymethylphenyl)phosphine

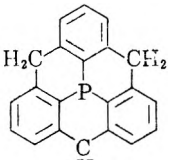
R. L. Letsinger, J. R. Nazy,[1] and A. S. Hussey

Received June 5, 1958

The intramolecular alkylation of the phosphine I or II would lead to the formation of III, an interesting new type of arylphosphine.



I, Y = CH_3O–
II, Y = Cl



III

While electrophilic substitution in the aromatic rings of triphenylphosphine is difficult, the nitration of triphenylphosphine to tris(*m*-nitrophenyl)phosphine oxide has been accomplished.[2] Further, the intramolecular alkylation of I would involve a reaction-assisting six-membered cyclic transition state. Accordingly, we have examined the effect of acids on phosphine I, using reagents ranging from formic acid, sulfuric acid in acetic acid, liquid hydrogen fluoride, stannic chloride, and aluminum chloride to concentrated sulfuric acid. All attempts to effect cyclization of I to III, however, have been unsuccessful. Some tris(*o*-methoxymethylphenyl)-phosphine oxide was recovered from a run employing aluminum chloride in nitromethane. Unreacted I and intractable tars were the only materials isolated from the other reactions.

Phosphine I was prepared by the reaction of *o*-lithiobenzyl methyl ether with phosphorus trichloride, the lithium reagent having been obtained by interchange between *n*-butyllithium and *o*-bromobenzyl methyl ether.[3] The phosphine reacted normally with hydrogen peroxide and with iodine to give the phosphine oxide, and with methyl iodide to give the methylphosphonium iodide.

Cleavage of the ether functions with boron trichloride[4] furnished tris(*o*-chloromethylphenyl)phosphine, II. Eighty-five percent of II was recovered unchanged from a reaction in liquid hydrogen fluoride. Aluminum chloride in nitromethane, however, converted II to tris(*o*-chloromethylphenyl)phosphine oxide (87%).[5] There was no indication that III was formed in either case.

(1) National Science Foundation Fellow.

(2) F. Challenger and J. Wilkinson, *J. Chem. Soc.*, 125, 2675 (1924).

(3) The corresponding Grignard reagent has been described by F. Holliman and F. G. Mann, *J. Chem. Soc.*, 1634 (1947).

(4) W. Gerrard and M. F. Lappert, *J. Chem. Soc.*, 1486 (1952).

(5) The oxidizing agent may have been air. Triphenylphosphine is oxidized in air in the presence of aluminum chloride to triphenylphosphine oxide; D. R. Lyon and F. G. Mann, *J. Chem. Soc.*, 666 (1942).

EXPERIMENTAL

Tris(o-methoxymethylphenyl)phosphine, I. Butyllithium (850 cc. of 0.86*M* solution; 0.73 mole) was dropped (2.5 hr.) into a cold (−75°), efficiently stirred solution of *o*-bromobenzyl methyl ether[3] (141 g., 0.701 mole) in 300 cc. of dry ether under nitrogen. (Carbonation with Dry Ice of a similar reaction mixture permitted the isolation of 62% of *o*-methoxymethylbenzoic acid, m.p. 89–92°, showing that the interchange had proceeded as desired. Recrystallization from hexane raised the melting point to 95–95.5°.)[6] The addition of 32 g. (0.233 mole) of phosphorus trichloride in 100 cc. of ether over a period of 15 min., warming to room temperature, followed by stirring for 20 hr. and 1 hr. at reflux converted the lithio derivative to the phosphine I. The reaction mixture was hydrolyzed by addition, with supplemental cooling, of 350 cc. of saturated aqueous ammonium chloride. Concentration of combined ether extracts furnished large, colorless crystals of the phosphine; 43.7 g., m.p. 105–106°. Another 8.8 g. of phosphine was collected on further evaporation of the solvent; total yield, 58%. Distillation of the liquid residue yielded 35.7 g. (38%) of *n*-butyl bromide.

An analytical sample was prepared by recrystallization of the phosphine from 95% ethanol; m.p. 105.5–106°.

Anal.[7] Calcd. for $C_{24}H_{27}O_3P$: C, 73.08; H, 6.90. Found: C, 72.79; H, 6.91.

Tris(o-methoxymethylphenyl)phosphine oxide. (*a*) Oxidation with Iodine. To a solution of 0.82 g. of phosphine I in 15 cc. of ether was added 0.6 g. of iodine in 30 cc. of ethanol and six drops of pyridine. In contrast to the reaction of triphenylphosphine with iodine, which decolorizes immediately, the iodine color in this preparation slowly faded during 20 min. heating on a steam bath. Excess iodine was reduced by a few drops of sodium bisulfite solution, then 10 cc. of water was added to the chilled solution. The precipitate was washed twice with water and dried; 0.70 g. (81%) of crude oxide; m.p. 146.5–147.5°. Two recrystallizations from alcohol raised the melting point to 147–147.5°; weight 0.49 g. (57%).

Anal.[7] Calcd. for $C_{24}H_{27}O_4P$: C, 70.23; H, 6.63. Found: C, 69.87; H, 6.71.

(*b*) Hydrogen peroxide. Hydrogen peroxide (0.3 g. of 30% solution) with a few cubic centimeters of water was added to a solution of 0.90 g. of phosphine I in 20 cc. of acetone. Most of the acetone was removed *in vacuo*, leaving 0.92 g. (97%) of the phosphine oxide; m.p. 145–146°; 146–147° after recrystallization. It did not depress the melting point of the oxide prepared by iodine oxidation.

Methyl tris(o-methoxymethylphenyl)phosphonium iodide. A mixture consisting of 1.42 g. of the phosphine I, 16.3 g. of methyl iodide, and 0.5 g. of fine copper wire was refluxed on a steam bath for 1 hr.; then excess methyl iodide was distilled. Removal of the copper left 1.93 g. (99%) of white crystals; m.p. 202–202.5°. Reactions carried out in the absence of copper developed a yellow color which was difficult to remove from the crystalline product. Two recrystallizations of the methiodide from ethanol gave 1.55 g. (80%) of product with a slightly higher melting point; 202.5–203°.

Anal.[7] Calcd. for $C_{25}H_{30}O_3PI$: C, 55.98; H, 5.64. Found: C, 56.29; H, 5.53.

Tris(o-chloromethylphenyl)phosphine, II. To 11.5 g. (0.098 mole) of boron trichloride in an ice cooled flask was slowly added 8.90 g. (0.0226 mole) of phosphine I. The mixture was kept cold for 8 hr., then 40 cc. of pentane was added and the mixture allowed to warm to room temperature overnight. The caked solid was washed with water, heated to remove pentane, and washed again with water. On drying 7.5 g. of solid, m.p. 117–131°, was obtained. Recrystallization from ethanol-water gave 4.03 g. of material melting at 132–137°. Subsequent recrystallizations from alcohol and from chloroform raised the melting point to 140–141°.

Anal.[7] Calcd. for $C_{21}H_{18}Cl_3P$: C, 61.86; H, 4.45. Found: C, 62.02; H, 4.33.

This phosphine was converted to its oxide in 94% yield with 30% hydrogen peroxide by the procedure described above; m.p. 178–181°. Recrystallization two times from chloroform-pentane gave the pure oxide, m.p. 185–185.5°, which exhibited the characteristic strong absorption in the infrared at 8.45μ attributed to P—O bonding.[8,9]

Anal.[7] Calcd. for $C_{21}H_{18}Cl_3OP$: C, 59.52; H, 4.28. Found: C, 59.56; H, 4.33.

Reaction of II with aluminum chloride. (*a*) Nitromethane solvent. The chloromethylphenylphosphine II, (0.42 g.) in 15 cc. of nitromethane was added to a solution of 0.55 g. of aluminum chloride in 20 cc. of nitromethane and the mixture was heated on a steam bath for 40 hr. The mixture was poured into dilute hydrochloric acid and nitromethane was removed by steam distillation. On cooling, a brown solid (0.38 g., 87%) was recovered, m.p. 172–175°. Its infrared spectrum was the same as that of the phosphine oxide, IV.

(*b*) Aluminum chloride. To 1.1 g. of aluminum chloride in 15 cc. of carbon disulfide was slowly added 0.75 g. of II in 15 cc. of carbon disulfide. The solution immediately turned a deep red. After standing at room temperature for 2 hr. it was poured onto ice, hydrochloric acid was added, and the organic layer was separated and washed with water, dried, and warmed to distill the carbon disulfide. Crystals (0.40 g., 53%) of phosphine II, as shown by the infrared spectrum, remained. Recrystallization from ether-pentane yielded 0.30 g. of recovered phosphine, m.p. 135–137°. Some tars insoluble in ether or concentrated hydrochloric acid were also obtained from the reaction mixture.

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(6) G. R. Clemo and G. A. Swan, *J. Chem. Soc.*, 617 (1946). H. Gilman, G. E. Brown, F. J. Webb, and S. M. Spatz, *J. Am. Chem. Soc.*, **62**, 977 (1940), and J. V. Braun, E. Anton, and K. Weissbach, *Ber.*, **63B**, 2847 (1930).

(7) Carbon and hydrogen analyses by Miss H. Beck.

(8) L. W. Daasch and D. C. Smith, *Anal. Chem.*, **23**, 853 (1951).

(9) Our infrared spectra were taken in a Baird double beam recording spectrophotometer. The sample was dispersed in a plate of potassium bromide.

2-Nitro-9,10-ψ-dinitrosophenanthrene[1]

J. H. BOYER AND G. MAMIKUNIAN

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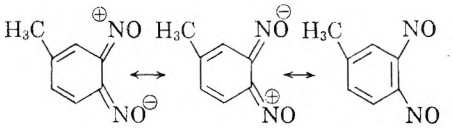
Symmetry requirements for *o*-dinitroso aromatic compounds, *e.g.* 4-methyl-1,2-ψ-dinitrosobenzene (I), do not allow the structural assignment as isomeric furoxanes, *e.g.* 5-(6-) methylbenzfuroxane (II), although they have been so described since 1912.[2,3] Meisenheimer, Lange, and Lamparter demonstrated the unsymmetrical nature of the furoxane ring in a preparation of isomeric furoxanes by an oxidation of corresponding γ-(*amphi*)

(1) Partial support of this work under contract DA-01-009-ORD-428 with the Office of Ordnance Research is gratefully acknowledged.

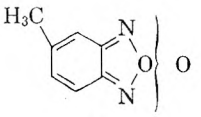
(2) A. G. Green and F. M. Rowe, *J. Chem. Soc.*, **101**, 2452 (1912).

(3) J. H. Boyer, R. F. Reinisch, M. J. Danzig, G. A. Stoner, and F. Sahhar, *J. Am. Chem. Soc.*, **77**, 5688 (1955).

dioximes of *p*-methoxy benzil.[4] Both furoxanes were obtained from *d*-(*anti*) and β-(*syn*) dioximes of the unsymmetrical benzil.[4] This method has now been chosen to establish the symmetry requirements for a mono-substituted derivative of 9,10-dinitrosophenanthrene.



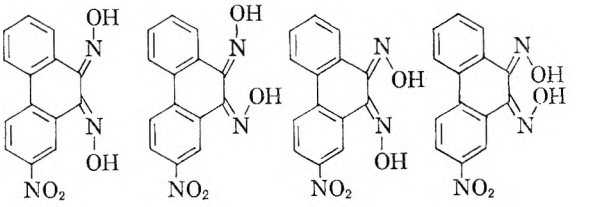
I



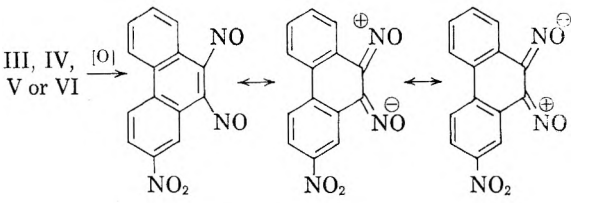
II

The preparation of 2-nitro-9,10-dinitrosophenanthrene (VII) by dehydrogenating 2-nitrophenanthrenequinone dioxime required mononitration[5] of phenanthrenequinone and the preparation, separation, and identification of the four isomeric dioximes. The dioximes were prepared from the quinone and hydroxylamine hydrochloride either in refluxing ethanol and pyridine or in ethanol and pyridine (or potassium carbonate) in heated pressure bottles. Structural assignment of the dioximes was based upon chelation tests. In chelation with nickel *bis*-aryl glyoximes with an α-(*anti*) modification give red insoluble precipitates and yellow or yellow-green precipitates are obtained from γ-(*amphi*) modifications.[6] There is no reaction between nickel salts and β-(*syn*) glyoximes.[6] Of the four isomers of 2-nitrophenanthrenequinone dioxime, one (m.p. 197°) gives a red insoluble nickel salt and is assumed to be the α-(*anti*) modification (III). Two others (m.p. 172° and 183°) afford yellow-green nickel salts and are therefore assumed to be the expected γ-(*amphi*) forms (IV, V). No attempt was made to differentiate between them. The last one (m.p. 190–191°) fails to form a nickel chelate and is assumed to be the β-(*syn*) isomer (VI).

The product (VII) obtained upon dehydrogenation of each 2-nitrophenanthrenequinone dioxime was not obtained in isomeric modifications. It presumably requires a symmetrical arrangement of the N_2O_2 moiety and is assigned the structure of 2-nitro-ψ-9,10-dinitrosophenanthrene (VII). It was also obtained upon treating phenanthrenequinone dioxime with nitric acid at room temperature.



III IV V VI



VII

Reduction of both furoxanes and *o*-dinitroso-aromatic compounds brings about the formation of dioximes. Whereas *amphi*-dioximes are obtained from furoxanes,[4] the structural modification of the dioximes obtained from *o*-dinitroso aromatic compounds has not previously been determined. In the present case reduction of 2-nitro-ψ-9,10-dinitrosophenanthrene with hydroxylamine in pyridine affords the lower melting *amphi* dioxime of 2-nitrophenanthrenequinone.

EXPERIMENTAL[7]

Preparation of 2-nitro-9,10-phenanthrenequinone dioximes. Procedure A.[8] A mixture of 1.0 g. (0.004 mole) of 2-nitro-9,10-phenanthrenequinone,[6] 20.0 g. (0.288 mole) of hydroxylamine hydrochloride, 10 ml. of pyridine, and 80 ml. of 95% ethanol was heated at reflux with mechanical stirring for 20 hr. as the color changed from yellow-orange to dark green. After 2 hr. at room temperature, pyridine hydrochloride as long colorless needles was isolated by filtration. Upon adding 150 ml. of water at room temperature to the filtrate a mixture, 1.0 g. (90%), of oximes precipitated and was purified from aqueous methanol. After three precipitations from methanol, a light green powder, one of the γ-(*amphi*) dioximes, 0.77 g. (68%), m.p. 172° (partial dec. at 167°), was collected. Upon the addition of a drop of nickel chloride solution to a sample in 5 ml. of ethanol a characteristic yellow-green precipitate was observed.

Anal. Calcd. for $C_{14}H_9N_3O_4$: C, 59.37; H, 3.20; N, 14.84; O, 22.60. Found: C, 59.49; H, 3.12; N, 14.88; O, 22.51.

From the combined filtrates a flaky light yellow solid precipitated during 24 hr. and was isolated and dried 10 hr. in the vacuum oven at 60°. A solution in ethanol gave a red precipitate, characteristic of an α-(*anti*) dioxime, with a nickel salt. The m.p. was 188–203° with decomposition, while charring occurred some 4° lower.

A mixture of 6.0 g. (0.023 mole) of 2-nitro-9,10-phenanthrenequinone, 120.0 g. (1.727 mole) of hydroxylamine hydrochloride, 80 ml. of pyridine, and 20 ml. of 95% ethanol was heated at reflux with mechanical stirring for 12 hr. as the color of the reaction mixture changed from light to dark green. After overnight standing, the solution was diluted with 1.5 liters of distilled water and a flaky yellow-

(4) J. Meisenheimer, H. Lange, and W. Lamparter, *Ann.*, **444**, 94 (1925).

(5) F. M. G. Bavin and M. J. S. Dewar, *J. Chem. Soc.*, 4477 (1955). Indian patent 50,970; *Chem. Abstr.*, **50**, 7870 (1956). S. Kato, M. Maezawa, S. Hirano, and S. Ishigaki, *Yuki Gôsei Kagaku Kyôkai Shi*, **15**, 29 (1957); *Chem. Abstr.*, **51**, 10462 (1957).

(6) A. E. Martell and M. Calvin, *Chemistry of the Metal Chelate Compounds*, Prentice-Hall, New York, 1952, 332.

(7) Analyses by Alfred Bernhardt, Microanalytisches Laboratorium, Muheim (Ruhr), Germany.

(8) W. E. Bachmann and C. H. Boatner, *J. Am. Chem. Soc.*, **58**, 2097 (1936).

green precipitate of a mixture of oximes was filtered, 5.99 g. (92%), m.p. 150–195°. The crude material was extracted with 600 ml. of boiling water and then with 500 ml. of boiling methanol. The light green methanol solution was filtered while still hot from an orange-green precipitate. Upon dilution with 200 ml. of water, 0.94 g. (13%), m.p. 172° (dec.) of a γ-(*amphi*) dioxime separated as a yellow powder (see above). The orange-green precipitate dissolved in 400 ml. of hot methanol over a period of 12 hr. A negligible amount of foreign material was removed by filtration and the filtrate, diluted with 100 ml. of distilled water was stored overnight at room temperature. The other γ-(*amphi*) dioxime as a flaky yellow powder, 2.22 g. (33%), m.p. 183–185° (charring at 180°) was reprecipitated from methanol and an analytical sample was dried in the vacuum oven for 12 hr. at 80–95°. A pale green precipitate was observed upon adding a drop of nickel chloride solution to an ethanol solution of this dioxime.

Anal. Calcd. for $C_{14}H_9N_3O_4$: C, 59.37; H, 3.20; N, 14.84. Found: C, 59.39; H, 3.38; N, 14.75.

Procedure B.[9] In a pressure bottle, 1.0 g. (0.004 mole) of 2-nitro-9,10-phenanthrenequinone was mixed with 10.0 g. (0.144 mole) of hydroxylamine hydrochloride, 4 ml. of pyridine, and 80 ml. of 95% ethanol. The bottle was sealed, and placed in boiling water for 4 hr. It was then cooled in a Dry Ice and acetone bath and carefully opened. Pyridine hydrochloride was removed by filtration, the filtrate was diluted with distilled water, a yellow flaky precipitate, m.p. 195–198°, 0.95 g. (85%), was removed, dissolved in 300 ml. of hot methanol and reprecipitated by the addition of 80 ml. of distilled water to the cold solution. A yellow-orange powder, after three additional reprecipitations from methanol, gave an analytical sample, m.p. 194.5–195.8° of the α-(*anti*) dioxime. In hot ethanol this dioxime reacted with one drop of a nickel salt solution with the formation of a red precipitate.

Anal. Calcd. for $C_{14}H_9N_3O_4$: C, 59.37; H, 3.20; N, 14.84. Found: C, 59.29; H, 3.29; N, 14.66.

In a pressure bottle 2.0 g. (0.008 mole) of 2-nitro-9,10-phenanthrenequinone was mixed with 20.0 g. (0.288 mole) of hydroxylamine hydrochloride in 80 ml. of 95% ethanol and 5.0 g. of potassium carbonate. The bottle was sealed and placed in boiling water for 22 hr. during which time the color of the reaction mixtures became yellow-orange. The pressure bottle was cooled in the refrigerator for a day at 15°, opened, and the precipitate was extracted twice with ether. The ether extracts were combined and evaporated over a steam bath to dryness. The residue was dissolved in 80 ml. of 95% ethanol and the solution was stored for one week in the refrigerator. A flaky pale green solid precipitated, 0.8 g. (35%), m.p. 188–189° (dec.). After three precipitations from methanol, the solid, m.p. 190–191° (dec.), gave no precipitate upon being treated with a solution of nickel chloride.

Anal. Calcd. for $C_{14}H_9N_3O_4$: C, 59.37; H, 3.20; N, 14.84. Found: C, 61.19; H, 2.67; N, 15.05.

Oxidation of 2-nitro-9,10-phenanthrenequinone dioxime. Procedure A. To 0.50 g. (0.002 mole) of each of the four isomeric 2-nitro-9,10-phenanthrenequinone dioximes, in 75 ml. of 50% ethanol, chlorine was added over a period of 10 min., during which time the temperature was held at 55–60°. As a colorless precipitate formed, the solution turned from dark red to pale yellow. The mixture was chilled and filtered. A colorless amorphous precipitate, m.p. 211–212°, was recrystallized from aqueous pyridine and washed with hot methanol, 0.45 g. (91%). An analytical sample, m.p. and mixture m.p. 211–212°, was dried in the vacuum oven for 12 hr. at 150°.

Anal. Calcd. for $C_{14}H_7O_4N_3$: C, 59.79; H, 2.50; N, 14.94. Found: C, 59.96; H, 2.48; N, 14.92.

(9) E. Mosettig and J. W. Krueger, *J. Am. Chem. Soc.*, **58**, 1311 (1936).

Procedure B. With stirring 0.5 g. (0.002 mole) of each of the four isomeric 2-nitro-9,10-phenanthrenequinone dioximes, was dissolved in 100 ml. of 69% nitric acid. The solution was poured into 400 ml. of ice cold water. A colorless precipitate was collected as a powder, 0.39 g. (70%), m.p. 210–213°. The crude product was dissolved in 20 ml. of hot pyridine and the hot solution was filtered. The filtrate was chilled and diluted with 20–30 ml. of distilled water. A colorless precipitate, m.p. 211–212°, after two reprecipitations with pyridine, gave an analytical sample, m.p. and mixture m.p. 211–212°.

Anal. Calcd. for $C_{14}H_7N_3O_4$: C, 59.79; H, 2.50; N, 14.94. Found: C, 59.48; H, 2.40; N, 14.11.

Nitration and oxidation of 9,10-phenanthrenequinone dioxime. With stirring 0.50 g. (0.002 mole) of 9,10-phenanthrenequinone dioxime, m.p. 199–200°, was added to 80 ml. of 69% nitric acid at room temperature. A pale brown flaky solid formed immediately and was dissolved in 100 ml. of boiling ethanol. The solution was filtered while still hot, chilled in a Dry Ice and acetone bath, and diluted with distilled water. A colorless precipitate of 2-nitro-9,10-ψ-dinitrosophenanthrene, 0.36 g. (62%), m.p. and mixture m.p. 211–212°, was collected.

Reduction of 2-nitro-9,10-dinitrosophenanthrene. To 0.40 g. (0.002 mole) of 2-nitro-9,10-dinitrosophenanthrene in 50 ml. of hot 95% ethanol and 5 ml. of pyridine, 10.0 g. (0.144 mole) of hydroxylamine hydrochloride was added. After heating at reflux temperature for 1 hr., the solution was poured into 300 ml. of distilled water at 0°. A yellow-green precipitate, 0.30 g. (72%), m.p. 172–174° (dec.), of a γ-(*amphi*) 2-nitro-9,10-phenanthrenequinone dioxime was collected.

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3,3-Dinitro-1-alkanols

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Of the aliphatic *gem*-dinitro-1-alkanols, the 2,2-dinitro-1-alkanols are readily prepared by the Henry reaction of 1,1-dinitroalkanes and formaldehyde:[1–3] The 4,4-dinitro-1-alkanols are pre-

$$RC(NO_2)_2H + CH_2O \longrightarrow RC(NO_2)_2CH_2OH$$

pared by the selective reduction of Michael adducts to 1,1-dinitroalkanes:[4,5]

$$RC(NO_2)_2H + CH_2{=}CHCO_2CH_3 \longrightarrow$$

$$RC(NO_2)_2CH_2CH_2CO_2CH_3 \xrightarrow{LiAlH_4} RC(NO_2)_2CH_2CH_2CH_2OH$$

This paper reports the synthesis of the hitherto unknown 3,3-dinitro-1-alkanols.

(1) P. Duden and G. Ponndorf, *Ber.*, **38**, 203 (1905).
(2) H. Feuer, G. B. Bachman, and J. P. Kispersky, *J. Am. Chem. Soc.*, **73**, 1360 (1951).
(3) M. B. Frankel and K. Klager, *J. Am. Chem. Soc.*, **79**, 2953 (1957).
(4) H. Shechter, D. Ley, and L. Zeldin, *J. Am. Chem. Soc.*, **74**, 3664 (1952).
(5) H. Feuer and T. J. Kucera, *J. Am. Chem. Soc.*, **77**, 5740 (1955).

3,3-Dinitro-1-butanol (II) was prepared by diazotization of 3,3-dinitrobutylamine hydrochloride (I).

$$CH_3C(NO_2)_2CH_2CH_2NH_2\cdot HCl \xrightarrow{NaNO_2} CH_3C(NO_2)_2CH_2CH_2OH$$

I II

3,3-Dinitro-1,5-pentanediol (VI) was synthesized from 4,4-dinitroheptanedioic acid (III). This acid was degraded by the Hunsdiecker reaction to 3,3-dinitro-1,5-dibromopentane (IV).[6] Compound IV was converted to 3,3-dinitro-1,5-pentanediol diacetate (V), which by ester interchange with methanol gave 3,3-dinitro-1,5-pentanediol (VI).

$$C(CH_2CH_2CO_2H)_2 \xrightarrow[2.\ Br_2\text{-}CCl_4]{1.\ AgNO_3} C(CH_2CH_2Br)_2$$

III IV

$$\xrightarrow{AgOAc} C(CH_2CH_2OAc)_2 \xrightarrow{CH_3OH} C(CH_2CH_2OH)_2$$

V VI

EXPERIMENTAL[7,8]

3,3-Dinitro-1-butanol (II). To a solution of 20 g. (0.1 mole) of 3,3-dinitrobutylamine hydrochloride[9] in 200 ml. of water was added a solution of 7.8 g. (0.11 mole) of sodium nitrite in 50 ml. of water. The reaction mixture was warmed to 45°, a vigorous evolution of nitrogen occurred and the temperature rose to 66°. After about 60 sec. a clear greenish solution was formed, which was kept for 10 min. at 60°. The aqueous solution was cooled and extracted twice with methylene chloride. The extracts were washed with saturated sodium chloride solution, dried, and concentrated. Distillation of the residue gave 9.2 g. (56.1%) of product, b.p. 70–80°/1μ, n_D^{25} 1.4660.

Anal. Calcd. for $C_4H_8N_2O_5$: C, 29.27; H, 4.91; N, 17.07. Found: C, 29.07; H, 4.66; N, 17.61.

3,3-Dinitro-1,5-dibromopentane (IV). The ammonium salt of 4,4-dinitroheptanedioic acid[10] was prepared by adding 50 ml. of concentrated ammonium hydroxide to a suspension of 50 g. (0.2 mole) of 4,4-dinitroheptanedioic acid in 1 liter of water. The resulting solution was boiled to evaporate the excess ammonia. The hot solution was added to a solution of 70 g. (0.41 mole) of silver nitrate in 2 liters of water. After the precipitate was digested for a short time, it was cooled, filtered, suspended in distilled water, and filtered. A slurry of the wet silver salt in 1 liter of carbon tetrachloride was heated under a Dean-Stark trap until all the water was removed. The amount of silver salt obtained (86–88%) was calculated by subtracting the weight of water collected from the weight of the wet salt.

A solution of 436 g. (2.7 moles) of dry bromine in 500 ml. of dry carbon tetrachloride was warmed to 50° and a slurry of 323 g. (0.7 mole) of silver 4,4-dinitroheptanedioate in 2 liters of carbon tetrachloride was added portionwise while the temperature of the mixture was maintained at 50–55°. After the addition was complete, the reaction mixture was stirred for two more hours, cooled, and filtered. The filtrate was decolorized by washing with sodium bisulfite solution, dried, and concentrated. Distillation of the residue gave 93.5 g. (41.8%) of a light yellow liquid, b.p. 110–120°/1 mm., n_D^{25} 1.5348.

Anal. Calcd. for $C_5H_8Br_2N_2O_4$: Br, 49.95; N, 8.76. Found: Br, 49.37; N, 8.17.

3,3-Dinitro-1,5-diacetoxypentane (V). A mixture of 65 g. (0.2 mole) of 3,3-dinitro-1,5-dibromopentane, 100 g. (0.6 mole) of silver acetate, and 600 ml. of glacial acetic acid was refluxed for 24 hr. The solution was diluted with ether to precipitate the dissolved salts, filtered, and the filtrate concentrated to about 200 ml. The filtrate was diluted with more ether, washed with dilute sodium bicarbonate solution until neutral, and treated with charcoal. The ether was then evaporated and the residue was crystallized from ethanol at −15° to give 41.6 g. (74%) of white crystals, m.p. 34–34.5°.

Anal. Calcd. for $C_9H_{14}N_2O_8$: C, 38.85; H, 5.07; N, 10.07. Found: C, 39.24; H, 5.12; N, 10.29.

3,3-Dinitro-1,5-pentanediol (VI). A solution of 40.4 g. (0.14 mole) of 3,3-dinitro-1,5-diacetoxypentane, 250 ml. of methanol, and 0.5 g. of anhydrous hydrogen chloride was refluxed for 14 hr. The methanol solution was then treated with charcoal and concentrated. The residue was recrystallized from benzene to give 25 g. (88.6%) of white needles, m.p. 72–73°.

Anal. Calcd. for $C_5H_{10}N_2O_6$: C, 30.93; H, 5.19. Found: C, 31.05; H, 4.98.

Acknowledgment. We are indebted to the office of Naval Research for the financial support of this work.

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(6) A similar reaction was reported for the conversion of 4,4-dinitropentanoic acid to 3,3-dinitro-1-bromobutane, H. Shechter and L. Zeldin, *J. Am. Chem. Soc.*, **73**, 1276 (1951).

(7) All melting points are uncorrected.

(8) Microanalyses by Elek Microanalytical Laboratories, Los Angeles, Calif.

(9) The preparation of this compound will be described in a future publication.

(10) L. Herzog, M. H. Gold, and R. D. Geckler, *J. Am. Chem. Soc.*, **73**, 749 (1951).

Preparation of Aliphatic Secondary Nitramines

MILTON B. FRANKEL AND CLINTON R. VANNEMAN

Received May 22, 1958

In connection with our work on the preparation of aliphatic secondary nitramines containing a nitrile group,[1] a simple, economical synthetic method was needed. Inasmuch as Chute, Herring, Toombs, and Wright[2] reported the preparation of nitriminodipropionitrile in 71% yield from iminodipropionitrile, it was decided to study this reaction in detail in order to find the optimum conditions for this conversion. In their procedure both nitric acid and acetic anhydride were employed in large excess. This is disadvantageous because of (*a*) waste of nitric acid and acetic anhydride, (*b*) the neces-

(1) M. B. Frankel and K. Klager, *J. Am. Chem. Soc.*, **78**, 5428 (1956).

(2) W. J. Chute, K. G. Herring, L. E. Toombs, and G. F Wright, *Can. J. Research*, **26B**, 89 (1948).

sity in large scale operation of recovering the excess acetic and nitric acids, and (*c*) the potential hazard since tetranitromethane is formed from the reaction of nitric acid and acetic anhydride.[3]

Using essentially the same procedure as employed by Chute *et al.*,[2] that is, the simultaneous addition of iminodipropionitrile, nitric acid, and hydrochloric acid to acetic anhydride, a systematic study of this nitration was undertaken to determine the conditions and reactant ratios for optimum yields. Using one mole of iminodipropionitrile and varying the molar quantities of nitric acid, acetic anhydride, and hydrochloric acid, it was found that an optimum yield of 73.1% was obtained with 1.1 moles of nitric acid, 1.4 moles of acetic anhydride, and 0.05 mole of hydrochloric acid. Several more runs were made with these quantities and consistent yields of 70–73% were obtained. On scaling the nitration up to a 15.0 mole batch, it was found that the yield decreased to 43.2%. This was substantiated in subsequent runs. In the larger run the addition of amine, nitric acid, and hydrochloric acid was carried out over a greater length of time than in the smaller run. Thus the amine was exposed to a large excess of acetic anhydride for a greater length of time in the larger run; this resulted in a reduced yield apparently owing to acetylation of the amine. In order to keep the concentration of the acetic anhydride at a minimum, the addition procedure was reversed. The amine was added to the nitric acid followed by the addition of acetic anhydride and hydrochloric acid. A yield of 77% of the nitramine was then obtained on a 15.0 mole batch. Subsequent runs substantiated this yield.

This procedure was then applied to improve the synthesis of *N*-methyl-3-nitraminopropionitrile, which was previously prepared by isolating the nitric acid salt of *N*-methyl-3-aminopropionitrile and then dehydrating the salt with an excess of nitric acid and acetic anhydride; the over-all yield was 50.7%.[1] Using a modification of the improved procedure, the direct nitration of *N*-methyl-3-aminopropionitrile gave *N*-methyl-3-nitraminopropionitrile in yields of 87–89%. This modification consisted in using methylene chloride as a solvent for the nitration reaction. In the preparation of nitriminodipropionitrile, the product precipitated when the reaction mixture was quenched with water. In the case of a liquid product, such as *N*-methyl-3-nitraminopropionitrile, a solvent was desirable to extract the nitramine from the acid mixture. Accordingly, the nitration was carried out in methylene chloride, which served not only as a solvent for the starting amine and the product but also as a diluent for the reaction. The importance of keeping the concentration of acetic anhydride at a minimum during the nitration was shown again. By reversing the mode of addition, that is adding the *N*-methyl-3-aminopropionitrile, nitric acid, and hydrochloric acid to acetic anhydride, the yield of *N*-methyl-3-nitraminopropionitrile was decreased to 43–57%.

(3) P. Liang, *Org. Syntheses*, **Coll. Vol. III**, (1955).

EXPERIMENTAL

Nitriminodipropionitrile. To 694.5 ml. (16.5 moles) of 98–99% nitric acid was added in 30 min. 900 ml. (7.5 moles) of iminodipropionitrile, keeping the temperature at 0–10° by external cooling. The reaction mixture consisted of a yellow slurry which still could be stirred uniformly. (If all of the amine is added at this point, the mixture becomes too thick for stirring.) The temperature of the reaction mixture was allowed to rise to 15° and the simultaneous addition of 900 ml. (7.5 moles) of iminodipropionitrile, 1980 ml. (21.0 moles) of acetic anhydride, and 62.6 ml. (0.75 mole) of 37% hydrochloric acid was made dropwise in 2.5 hr., keeping the temperature at 15–20° by external cooling. The amine and acetic anhydride were added at the same rate, so as to ensure that the addition of the amine will be completed while only about half of the acetic anhydride has been added. The addition of the acetic anhydride and hydrochloric acid were completed at about the same time. The reaction mixture was stirred for 3 hr. at 25–30°, intermittent cooling being required during this period in order to stay within this temperature range. The mixture was then cooled to 5–10° and quenched with 4 liters of ice water. The white solid was collected, washed thoroughly with ice water, and dried to give 1940.4 g. (77.0%), m.p. 54–55° (lit. value, 53.5–55.5°[2]).

N-Methyl-3-nitraminopropionitrile. A solution of 84.1 g. (1.0 mole) of *N*-methyl-3-aminopropionitrile in 100 ml. of methylene chloride was cooled to 0–10° and 46.3 ml. (1.1 moles) of 98–99% nitric acid was added dropwise in 30 min., keeping the temperature at 0–10°. The temperature of the reaction mixture was allowed to rise to 20° and 132 ml. (1.4 moles) of acetic anhydride and 2.5 ml. (0.03 mole) of 37% hydrochloric acid was added dropwise in 30 min., keeping the temperature at 20–25° by external cooling. The reaction mixture was stirred at 25–30° for 2.5 hr., cooled to 5–10° and quenched by the addition of 100 ml. of ice water. The methylene chloride layer was separated and the aqueous layer was extracted with two 100-ml. portions of methylene chloride. The combined methylene chloride extracts were washed with saturated sodium carbonate solution until the aqueous phase reached a *p*H of 8. After a final wash with water, the methylene chloride solution was concentrated *in vacuo* leaving 115.2 g. (89.2%) of light yellow liquid, n_D^{25} 1.4855 (lit. value of distilled product, n_D^{25} 1.4863).[1]

Acknowledgment. The authors are indebted to the Bureau of Ordnance for the financial support of this work and to Mr. Otto Schaeffler for aid in the experimental work.

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Derivatives of *N*-Methylnitraminoacetonitrile

MILTON B. FRANKEL

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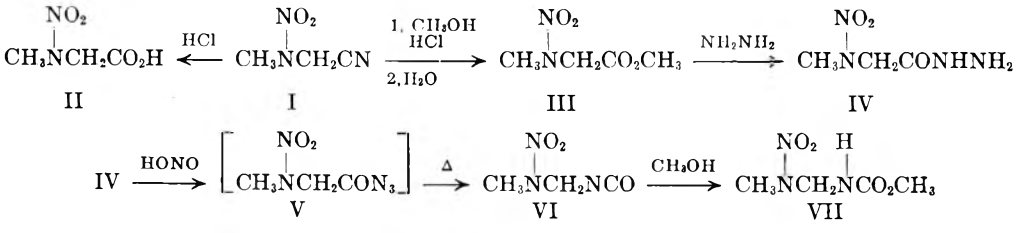
The preparation of *N*-methyl-3-nitraminopropionitrile and its conversion to *N*-methyl-3-nitraminopropionyl chloride, *N*-methyl-2-nitraminoethyl

isocyanate, and *N*-methyl-2-nitraminoethylamine were recently described.[1] In continuation of the study of the chemistry of simple aliphatic secondary nitramines containing a nitrile group, the synthesis and reactions of the lowest member of this series, *N*-methylnitraminoacetonitrile (I), are reported in the present paper.

N-Methyl-3-nitraminopropionitrile was prepared by dehydrating the nitric acid salt of *N*-methyl-3-aminopropionitrile using acetic anhydride and chloride ion catalyst. It was not possible to isolate the nitric acid salt of *N*-methylaminoacetonitrile because of its hygroscopicity. The nitration of *N*-methylaminoacetonitrile was effected by preparing the nitric acid salt *in situ*, and treating it directly with acetic anhydride and chloride ion catalyst to give a 60.9% yield of I. Without the chloride catalyst the yield was decreased to 3.1%.

Hydrolysis of I with concentrated hydrochloric acid gave *N*-methylnitraminoacetic acid (II). Attempts to convert II to the corresponding acid chloride using thionyl chloride or phosphorus pentachloride were unsuccessful owing to the decomposition of II. Methyl *N*-methylnitraminoacetate (III) was prepared by treating I with methanolic hydrogen chloride and hydrolyzing the intermediate imido ester hydrochloride. *N*-methylnitraminoacetohydrazide (IV) was readily formed from III and hydrazine. Compound IV was converted to the corresponding azide (V), which was decomposed *in situ* to give *N*-methylnitraminomethyl isocyanate (VI). The isocyanate reacted very readily with methanol to form the methyl carbamate (VII). Attempts to convert VI to *N*-methylnitraminomethylamine hydrochloride by treatment with concentrated hydrochloric acid, in the same manner in which *N*-methyl-2-nitraminoethylamine hydrochloride was prepared from *N*-methyl-2-nitraminoethyl isocyanate, were unsuccesful. The only compound isolated from this reaction was ammonium chloride. The above reactions are summarized in Chart I.

CHART I



EXPERIMENTAL[2,3]

N-Methylnitraminoacetonitrile (I). A solution of 490 g. (7.0 moles) of *N*-methylaminoacetonitrile[4] in two liters of methylene chloride was cooled to 0–5° and 325 ml. (7.7 moles) of 98–99% nitric acid was added dropwise with good stirring. After the addition was complete, the temperature was allowed to rise to 20° and 928 ml. (9.8 moles) of acetic anhydride and 17.7 ml. (0.21 mole) of 37% hydrochloric acid were added simultaneously at proportionate rates in 1 hr., keeping the temperature at 20–25°. After the addition was complete, the solution was stirred at 25–30° for 2 hr., then cooled to 5° and quenched by the addition of 400 ml. of ice water. The mixture was stirred for 15 min. and the methylene chloride layer was separated. The aqueous layer was extracted with two 500-ml. portions of methylene chloride. The combined methylene chloride extracts were washed with saturated sodium carbonate solution until the *p*H of the aqueous wash was at least 8, dried over sodium sulfate and concentrated *in vacuo*. The light yellow liquid residue was crystallized at −20° from 750 ml. of methanol to give 490 g. (60.9%) of white needles, m.p. 26–27°, n_D^{25} 1.4792.

Anal. Calcd. for $C_3H_5N_3O_2$: C, 31.31; H, 4.38; N, 36.51. Found: C, 31.49; H, 4.39; N, 37.14.

N-Methylnitraminoacetic acid (II). One hundred fifteen ml. of 37% hydrochloric acid was warmed to 60° and 111 g. (0.97 mole) of *N*-methylnitraminoacetonitrile was added dropwise. The temperature of the reaction mixture rose to 90° during the addition. After the addition was complete, the mixture was heated on the steam bath with stirring for 5.5 hr. The mixture was cooled and the products were collected and dried to give 159 g. of white solid. The solid was extracted with four 200-ml. portions of ether leaving 44.4 g. (86.0%) of ammonium chloride. The combined ether extracts were concentrated *in vacuo* leaving 111.6 g. (86.5%) of white solid, m.p. 96.5–98.5°. Recrystallization from 37% hydrochloric acid raised the melting point to 99–100°.

Anal. Calcd. for $C_3H_6N_2O_4$: C, 26.87; H, 4.51; N, 20.89; Eq. Wt., 134.10. Found: C, 27.02; H, 4.72; N, 20.95; Eq. Wt., 134.06.

Methyl N-methylnitraminoacetate (III). A solution of 817 g. (7.1 moles) of *N*-methylnitraminoacetonitrile, 1500 ml. of methanol, and 2500 ml. of absolute ether was cooled to 0–5° and a rapid stream of anhydrous hydrogen chloride gas was bubbled through until the solution was saturated, keeping the temperature at 0–5°. The white crystalline imido ester hydrochloride precipitated. The solid was collected, washed with absolute ether, and added to one liter of water while stirring. The solid dissolved and a colorless oil gradually separated from the solution. The oil was separated and the aqueous phase was extracted with two 1000-ml. portions of methylene chloride. The oil and extracts were combined and washed with 500 ml. of water, 1000 ml. of saturated sodium bicarbonate solution, and 500 ml. of water. The methylene chloride solution was dried over sodium sulfate and concentrated *in vacuo* leaving 869 g. (82.8%) of faint yellow liquid, n_D^{25} 1.4617. Distillation from a Claisen flask gave a colorless liquid, b.p. 87°/0.75 mm., n_D^{25} 1.4615.

Anal. Calcd. for $C_4H_8N_2O_4$: C, 32.43; H, 5.44; N, 18.92. Found: C, 32.59; H, 5.40; N, 18.31.

(1) M. B. Frankel and K. Klager, *J. Am. Chem. Soc.*, **78**, 5428 (1956).

(2) All melting points and boiling points are uncorrected.

(3) Microanalyses by Dr. A. Elek, Elek Microanalytical Laboratories, Los Angeles, Calif.

(4) L. J. Exner, L. S. Luskin, and P. L. deBenneville, *J. Am. Chem. Soc.*, **75**, 4841 (1953).

N-Methylnitraminoacetohydrazide (IV). To a solution of 180 ml. (2.39 moles) of 85% hydrazine hydrate and 200 ml. of methanol was added dropwise, with stirring, 235.2 g. (1.60 moles) of methyl *N*-methylnitraminoacetate. The temperature of the solution rose from 25 to 32°. After stirring for 30 min., the solution was cooled and a white solid precipitated. The product was collected, washed with cold methanol, and dried to give 179.3 g. (76.3%) of white solid, m.p. 81–84°. Recrystallization from ethanol raised the melting point to 84–85°.

Anal. Calcd. for $C_3H_8N_4O_3$: C, 24.32; H, 5.44; N, 37.83. Found: C, 24.70; H, 5.64; N, 38.00.

N-Methylnitraminomethyl isocyanate (VI). A mixture of 14.8 g. (0.1 mole) of *N*-methylnitraminoacetohydrazide, 125 ml. of water, and 125 ml. of chloroform was cooled to 0° and 9.2 ml. (0.11 mole) of 37% hydrochloric acid was added. Then a solution of 10.0 g. (0.11 mole) of 93% potassium nitrite in 20 ml. of water was added dropwise, keeping the temperature at 0–5°. The mixture was stirred for 15 min. and the chloroform layer was separated. The aqueous layer was extracted with two 150-ml. portions of chloroform. The combined chloroform extracts were washed with three 100-ml. portions of ice water, dried over sodium sulfate, and filtered. The solution was concentrated on the water aspirator at a temperature of 10–20° until the volume was decreased by half, to ensure the removal of the last traces of water. The solution was then warmed under a reflux condenser. At 40–50° the decomposition of the azide commenced. After the decomposition started, the solution was slowly heated to reflux. The solution was refluxed until the evolution of nitrogen had ceased (about 2 hr.) and concentrated *in vacuo*. The residue was distilled from a Claisen flask to give 9.0 g. (68.7%) of colorless liquid, b.p. 81–81.5° (2 mm.), n_D^{25} 1.4787.

Anal. Calcd. for $C_3H_5N_3O_3$: C, 27.70; H, 3.87; N, 32.30. Found: C, 27.32; H, 3.81; N, 32.74.

Methyl N-methylnitraminocarbamate (VII). A solution of 2.62 g. (0.02 mole) of *n*-methylnitraminomethyl isocyanate and 5 ml. of methanol was refluxed for 30 min. and concentrated *in vacuo* to give 3.0 g. (92.1%) of white needles, m.p. 65–67°. Recrystallization from methanol raised the melting point to 66–67°.

Anal. Calcd. for $C_4H_9N_3O_4$: C, 29.45; H, 5.56. Found: C, 29.76; H, 5.60.

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Reactions of Aliphatic Nitro Compounds

MILTON B. FRANKEL AND KARL KLAGER

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The preparation of derivatives of the carboxylic acid groups in methyl 4,4-dinitropentanoate,[1] methyl 4-nitrazapentanoate,[2] and methyl 3-nitrazabutyrate[3] has been described. Aliphatic monoesters containing both the *gem*-dinitro and nitraza groups have also been reported. Feuer, Bachman, and May[4] prepared ethyl 3,5,5-trinitro-3-azapentanoate (I) and Frankel and Klager[5] reported the synthesis of methyl 3,5,5-trinitro-3-azahexanoate (II). Attempts by Feuer *et al.*[4] to hydrolyze I with concentrated hydrochloric acid resulted only in decomposition with evolution of oxides of nitrogen. The preparation of derivatives of the carboxylic acid group in II is reported in the present work.

$HC(NO_2)_2CH_2N(NO_2)CH_2CO_2C_2H_5$
I

$CH_3C(NO_2)_2CH_2N(NO_2)CH_2CO_2CH_3$
II

Hydrolysis of II with concentrated hydrochloric acid gave 3,5,5-trinitro-3-azahexanoic acid (II) in good yield, indicating that replacement of the acidic hydrogen atom in I with an alkyl group has a stabilizing influence on the molecule. Compound III was converted to 3,5,5-trinitro-3-azahexanoyl chloride (IV) and the corresponding azide (V). The azide was not isolated but decomposed *in situ* to form 2,4,4-trinitro-2-aza-1-pentyl isocyanate (VI). The isocyanate exploded violently on standing at ambient temperature but could be stored safely at −20° for several months. It reacted readily with methanol to form methyl *N*-(2,4,4-trinitro-2-aza-1-pentyl) carbamate (VII). Attempts to convert VI to 2,4,4-trinitro-2-aza-1-pentylamine hydrochloride (VIII) by treatment with concentrated hydrochloric acid were unsuccessful; the only compound isolated from this reaction was ammonium chloride.[6]

$$II \xrightarrow{HCl} CH_3C(NO_2)_2CH_2N(NO_2)CH_2CO_2H \xrightarrow{SOCl_2}$$
III

$$CH_3C(NO_2)_2CH_2N(NO_2)CH_2COCl$$
IV

$$\xrightarrow{NaN_3} [CH_3C(NO_2)_2CH_2N(NO_2)CH_2CON_3] \xrightarrow{\Delta}$$
V

$$CH_3C(NO_2)_2CH_2N(NO_2)CH_2NCO$$
VI

$$CH_3C(NO_2)_2CH_2N(NO_2)CH_2NHCO_2CH_3 \xleftarrow{CH_3OH} \text{VI} \xrightarrow{HCl} CH_3C(NO_2)_2CH_2N(NO_2)CH_2NH_2\cdot HCl$$
VII VIII

(1) H. Schechter and L. Zeldin, *J. Am. Chem. Soc.*, **73**, 1276 (1951).

(2) M. B. Frankel and K. Klager, *J. Am. Chem. Soc.*, **78**, 5428 (1956).

(3) M. B. Frankel, *J. Org. Chem.*, **23**, 1811 (1958).

(4) H. Feuer, G. B. Bachman, and W. May, *J. Am. Chem. Soc.*, **76**, 5124 (1954).

(5) M. B. Frankel and K. Klager, *J. Am. Chem. Soc.*, **79**, 2953 (1957).

(6) The same results were observed in attempting to convert 2-nitrazapropyl isocyanate to 2-nitrazapropylamine hydrochloride.[3] This is in marked contrast to the facile preparation of 3-nitrazabutylamine hydrochloride from 3-nitrazabutyl isocyanate,[2] where the primary amino group is in a β position to the nitraza group.

EXPERIMENTAL[7,8]

3,5,5-Trinitro-3-azahexanoic acid (III). A mixture of 26.6 g. (0.10 mole) of methyl 3,5,5-trinitro-3-azahexanoate[5] and 75 ml. of concentrated hydrochloric acid was heated on the steam bath for 8 hr. On cooling, 15.1 g. (60.0%) of white solid separated, m.p. 133–136°. Recrystallization from ethylene dichloride raised the melting point to 139–140°.

Anal. Calcd. for $C_5H_8N_4O_8$: C, 23.82; H, 3.20; N, 22.22. Found: C, 23.96; H, 3.25; N, 22.56.

3,5,5-Trinitro-3-azahexanoyl chloride (IV). A mixture of 5.0 g. (0.02 mole) of 3,5,5-trinitro-3-azahexanoic acid and 25 ml. of redistilled thionyl chloride was refluxed for 8.5 hr. and concentrated *in vacuo* leaving 5.2 g. (96.8%) of white solid, m.p. 85–87°. Recrystallization from carbon tetrachloride raised the melting point to 87–88°.

Anal. Calcd. for $C_5H_7ClN_4O_7$: C, 22.19; H, 2.61; Cl, 13.10; N, 20.71. Found: C, 22.65; H, 2.95; Cl, 13.89; N, 21.27.

2,4,4-Trinitro-2-aza-1-pentyl isocyanate (VI). A solution of 35.1 g. (0.54 mole) of sodium azide in 250 ml. of water was cooled in an ice bath and a solution of 73.0 g. (0.27 mole) of 3,5,5-trinitro-3-azahexanoyl chloride in 200 ml. of acetone was added dropwise, keeping the temperature below 10°. The reaction mixture was stirred for 30 min. and extracted with three 150-ml. portions of chloroform. The chloroform solution was dried for 30 min. over sodium sulfate and placed in a one-liter flask arranged for distillation. About 110 ml. of chloroform was stripped off with the water aspirator to remove the last traces of water. The temperature was raised to 60° with a water bath and the azide was decomposed at atmospheric pressure. Dry chloroform was added periodically to keep the volume constant. After the nitrogen evolution had ceased, the solution was cooled to −10°, causing a white solid to separate. The product was collected and dried, the yield was 48.1 g. (72.0%), m.p. 97–100°. Recrystallization from ethylene dichloride raised the melting point to 102–103°. The compound exploded violently on standing at ambient temperatures but could be stored safely at −20° for several months.

Anal. Calcd. for $C_5H_7N_5O_7$: C, 24.10; H, 2.83; N, 28.11. Found: C, 24.31; H, 3.11; N, 28.05.

Methyl N-(2,4,4-trinitro-2-aza-1-pentyl) carbamate (VII). A solution of 2.49 g. (0.01 mole) of 2,4,4-trinitro-2-aza-1-pentyl isocyanate and 15 ml. of methanol was refluxed for 4 hrs. and concentrated *in vacuo* leaving a quantitative yield of white solid, m.p. 98–100°. Recrystallization from isopropyl alcohol raised the melting point to 100–102°.

Anal. Calcd. for $C_6H_{11}N_5O_8$: C, 25.63; H, 3.94; N, 24.91. Found: C, 25.75; H, 3.81; N, 24.67.

Acknowledgment. We are indebted to the Office of Naval Research for the financial support of this work.

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(7) All melting points are uncorrected.

(8) Microanalyses by Dr. A. Elek, Elek Microanalytical Laboratories, Los Angeles, Calif.

Isolation of β-Sitosterol from *Cassia Absus*, Linn.

A. WILLIAM JOHNSON

Received June 16, 1958

In 1935 Ahmad[1] examined an oil obtained from *Cassia absus*, Linn., and determined its composition in terms of the percentages of fatty acid (80%), glycerol (10.4%), and nonsaponifiable matter (8.4%) present. The latter was not further investigated. In 1954 Sen Gupta *et al.*[2] obtained a 2.2 % yield of an oil upon extracting the seeds of Cassia with petroleum ether. They too determined the fatty acid composition of the oil and also isolated a nonsaponifiable fraction. This material, m.p. 130,° afforded a benzoate, m.p. 142°, and an acetate, m.p. 115°, but was not investigated further.

In following the procedure of Siddiqui *et al.*[3] for the isolation of the alkaloid *Chaksine* from the seeds of *Cassia absus*, an ether-soluble, water-soluble fraction was obtained in 2% yield. Saponification of this oily substance afforded a semisolid nonsaponifiable fraction in 5% yield. From this material, by direct crystallization, was obtained β-sitosterol, m.p. 137–138, $\alpha]_D^{25}$ −30°, λ_{max}^{Nujol} 3400 cm.$^{-1}$ (OH), 840, 803 (tri-substituted olefin). It afforded a benzoate, m.p. 139–140°, λ_{max}^{Nujol} 1700 cm.$^{-1}$(—COO—), 1604, 1591, 715 (C_6H_5—), 840, 800 (trisubstituted olefin), and an acetate, m.p. 126–128°. Reduction over platinum resulted in the uptake of one mole of hydrogen and the formation of stigmastanol, m.p. 139–140°, λ_{max}^{Nujol} 3230 cm.$^{-1}$ (OH), $\alpha]_D^{25}$ + 30°. The properties of the compound, its acetate, benzoate, and dihydro derivative agree with those reported by Bernstein and Wallis[4] for β-sitosterol isolated from cottonseed oil. It is likely that β-sitosterol was the material isolated in crude form by Sen Gupta *et al.*[2]

The mother liquors from the crystallization of β-sitosterol were acetylated and chromatographed on alumina. In this manner additional β-sitosterol was isolated (as its acetate) together with an oily saturated hydrocarbon of as yet unknown structure.

Note added in proof: Since the completion of this work, I. Sen Gupta and E. Mosettig, *J. Ind. Chem. Soc.* **35,** 210 (1958) have identified the material isolated in ref. 2 as β-sitosterol.

EXPERIMENTAL[5]

β-Sitosterol. One kilogram of ground seeds of *Cassia absus*, Linn., was stirred three times as a slurry in 1500 ml. of 0.3% methanolic hydrogen chloride, each for 24 hr. at room temperature, and then filtered. The filtrates were each neutralized with ammonia, brought to *p*H 5 with acetic acid and evaporated to dryness. A total of 212 g. of brown sirup was obtained in this manner. The sirup was taken up in 600 ml. of water and exhaustively extracted with ethyl ether.

(1) Z. Ahmad, *Z. Untersuch. Lebensm.*, **70,** 166 (1935).

(2) I. Sen Gupta, K. Singh and R. P. Sood, *Research Bull. East Panjab Univ.*, No. 48, 63 (1954).

(3) S. Siddiqui and Z. Ahmad, *Proc. Ind. Acad. Sci.*, **2A,** 421 (1935).

(4) S. Bernstein and E. S. Wallis, *J. Org. Chem.*, **2,** 341 (1937–38).

(5) Melting points are uncorrected. Analyses by Schwarzkopf Microanalytical Laboratory, Woodside 77, N. Y. Infrared spectra were determined in Mellon Institute by H. M. Nelson and G. L. Carlson on a Baird model A infrared spectrophotometer.

From the aqueous layer was eventually isolated chaksine iodide in 1.1% yield. The ethereal layer was dried and evaporated to afford 20 g. (2%) of a dark viscous neutral oil.

Saponification of 75 g. of neutral oil *via* ethanolic sodium hydroxide followed by the usual workup afforded 3.9 g. of a neutral, orange semisolid mass. The latter was crystallized from ethanol as a colorless solid (1.1 g.), m.p. 134–136°. Recrystallization from ethanol afforded β-sitosterol as colorless plates, m.p. 137–138°, $\alpha]_D^{25}$ −30° (*c*, 1.1 $CHCl_3$). (Lit.,[4] m.p. 136–137°, $\alpha]_D^{25}$ −36.) Its infrared spectrum was superimposable on that of an authentic sample.

Anal. Calcd. for $C_{29}H_{50}O$: C, 84.0; H, 12.1. Found: C, 84.1; H, 11.9.

The mother liquors remaining after the crystallization of β-sitosterol were evaporated to dryness, then acetylated with acetyl chloride and pyridine. The crude mixture (2.0 g.) was chromatographed on neutral alumina (40 g.) to yield 0.7 g. of β-sitosteryl acetate, m.p. 127–128°, and 0.3 g. of a colorless viscous liquid, n_D^{27} 1.4954. It showed absorption in the infrared characteristic of a saturated hydrocarbon, $\lambda_{max.}$ 2950 cm^{-1}, 2880, 1460, 1380.

β-Sitosterol acetate was prepared by treating 150 mg. of β-sitosterol with 8 ml. of acetyl chloride and a few drops of pyridine at 0°. Pouring the mixture on ice gave a colorless precipitate which crystallized from ethanol as colorless needles, m.p. 126–128°. (Lit.,[4] m.p. 125-126).

Anal. Calcd. for $C_{31}H_{52}O$: C, 81.5; H, 11.5. Found: C, 81.1; H, 11.4.

To 100 mg. of β-siterosterol in 3 ml. of pyridine at 0° was added 3 ml. of benzoyl chloride. The solution was warmed on a steam bath for 10 min. after the initial exothermic reaction had subsided. The solution was poured on ice and the colorless precipitate removed by filtration. The *β-sitosterol benzoate* crystallized from ethanol as colorless needles, m.p. 139–140°. (Lit.,[4] m.p. 145°).

Dihydro-β-sitosterol (*Stigmastanol*). To 100 mg. of platinum oxide in 13 ml. of acetic acid and 27 ml. of ethyl acetate was added 200 mg. of β-sitosterol and the mixture was shaken for 10 hr. under 40 lbs. of hydrogen pressure. The catalyst was filtered and the filtrate added to water to afford a colorless precipitate which crystallized from ethanol as colorless plates, m.p. 139–140°, depressed to 121–130° on admixture with β-sitosterol, $\alpha]_D^{25}$ +30° (*c*, 0.9 $CHCl_3$). (Lit.,[4] m.p. 138–139°, $\alpha]_D^{20}$ + 25°).

Anal. Calcd. for $C_{29}H_{52}O$: C, 83.6; H, 12.6. Found: C, 83.5; H, 12.4.

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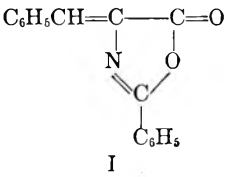
Chemistry of Lactones. II. Reaction of 2-Phenyl-4-benzylidene-5(4*H*)oxazolone with Benzene under Friedel-Crafts Conditions

ROBERT FILLER AND LOURDES M. HEBRON[1]

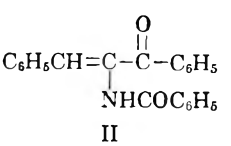
Received June 17, 1958

Oxazolones are often considered similar to cyclic anhydrides in their chemical reactions and might be expected to behave as acylating agents when treated with aromatic hydrocarbons in the presence of anhydrous aluminum chloride. Thus, succinic anhydride reacts with benzene under these conditions to form 3-benzoylpropionic acid. It was therefore of interest to study this reaction using 2-phenyl-4-benzylidene-5(4*H*)oxazolone (I) in place of anhydride. I has the added feature of an α,β-unsaturated carbonyl system.

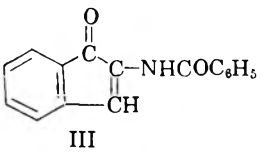


I

By analogy with cyclic anhydrides, it might be anticipated that I would react with benzene to give either 2-benzamidobenzalacetophenone (II) or 2-benzamidoindenone (III), formed by intramolecular cyclization.[2]

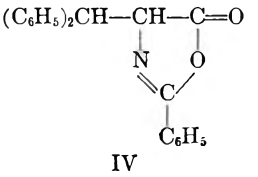


II



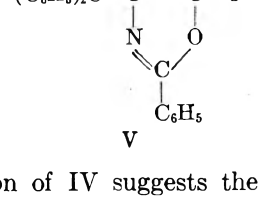
III

However, we did not isolate either II or III, the sole product being the saturated azlactone, 2-phenyl-4-diphenylmethyl-5(4*H*)oxazolone (IV), arising by 1,4 addition of benzene. The yield of IV after recrystallization was 62%.



IV

This saturated azlactone has not been described previously and compounds with this type of structure are not readily obtainable by other routes, especially since attempts to prepare the unsaturated precursor, V, have failed.



V

The isolation of IV suggests the possibility of preparing interesting new compounds containing the diphenylmethyl moiety.

The structure of IV was established by elemental analysis, infrared and ultraviolet spectra, and by formation of the benzylamide by aminolysis.

Whereas I exhibits a strong lactone carbonyl band at 1785 $cm.^{-1}$,[3a] typical of β,γ-unsaturated

(1) From the M.S. thesis of L.M.H., to be submitted to the Graduate School of Illinois Institute of Technology, 1958.

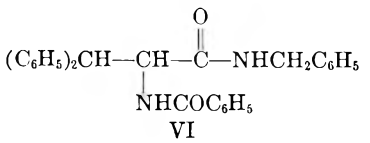
(2) M. S. Newman and L. M. Joshel, *J. Am. Chem. Soc.*, 62, 972 (1940).

(3) (a) H. W. Thompson, R. R. Brattain, H. M. Randall, and R. S. Rasmussen in *The Chemistry of Penicillin*, Princeton University Press, Princeton, N. J., 1949, p. 387. (b) D. H. Whiffen and H. W. Thompson, *J. Chem. Soc.*, 1005 (1946).

γ-lactones,[3b] and >C=N absorption[3a] at 1650 cm.$^{-1}$, IV shows strong absorption at 1810 cm.$^{-1}$ and 1645 cm.$^{-1}$ The latter bands are almost identical with those observed for the 4-isopropyl analog[3a] and this shift of carbonyl absorption is consistent with removal of the conjugation created by attachment of an exocyclic double bond in the 4-position, as in I. It has also been shown that the frequency of the >C=N stretching mode is not appreciably affected by changes in the 4-position of these oxazolones.[3a]

The ultraviolet spectrum further supports structure IV. The intense maximum observed with I at 360 mμ has been attributed to the $C_6H_5CH{=}C{-}N{=}C{-}C_6H_5$ chromophore.[4] The disappearance of this maximum in IV is evidence that this chromophore is absent, whereas the presence of λ_{max}^{EtOH} 245 mμ (ε 5450) is characteristic of the *N*-benzylidene group, $-N{=}C(-)-C_6H_5$.[5] The end absorption observed is also typical of such oxazolones.[5]

Saturated azlactones are generally very susceptible to hydrolysis and particularly to aminolysis.[6] However, IV was stable to a boiling water-acetone mixture, but reacted readily with benzylamine to form the 2-benzamidobenzylamide, VI, in nearly quantitative yield. The formation of an amide has at times been the sole evidence of the presence of an oxazolone and benzylamine is used for determining the proportion of oxazolone in a mixture ("azlactone equivalent").[7]



VI

In contrast to these results, I reacts with phenylmagnesium bromide by ring opening followed by 1,2-addition to give the tertiary alcohol.[8] Results of similar studies on the structurally related α-benzylidene-γ-phenyl-Δ β,γ-butenolide will be reported in a forthcoming paper and compared with those observed with the oxazolone.

EXPERIMENTAL[9]

Reaction of 2-phenyl-4-benzylidene-5(4H)-oxazolone (I) *with benzene.* In a 1-l., round-bottom flask, fitted with a mechanical stirrer, dropping funnel, and reflux condenser, were placed 9.5 g. (0.072 mole) of anhydrous aluminum chloride in 125 ml. of dry, thiophene-free benzene. The mixture was cooled to 10° and stirred for 1 hr. To this solution was added dropwise with stirring a solution containing 6 g. (0.024 mole) of 2-phenyl-4-benzylidene-5(4*H*)oxazolone in 125 ml. dry benzene, the temperature being maintained at 10–20° during the addition. The mixture turned brick red. When all of the oxazolone had been added, the mixture was stirred for an additional 3 hr. at room temperature. The complex was decomposed with 250 ml. dilute (1:15) HCl and two clear layers were obtained. The benzene layer was separated, the aqueous layer extracted with benzene, and the combined benzene extracts washed with dilute HCl, then with water until neutral to litmus. Benzene was removed by evaporation on a steam bath to give a yellow oil which was dissolved in ether and on addition of petroleum ether formed a light yellow precipitate. The product was recrystallized from 95% ethanol to give 4.8 g. (62%) of light yellow crystals, m.p. 158–159°.

Anal. Calcd. for $C_{22}H_{17}NO_2$: C, 80.71; H, 5.24; N, 4.28. Found: C, 80.87; H, 5.23; N, 4.25.

Reaction of 2-phenyl-4-diphenylmethyl-5(4H)-oxazolone (IV) *with benzylamine.* A mixture of 1.96 g. (0.006 mole) of oxazolone in 10 ml. dry benzene and 0.64 g. (0.06 mole) of benzylamine was heated under reflux for 30 min. On cooling, white crystals separated, which were washed with petroleum ether and recrystallized from 85% ethanol (H_2O as diluent) to give 2.4 g. (92%) of VI, m.p. 260–261°.

Anal. Calcd. for $C_{29}H_{26}N_2O_2$: N, 6.45. Found: N, 6.57.

Spectral measurements and analyses. Infrared spectra were obtained on a Perkin-Elmer 21 spectrophotometer and Perkin-Elmer "Infracord." The samples were examined either as Nujol mulls or by use of a KBr disk.

Ultraviolet spectra were measured in 95% ethanol using a Beckman DK-2 spectrophotometer.

The elemental analyses were carried out by Micro-Tech Laboratories, Skokie, Ill.

Acknowledgment. The authors are grateful to the Research Corp. for financial support of this work.

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(4) D. A. Bassi, V. Deulofeu, and F. A. F. Ortega, *J. Am. Chem. Soc.*, **75**, 171 (1953).

(5) R. B. Woodward, A. Neuberger, and N. R. Trenner, in *The Chemistry of Penicillin*, Princeton University Press, Princeton, N. J., 1949, p. 429.

(6) (a) H. E. Carter in *Org. Reactions*, III, 215 (1946). (b) E. Baltazzi, *Quart. Revs.* IX, No. 2 (1955), p. 160.

(7) J. W. Cornforth in *The Chemistry of Penicillin*, Princeton University Press, Princeton, N. J., 1949, p. 735.

(8) (a) R. Filler and J. D. Wismar, *J. Org. Chem.* **22**, 853 (1957). (b) A. Mustafa and A. H. E. Harhash, *J. Org. Chem.* **21**, 575 (1956).

(9) Melting points were determined on a Fisher-Johns block and are not corrected.

8-(2-Methoxyethoxy)caffeine

CARL TABB BAHNER, JOSEPH A. DIPAOLO, AND HELEN JONES

Received June 17, 1958

Kihlman[1] has reported that 8-ethoxycaffeine produced structural chromosomal changes in the root tips. This and closely related compounds have been studied at the Roswell Park Memorial Institute as possible anti-cancer agents. 8-(2-Methoxyethoxy)caffeine was prepared from 8-chlorocaffeine and sodium 2-methoxyethoxide by the general method of Huston and Allen.[2] The crude product, obtained in 80% yield, was recrystallized twice from hot water and once from carbon tetrachloride; m.p. 98.5–99.5° (Fisher-Johns melting

(1) B. Kihlman, *Exptl. Cell Research* 1, 135 (1950).

(2) R. C. Huston and W. F. Allen, *J. Am. Chem. Soc.*, 56, 1356 (1934).

point apparatus); ultraviolet absorption maximum 279mμ.[3]

Anal. Calcd. for $C_{11}H_{16}N_4O_4$: C,49.24; H, 6.02; N, 20.89. Found C, 49.02; H, 6.04; N, 21.09.[4]

When S-180 bearing animals were treated with 125 mg./kg. or 500 mg./kg., tumor growth appeared inhibited about 15%. This compound was not effective in prolonging the survival time of mice that had received injections of Ehrlich ascites cells, Krebs-2 ascites cells, or L-1210 cells.

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CARSON-NEWMAN COLLEGE
JEFFERSON CITY, TENN.

(3) The ultraviolet absorption peak was determined by Mr. Oakley Crawford.

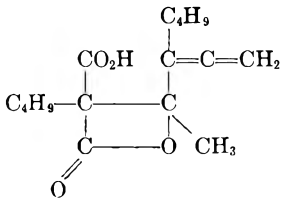
(4) Analyses by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

Reinvestigation of the Structure of the "Dimeric" Acid Found in the Carbonation Products of the Grignard Reagent Formed from 1-Bromo-2-heptyne

JOHN H. WOTIZ,[1] JOSEPH S. MATTHEWS,[2] AND HOWARD E. MERRILL[3]

Received June 23, 1958

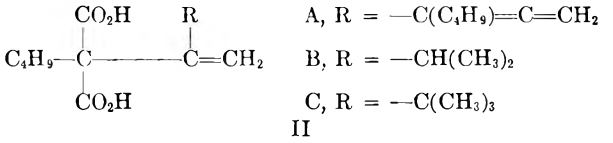
It was reported[4] that the "dimeric" acid found in the carbonation products of the Grignard reagent formed from 1-bromo-2-heptyne is the β-lactonic acid (I)



I

The structure assignment was based on degradation studies, catalytic hydrogenation studies in which two moles of hydrogen were absorbed, and especially in the fact that the "dimeric" acid titrated as a monobasic acid.

In the light of the recent findings that highly substituted malonic acids titrate as monobasic acids in 50% alcohol,[5] the structure of the "dimeric" acid was reinvestigated. We are now favoring the structure IIA, butyl [1-(3-hepta-1,2-dienyl)vinyl]-malonic acid.

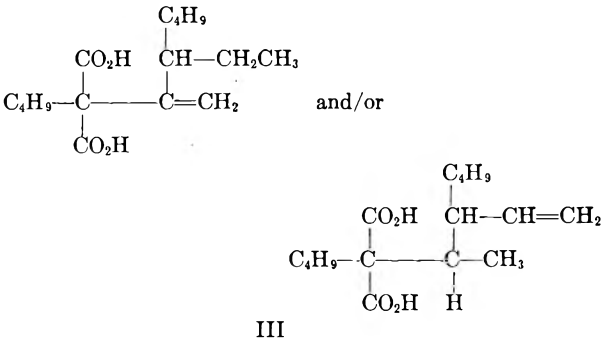


II

The K_1 to K_2 ratio in IIA of 7,760,000 is very high which indicates a highly branched malonic acid. However, it is not as high as in IIB, 28,000,000, or IIC, 57,600,000.[5] The ionization of the acid could be affected in parts by the electronic and electrostatic effects of the unsaturation in R.

It was previously reported[4] that in the presence of Adams' catalyst the "dimeric" acid absorbs hydrogen to the extent of 100% of theory calculated for two double bonds. Additional hydrogenation studies, using a different and more "active" lot of Adams' catalyst, have now shown that the "dimeric" acid absorbs hydrogen to the extent of 100% of theory calculated for three double bonds. In fact, there was no sharp decrease in the rate of the hydrogen uptake after the addition of two moles of hydrogen.

The infrared spectrum of IIA has a single band near 1920 cm.$^{-1}$ characteristic of the allenic linkage,[6] a single, sharp carbonyl band near 1740, and bands near 1635 and 900 cm.$^{-1}$ characteristic of $-\overset{|}{C}=CH_2$. When the hydrogenation is interrupted after the addition of two moles of hydrogen, the product is III.



III

The infrared spectrum of III shows the presence of the 1635 and 900 cm.$^{-1}$ bands and the absence of the 1920 cm.$^{-1}$ band. All three bands are absent after the uptake of three moles of hydrogen.

Quantitative esterification of IIA and of the hydrogenated products of IIA, also favors the substituted malonic acid structure. When IIA reacted with diazomethane, two moles of nitrogen, per mole of acid, were liberated and the distilled product analyzed for the dimethyl ester. However, its infrared spectrum indicated that a molecular rearrangement had taken place since the characteristic

(1) Research Center, Diamond Alkali Company, Painesville, Ohio.

(2) Gulf Research, Pittsburgh, Pa.

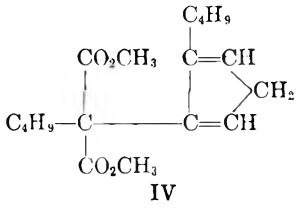
(3) Abstracted from a portion of the Ph.D. dissertation of H.E.M., present address, Esso, Baton Rouge, La.

(4) J. H. Wotiz and J. S. Matthews, *J. Org. Chem.*, **20**, 155 (1955).

(5) J. H. Wotiz and H. E. Merrill, *J. Am. Chem. Soc.*, **80**, 866 (1958).

(6) J. H. Wotiz and D. E. Mancuso, *J. Org. Chem.*, **22**, 207 (1957).

allene absorption at 1920 cm.$^{-1}$ and the terminal methylene group absorption bands near 1635 and 900 cm.$^{-1}$, were absent. Two new, strong and sharp absorption bands at 1620 and 1670 cm.$^{-1}$ were found which we attribute to the presence of conjugated double bonds of a cyclopentadienyl ring in IV.



IV

The presence of the cyclopentadienyl ring is also favored by the fact that IV reacted with maleic anhydride and that a highly red-colored product (substituted fulvene) was obtained when IV was condensed with benzaldehyde.

The half esterification of IIA yielded an acid which contained all the characteristic bands of IIA. The carbonyl group absorption region showed two absorption bands at 1725 and 1680 cm.$^{-1}$, due to the ester and acid linkages.

The esterification of III also yielded two moles of nitrogen and the product contained a terminal methylene group as evidenced by the bands at 1625 and 910 cm.$^{-1}$ The half esterification of III produced a monobasic acid with two different carbonyl groups (bands at 1725 and 1690 cm.$^{-1}$) and a terminal methylene group (1630 and 912 cm.$^{-1}$).

Hydrogenation studies have shown the presence of three double bonds, esterification with diazomethane the presence of two carboxy groups, and the titration studies are in accord with the behavior of other highly branched malonic acids.[5] On that basis we are assigning the dimeric acid to have the structure IIA, a structure previously considered[4] but not adopted.

EXPERIMENTAL

IIA. The preparation was previously described,[4] m.p. 99–100°: The esterification was carried out by treating 0.7043 g. (0.00251 mole) of IIA with 0.00595 mole of diazomethane in ether. The volume of evolved nitrogen was 119 ml. (S.T.P.), 105% of theory based on two acid groups. The product distilled at 178° at 17 mm.

Anal. Calcd. for $C_{18}H_{28}O_4$: C, 70.1; H, 9.1. Found: C, 70.1; H, 9.1.

The distillate gave a deep red colored solution when treated with benzaldehyde in the presence of sodium ethoxide. When refluxed with a saturated solution of maleic anhydride in toluene, a white crystalline solid separated.

The half esterification was carried out by treating 0.3769 g. (0.001345 mole) of IIA with 0.00159 mole of diazomethane dissolved in ether. The evolved nitrogen, 31.5 ml. (S.T.P.), was 52% of theory based on two acid groups. The ether was evaporated and the crude residue had a neutralization equivalent of 304.

Anal. Calcd. for $C_{17}H_{26}O_4$: neut. equiv. 294.

III. The preparation was previously described.[4] The dimethyl ester was prepared by treating 0.5672 g. (0.00235 mole) of III with an excess of diazomethane. The volume of nitrogen was 102 ml. (S.T.P.) which is 97% of theory based on two acid groups. Upon the evaporation of the ether, the product boiled at 132–134° at 4 mm.

Anal. Calcd. for $C_{18}H_{32}O_4$: C, 69.2; H, 10.2. Found: C, 70.6; H, 9.7.

The monomethyl ester was prepared as previously described.[4]

Anal. Calcd. for $C_{17}H_{30}O_4$: neut. equiv. 298. Found: neut. equiv. 296.

In the complete hydrogenation of IIA, 0.0812 g. (0.00029 mole) of IIA absorbed 19.7 ml. (S.T.P.) of hydrogen in 100 min. when an "active" lot of platinum oxide catalyst (0.0077 g.) was used. After the removal of the acetic acid solvent, the residue was crystallized from petroleum ether, m.p. 104–105°.

Anal. Calcd. for $C_{16}H_{30}O_4$: C, 67.1; H, 10.5; mol. wt. 286. Found: C, 66.0; H, 10.1; mol. wt. 304 (titration), 277 (cryoscopic).

CONTRIBUTION NO. 1030 FROM THE DEPARTMENT OF CHEMISTRY,
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Ammajin, a New Constituent of *Ammi Majus* (L.)

NICOLAS A. STARKOWSKY AND NASRY BADRAN

Received May 26, 1958

The fruits of the umbelliferous plant *Ammi majus* (L.) which grows freely in the Nile Delta have been used for centuries as a remedy for leukoderma (vitiligo). The active constituents responsible for the photodynamic properties of this Egyptian plant have been identified with the furocoumarins xanthotoxin, bergapten and imperatorin.[1] Recently, there was an increase of interest in the physiologically active furocoumarins because of the development of the psoralen (furocoumarin) treatment of pigmentation diseases[2a] and alopecia areata,[2b] and the discovery of the effect of these photosensitizing agents on skin carcinogenesis.[2c]

As many plants containing free furocoumarins have, among their other constituents, glycosidic compounds whose aglucones are related coumarins, it was worth studying the glycoside fraction of the fruits of *Ammi majus* (L.) and isolating such compounds. It has been reported in the literature that the fruits of this plant contain about 1% of an amorphous glucosidal principle,[3] but until now no

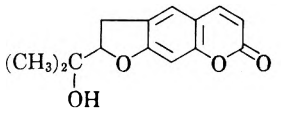
(1) I. R. Fahmy, H. Abu-Shady, A. Schönberg, and A. Sina, *Nature*, **160**, 468 (1947); I. R. Fahmy and H. Abu-Shady, *Quart. J. Pharm. and Pharmacol.* **20**, 281 (1947); *Quart. J. Pharm. and Pharmol.* **21**, 499 (1948).

(2) (a) Comp. E. Sidi, J. Bourgeois-Spinasse, and P. Planat, *Dyschromies et Vitiligo*, Expansion scientifique française, Paris, France, 1957; (b) E. Sidi and J. Bourgeois-Spinasse, *Presse med.*, **63**, 458 (1955); (c) M. A. O'Neal and A. C. Griffin, *Cancer Research* **17**, 911 (1957).

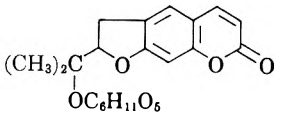
(3) I. R. Fahmy and M. A. El Keiy, *Rep. Pharm. Soc. Egypt*, **3**, 72 (1931).

crystalline substance has been isolated from this material. The study of the aqueous fraction obtained by concentrating the aqueous alcoholic extract of the seeds of *Ammi majus* (L.) has revealed the presence of a crystalline glycoside $C_{20}H_{24}O_9$, melting at 260°, having an optical rotation $[\alpha]_D^{25}$ −60° and showing the characteristic properties of coumarins. By acid hydrolysis, this compound gave D-glucose and an optically active aglucone $C_{14}H_{14}O_4$ (I), identical with the coumarin marmesin occurring in the bark of the tree *Aegle marmelos* Correâ.[4] Marmesin is the optical antipode of nodakenetin, which occurs in nature as a glucoside, nodakenin[5] ($[\alpha]_D^{30}$ +56.6°;$[\alpha]_D^{18}$ +57°[6]). However, the isolation of a glycoside of marmesin has not been reported up to the present time.

The proposed structure for the new glucoside, which we have named ammajin (II), is supported by the partial synthesis of this product from its aglucone marmesin and D-glucose, by the method based on the reaction of hydroxy compounds with pentaacetylglucose under the catalytic action of toluenesulfonic acid.[6]



I Marmesin



II Ammajin

EXPERIMENTAL[7]

Extraction of ammajin (II) *from the seeds of Ammi Majus* (L.). Two hundred grams of the finely powdered seeds were exhausted by percolation with 70% ethanol and the extract distilled in vacuum to remove the alcohol. After extraction of the remaining residue with chloroform in order to remove the last traces of the substances soluble in this solvent, the sirupy liquid thus obtained (50 ml.) was treated with a mixture of lead acetate and lead hydroxide (prepared by mixing 5 g. of lead acetate with 2 ml. of 2% sodium hydroxide solution). The mixture was stirred well, diluted to 5 times its volume with water and left to stand in the cold for 24 hr. After filtration, the solution was treated with 5 ml. of 20% sodium sulfide solution and filtered again. It was then concentrated to 40 ml. by vacuum distillation and extracted with 5 successive portions of a chloroform-alcohol mixture (1:1, v./v.). The combined organic layers were dried over sodium sulfate and evaporated to dryness. The brown solid residue (about 1 g.) was crystallized from boiling water to give 450 mg. of a crude crystalline glucoside melting at 220–230°. Further recrystallization from water gave colorless shining platelets of ammajin (II), m.p. 259–260° (dec.), $[\alpha]_D^{25}$ −60° (in 50% ethanol). Yield of the pure glucoside with respect to the seeds: 0.145%. II is sparingly soluble in cold water and alcohol and moderately soluble (about 1 g. in 300 ml.) in these solvents on boiling. It dissolves in glacial acetic acid on heating and is practically insoluble in methanol, acetone, and ethyl acetate. Dilute aqueous solutions of II fluoresce blue in ordinary light; under ultraviolet light, the fluorescence is intense violet-blue. II dissolves in concentrated sulfuric acid and alcoholic potash with a yellow color.

Anal. Calcd. for $C_{20}H_{24}O_9$: C, 58.81; H, 5.92. Found: C, 58.47; H, 6.01.

Acetylation of ammajin. One half gram of II was refluxed for 2 hr. with 15 ml. of acetic anhydride and 1 g. of anhydrous sodium acetate. The cooled mixture was decomposed with ice and water, and the colorless precipitate which separated out was crystallized from dilute ethanol to give 450 mg. of ammajin tetraacetate, m.p. 227°.

Anal. Calcd. for $C_{28}H_{32}O_{13}$: C, 58.31; H, 5.60. Found: C, 58.31; H, 5.71.

Hydrolysis of ammajin. One-half gram of II was refluxed for 2 hr. with 25 ml. of 5% hydrochloric acid. The precipitated aglucone (I) was collected and crystallized from benzene as colorless rods, (250 mg.) m.p. 189–190°; $[\alpha]_D^{25}$ +25° (in chloroform) [reported for marmesin: m.p. 189.5°; $[\alpha]_D^{25}$ +26.8° (in chloroform)[4]]. Addition of I to an authentic sample of marmesin from *Aegle marmelos* Correâ did not depress its melting point. I was soluble in chloroform, moderately soluble in alcohol and acetone, sparingly soluble in benzene, and practically insoluble in petroleum ether and water. Very dilute aqueous or alcoholic solutions of I had a strong blue-violet fluorescence in ultraviolet light.

The ultraviolet spectrum of I (0.008 mg./ml. in ethanol, 25°) showed a characteristic peak at 337 mμ and a much less sharp maximum at 260 mμ, with minima at 245 and 266 mμ. The R_f value of I (ascending paper chromatography; water as a solvent, temp. 30°) was 0.65 (reported for marmesin: 0.66[8]). The untreated spot appeared violet-blue under ultraviolet light (and silvery blue after spraying with dilute sodium hydroxide solution).

Anal. Calcd. for $C_{14}H_{14}O_4$: C, 68.30; H, 5.74; m.wt., 246. Found: C, 68.15; H, 5.83; equivalent weight (by titration): 249.

Acetylation of I with acetic anhydride–sodium acetate gave a monoacetyl derivative, m.p. 132° (from alcohol) (reported for marmesin acetate: 130°[4]).

Anal. Calcd. for $C_{16}H_{16}O_5$: C, 66.66; H, 5.55; m.wt., 288. Found: C, 66.52; H, 5.61; equiv. wt. (by titration): 142.

When a mixture of I and phosphorus pentoxide was either heated as such in a sublimation apparatus,[9] or refluxed in benzene, a dehydrated compound, m.p. 138–138.5° was obtained (reported for desoxyoreoselone obtained by the dehydration of nodakenetin: 138–139°[9] and of marmesin: 138–140°[4]).

Anal. Calcd. for $C_{14}H_{12}O_3$: C, 73.69; H, 5.26. Found: C, 73.8; H, 5.12.

By refluxing with dilute sodium hydroxide in the presence of mercuric oxide, I was converted to the corresponding *trans*-coumaric acid, m.p. 204–205° (dec.) (reported for *trans*-marmesic acid: 204° dec.[4]).

Oxidation of I with chromic acid gave pale yellow needles, m.p. 258–262° (dec.) having a violet ferric chloride reaction in alcohol (reported melting point for umbelliferone-6-carboxylic acid from marmesin: 260°[4]).

Bromination of II with one equivalent of bromine in alcoholic or acetic acid medium, at room temperature, gave colorless shining plates of a monobromide, m.p. 230–231°.

Anal. Calcd. for $C_{14}H_{13}O_4Br$: C, 51.71; H, 4.03; Br, 24.58. Found: C, 51.58; H, 3.93; Br, 25.32.

Identification of the sugar part of ammajin. The aqueous filtrate from I (see under "Hydrolysis of Ammajin") was extracted with chloroform, neutralized with sodium bicarbonate, treated with sodium acetate (2 g.) and phenylhydrazine hydrochloride (0.5 g.), and the mixture was heated on a water bath for 1 hr. The yellow precipitate which crystallized out on cooling had m.p. 204–205°, after recrystalliza-

(4) A. Chatterjee and S. S. Mitra, *J. Am. Chem. Soc.*, **71**, 606 (1949).

(5) J. Arima, *J. Chem. Soc. Japan*, 48, 88 (1927).

(6) Comp. E. Späth and E. Tyray, *Ber.*, **72**, 2089 (1939).

(7) All melting points are uncorrected. Elementary microanalyses by Dr. A. Bernhardt, Mülheim, Germany. Determination of ultraviolet spectra and optical rotations by courtesy of Dr. M. F. Messeid, Cairo.

(8) D. P. Chakraborty and P. K. Bose, *J. Indian Chem. Soc.*, **33**, 905 (1956).

(9) E. Späth and P. Kainrath., *Ber.*, **69**, 2062 (1936).

tion from alcohol (undepressed by an authentic sample of D-glucose osazone).

Partial synthesis of ammajin. Marmesin (I) (obtained by the hydrolysis of II) (0.30 g.), β-pentaacetyl-D-glucose (0.5 g.) and 10 mg. of *p*-toluenesulfonic acid were mixed and heated in a test tube at 130–135° for 1 hr. The dark melt was warmed with 5 ml. of benzene and filtered. The filtrate was then treated, while warm, with isoheptane, until a precipitate appeared. The mixture was cooled in ice and the clear supernatant liquid was decanted from the yellow resinous product sticking to the bottom of the flask. The solution was warmed and treated again with isoheptane to incipient turbidity, and left in the cold overnight. The almost colorless product which separated out was crystallized from dilute ethanol twice to give 100 mg. of colorless needles, m.p. 225–227°, giving no depression with a sample of the tetraacetate prepared from natural ammajin.

The synthetic acetate (250 mg.) was hydrolyzed with dry ammonia in methanol[6] to give 120 mg. of ammajin, identified by its melting point (258–260°) and its mixed melting point (no depression) with the natural glucoside obtained from the plant.

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Communications TO THE EDITOR

Isotope Effects in the Free Radical Arylation of Aromatic Hydrocarbons

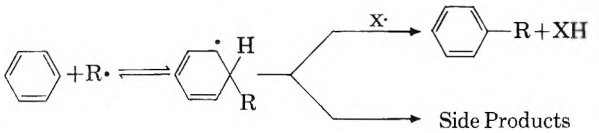
Sir:

There have been several recent reports[1-4] that the free radical arylation reaction of aromatic hydrocarbons by external reagents proceeds without an isotope effect. On the other hand, an isotope effect has recently been observed in certain intramolecular free radical aromatic substitution reactions.[5] It has already been pointed out[1c] that experiments[1b,2] involving low conversions and utilizing tritium at the tracer level are not conclusive.

We wish to report data indicating that there *is* an isotope effect in the free radical arylation and alkylation of benzene-*d*, at least with certain peroxides and under certain experimental conditions. The data are summarized below. The radicals indicated were, in all cases, generated by decomposing the appropriate diaroyl (or dialkyl) peroxide in benzene-*d* at 78°. The benzene-*d* was analyzed mass spectrometrically. The carefully purified biphenyls (purity checked by elementary analysis) were analyzed for deuterium by combustion and the falling drop method.[6] Product toluene was analyzed mass spectrometrically.

In all but two cases—*p*-nitrobenzoyl peroxide and benzoyl peroxide at the higher concentration—unequivocal isotope effects were observed.

The most likely mechanism of free radical aromatic substitution involves addition of the radical to the aromatic followed by hydrogen abstraction by some species X. In writing an adequate scheme for these steps one must consider that the addition step may be reversible and that the intermediate adduct radical may undergo side reactions (such as dimerization, tar formation, etc.[7,8]), as well as conversion to substitution product:



An isotope effect will be observed if *either* the reversal of the addition step *or* the step forming side products competes with the hydrogen abstraction step. In either case the intermediate formed by addition of R· at a hydrogen-bearing position of the aromatic ring will be converted to alkylation product in preference to intermediate formed by addition of R· at a deuterium-bearing position.

One can*not*, therefore, conclude from our results that the first step (addition of radical to aromatic) is appreciably reversible under the conditions of the substitution.[9] In fact, since substrate recovered from an arylation of a *m*-dinitrobenzene-2,4-dinitrobenzene-*t* mixture, driven to high conversion, showed no significant change in nuclide content,[1a] it appears that the isotope effect is *not* due to reversal of the first step, but due to the side reactions.[10] Experiments are presently under way in

Radical	Moles PhD / Moles $(RCOO)_2$	Isotopic Purity Benzene-*d*, %	Product M.P.	Product Atom % D	Product Isotope Effect
C_6H_5	42:1	93.7	71–72°	7.81	1.0
	420:1	98.2	71–72°	9.10	2.6
p-$CH_3C_6H_4$	50:1	97.9	47.5–48°	7.61	2.9
p-$CH_3OC_6H_4$	50:1	96.6	89°	6.98	1.3
p-ClC_6H_4	50:1	98.5	78.5–79°	9.80	1.7
	25:1	93.9	78.5–79°	9.30	1.7
p-$O_2NC_6H_4$	41:1	98.5	115.5–116°	9.13	1.0
CH_3	24:1	97.86	Liq.	11.05	1.7
	615:1	98.16	Liq.	11.00	1.7

(1) (*a*) C. C. Price and R. J. Convery, *J. Am. Chem. Soc.*, **80**, 4101 (1958); (*b*) *J. Am. Chem. Soc.*, **79**, 2941 (1957); (*c*) *J. Am. Chem. Soc.*, **79**, 6579 (1957) (Correction).

(2) G. H. Williams, Abstracts, XIVth International Congress of Pure and Applied Chemistry, Paris, France, 1957, p. 27.

(3) Milyutinskaya, Bagdasaryan, and Izrailevich, *J. Phys. Chem.* (*U.S.S.R.*), **31**, 1019 (1957).

(4) See also D. R. Augood and G. H. Williams, *Chem. Revs.*, **57**, 167 (1957).

(5) D. B. Denney and P. P. Klemchuk, *J. Am. Chem. Soc.*, **80**, 3289 (1958).

(6) By Mr. Josef Nemeth, University of Illinois.

(7) The importance of this point has been stressed previously by K. H. Pausacker, *Austral. J. Chem.*, **10**, 49 (1957).

(8) An important new side reaction, namely disproportionation, has very recently been uncovered by D. F. De Tar and R. A. J. Long, *J. Am. Chem. Soc.*, **80**, 4742 (1958).

(9) This point appears not to have been considered in ref. 5.

(10) Still other possible causes of the isotope effect will be discussed at a later date.

our laboratories to elucidate the exact origin of the observed isotope effects and the reason for their variation with nature and concentration of the peroxide.

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Pyrolysis of Esters. I. Nonselectivity in the Direction of Elimination by Pyrolysis

Sir:

We wish to report that published generalizations regarding the direction of elimination on pyrolysis of esters are in grave error. We now find that pyrolysis of secondary acetates gives in appreciable amounts both possible alkenes as well as *cis* and *trans* isomers when such isomerism is possible. Pyrolysis of 1-heptyl acetate (b.p. 186–187°, n_D^{25} 1.4120; lit.[2] b.p. 192.5°, $n_{He\,(vel.)}^{15}$ 1.41653) at 540° and a flow rate of 0.6 g. per minute gave pure 1-heptene (b.p. 90–93°, n_D^{25} 1.3962; lit.[3] b.p. 93.5°, n_D^{20} 1.3998) in 56% yield. Homogeneity of this material was established by gas chromatographic analysis using the Wilkins Aerograph equipped with a 5-foot silicone column and with a 10-foot Ucon Polar column. Pyrolysis of 2-heptyl acetate (b.p. 171–173°, n_D^{25} 1.4050; lit.[4] b.p. 71° at 17 mm., n_D^{20} 1.4089) at 485° and a flow rate of 0.67 g. per minute gave a mixture of isomeric heptenes (b.p. 92–98°, n_D^{25} 1.3994; lit.,[5] *trans*-2-heptene, b.p. 97.5–99°, n_D^{24} 1.4056, *cis*-2-heptene, b.p. 98.5–99.5°, n_D^{25} 1.4052) in 84% yield. Gas chromatographic analysis over the 10-foot Ucon Polar column showed 53.9% 1-heptene, 29.3% *trans*-2-heptene (low boiling), and 16.8% *cis*-2-heptene (higher boiling). Above a critical lower temperature, the composition of the pyrolyzate appears to be independent of the temperature and extent of pyrolysis. Thus, pyrolysis of 2-heptyl acetate at 450° and a flow rate of 1 g. per minute gave only 35% of heptenes identical in composition with the product described above.

Pyrolysis of 4-heptyl acetate, which can lead to only one structural isomer without bond rearrangement, on pyrolysis at 485° and flow rate 0.8 g. per minute gave 86% of 3-heptene (b.p. 93–95.5°, n_D^{25} 1.4012; lit.[6] b.p. 95.8–96.1°, n_D^{20} 1.4090). This material was homogeneous to the Ucon chromatographic column except for a small shoulder on the high-retention side of the single peak; this shoulder is interpreted as being due to the presence of a small amount of *cis*-3-heptene, the major component being the *trans*-isomer. Pyrolysis of 3-heptyl acetate at 485° and flow rate 0.6 g. per minute gave a mixture of heptenes (b.p. 91–97°, n_D^{25} 1.4022) in 84% yield. Gas chromatographic analysis over the Ucon column showed 53.5% of 3-heptene, 34.7% of *trans*-2-heptene, and 11.8% of *cis*-2-heptene. The 3-heptene peak showed a shoulder on the high-retention side indicating the presence of a small amount of the *cis*-isomer.

We have also reinvestigated a specific example reported by Bailey and King.[1] Pyrolysis of methylisobutylcarbinyl acetate at 485° and flow rate 0.75 g. per minute gave in 72.2% yield an olefin mixture which on chromatographic analysis over the Ucon column showed two components in the amounts of 44.5% (low retention) and 55.4% (high retention). We assume that the low retention isomer is the lower boiling[7] 4-methyl-1-pentene, while the high retention isomer is the higher boiling[7] 4-methyl-2-pentene.

In view of these results, we must regretfully conclude that the generalizations and the experimental observations of Bailey and associates[1] are in error. We attribute this experimental error to failure of the earlier investigators to utilize precise fractional distillation, thus necessitating the assignment of structure and estimation of homogeneity on infrared analysis alone. Infrared analysis is not an infallible criterion when mixtures are being compared.

We do not wish to generalize our observations at this time. Extensive further investigations are planned.

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(1) W. J. Bailey and C. King, *J. Am. Chem. Soc.*, **77**, 75 (1955); W. J. Bailey, J. J. Hewlitt, and C. King, *J. Am. Chem. Soc.*, **77**, 357 (1955).

(2) R. Bilterys and J. Gisseleire, *Bull. soc. chim. Belg.*, **44**, 576 (1935).

(3) M. L. Sherrill, K. E. Mayer, and G. F. Walter, *J. Am. Chem. Soc.*, **56**, 927 (1934).

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